DIFFERENT PERSPECTIVES IN MEDICINAL AND AROMATIC PLANTS

EDITORS
Assoc. Prof. Dr. Gülen ÖZYAZICI
Assoc. Prof. Dr. Esra UÇAR

İKSAD
Publishing House

DIFFERENT PERSPECTIVES IN MEDICINAL AND AROMATIC PLANTS

EDITORS

Assoc. Prof. Dr. Gülen ÖZYAZICI

Assoc. Prof. Dr. Esra UÇAR

AUTHORS

Prof. Dr. Ahmet GÜMÜŞÇÜ
Prof. Dr. Ayşe Gül İNCE
Prof. Dr. Fatih SEYİS
Prof. Dr. Mehmet KARACA
Prof. Dr. Mehmet ŞİMŞİR
Assoc. Prof. Dr. Ahmet DEMİRBAŞ
Assoc. Prof. Dr. Cennet YAMAN
Assoc. Prof. Dr. Ebru YABAŞ
Assoc. Prof. Dr. Ferda SARI
Assoc. Prof. Dr. Hülya KAYNAR
Assoc. Prof. Dr. İlknur ŞENTÜRK
Assoc. Prof. Dr. Neşe KEKLİKCİOĞLU ÇAKMAK
Assoc. Prof. Dr. Nuraniye ERUYGUR
Assoc. Prof. Dr. Tuğba GÜRKÖK TAN
Assist. Prof. Dr. Doğan ARSLAN
Assist. Prof. Dr. Emine YURTERİ
Assist. Prof. Dr. Fuat ERDEN
Assist. Prof. Dr. Gülşen GÜÇLÜ
Assist. Prof. Dr. Hasan DURUKAN
Assist. Prof. Dr. Sadiye Ayşe ÇELİK
PhD. Ayşe SARI
PhD. Bahar TÜRKMENOĞLU
PhD. Dilara ÜLGER ÖZBEK
PhD. Gamze TOPAL CANBAZ
Res. Assist. Aysel ÖZCAN AYKUTLU
Res. Assist. Haydar KÜPLEMEZ
Lecturer Emine TONUS
MSc. Student Ebru ERDEM
MSc. Hatice Kübra ÇELEBİ
MSc. Yakup SÜRÜCÜ
Dietician Betül Eylül ÇİÇEKLİYURT

İKSAD
Publishing House

(The Licence Number of Publicator: 2014/31220)
TURKEY TR: +90 342 606 06 75
USA: +1 631 685 0 853
E mail: iksadyayinevi@gmail.com
www.iksadyayinevi.com

It is responsibility of the author to abide by the publishing ethics rules.

ISBN: 978-625-6955-52-3
Cover Design: İbrahim KAYA
December / 2022
Ankara / Turkey
Size = 16x24 cm

CONTENTS

PREFACE

Türkiye is at the intersection of three floristic regions, namely Europe-Siberia, Iran-Turanian and Mediterranean, and is located in the Fertile Crescent region. Due to the geographical location of Turkey, the diversity of plant species in its natural flora is quite high, and about one-third of them are endemic. About 500 of the 10,000 plant species spread throughout Türkiye are used for medicinal and aromatic purposes.

Today, medicinal and aromatic plants are used in many fields such as medicine and pharmacy, cosmetics and perfumery, spices, food additives, plant protection, animal health and feed additives, natural dyestuffs and landscape applications. Phenolic compounds, terpenoids and alkaloids possessed by aromatic plants give plants their medicinal and aromatic properties. These compounds constitute the raw material of many drugs in the pharmaceutical industry today, either by isolating or synthesizing. According to the WHO (World Health Organization), 25% of prescription drugs are medicinal and aromatic plant-based and when the FAO (Food and Agriculture Organization) data are examined, 30% of the drugs sold worldwide consist of compounds derived from medicinal plant. Some compounds found in plants can be produced by synthesis, while others cannot. Although drugs produced from synthetic compounds have an important place today, they can be seen in cases where synthetic drugs have side effects or fail to respond to treatment over time. At the same time, some bacteria may become resistant to antibiotic-style drugs. In such cases, there is a rapid return to natural products and nature.

This book consists of twenty chapters from different disciplines related to medicinal and aromatic plants. We would like to express my special thanks to our valuable authors who shared their research with us in this book.

Assoc. Prof. Dr. Gülen ÖZYAZICI

Assoc. Prof. Dr. Esra UÇAR

EDITORS

CHAPTER 1

CHEMICAL COMPOSITIONS OF VOLATILE AND NONVOLATILE SECONDARY METABOLITES IN THYME (*THYMUS* L.)

Mehmet KARACA[1]
Ayse Gul INCE[2]
Safinaz YASAK ELMASULU[3]

[1]Akdeniz University, Faculty of Agriculture, Field Crops Department, Antalya, Türkiye, e-mail: mkaraca@akdeniz.edu.tr, ORCID ID: 0000-0003-3219-9109
[2] Akdeniz University, Vocational School of Technical Sciences, Antalya, Türkiye. e-mail: aince@akdeniz.edu.tr, ORCID ID: 0000-0002-9015-6580
[3] Akdeniz University, Korkuteli Vocational School, Korkuteli, Antalya, Türkiye. e-mail: hselmasulu@akdeniz.edu.tr, ORCID ID: 0000-0003-2794-037X

INTRODUCTION

The family Lamiaceae (Labiatae) has more than 236 genera and 7200 species (Harley et al., 2004; Nieto, 2007; Tzima et al., 2018). The genus *Thymus* is one of the most known genera of Lamiaceae, along with *Salvia, Hyptis, Scutellaria, Stachys, Teucrium*, and *Plectranthus* (Stahl-Biskup and Saez, 2002; Li et al., 2019). The genus *Thymus* contains about 350 species, and the Mediterranean area (specifically Southern and Western Europe) is considered the origin of the genus *Thymus*. Today, many species are distributed throughout North Africa, Iberian Peninsula, Greece, and Türkiye (Figure 1). There are at least 45 *Thymus* species naturally grown in Türkiye (Baser et al., 2002; Sevindik et al., 2016), and the number of endemic species in Türkiye is increasing in comparison to previous records (Ozturk et al., 2022).

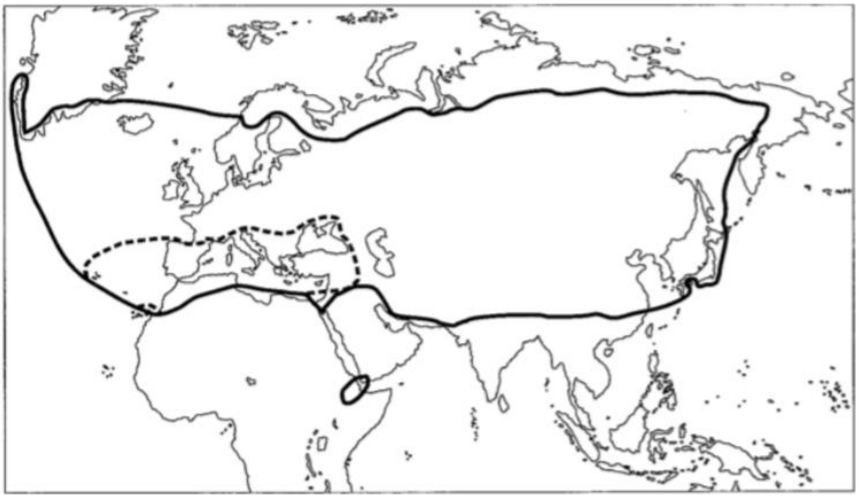


Figure 1: Distribution of Species in the Genus *Thymus*. Please note that regions with a dotted line represent species in all sections except sections *Serpyllum* and *Hyphodromi*, and subsection *Serpyllastrum* (Morales, 2012).

It is assumed that the Latin word *Thymus* comes from the Greek word "thyo" meaning perfume, or "thymos" word meaning courage or strength (Cumo, 2013). We know that species of *Thymus* were known before and after Carolus Linnaeus (also known as Carl von Linné) by other botanists (Li et al., 2019). After Linnaeus, Boisser in Flora of Orientalis (1888) described additional new species of *Thymus*. Klokov in Flora of the USSR (1954) had 136 species and five sections: *Goniothymus*, *Verticillati*, *Euserpyllum*, *Kotschyani*, and *Subbrecteati*. Jalas in Flora of Europaea (1972) and Flora of Turkey (1982) added new species to the genus *Thymus* grouped in *Micantes*, *Mastichina*, *Piperella*, *Teucrioides*, *Pseudothymbra* (two subsections: *Pseudothymbra* and *Anomalae*), *Thymus* (two subsections: *Thymastra* and *Thymus*), *Hyphodromi* (3 subsections: *Subbracteati*, *Serpyllastrum* and *Thymbropsis*) and *Serpyllum* (seven sections: *Insulares, Kotschyani, Pseudopiperallae, Isolepides, Alternantes, Pseudomarginati, Serpyllum* (Jalas, 1982; Halat et al., 2022).

Chromosomes of the genus *Thymus* are generally small, and the numbers vary from 2n = 24 to 2n = 90. The diploid genome size of *T. persicus* (2n = 2x = 28, 2C DNA) is 1.20 picograms (pg), while the induced autotetraploid genome of the same species (2n = 4x = 56, 2C DNA) is 2.39 (Tavan et al., 2015). Various levels of ploidy exist in *Thymus* with chromosome numbers of 2n = 24, 26, 28, 30, 32, 42, 48, 50, 52, 54, 56, 58, 60, 84, and 90, corresponding to the diploid, tetraploid, and hexaploid levels (Federici et al., 2013). Analyses revealed the existence of new cytotypes in *T. mastichina* subsp.

mastichina 2n = 2x = 24, 2n = 2x = 28 and 2n = 2x = 30, and tetraploid species include 2n = 4x = 56, 2n = 4x = 58, and 2n = 4x = 60 (Giron et al., 2012).

Variations in chromosome numbers in ploidy levels indicate the presence of aneuploidy, which has been an important phenomenon during the evolution of this genus and is responsible for the great genetic variations in the species (Karaca et al., 2015). The secondary basic numbers x = 14 and x = 15 originate from a basic number x = 7. The most common chromosome numbers are 2n = 28, 30, 56, and 60. Some species have more than one ploidy levels such as *T. mastichina* with 2n = 30 and 2n = 60; *T. vulgaris* 2n = 28, 58; *T. zygis*, T. *leptophylhs*, *T. glabrescens*, *T. longicaulis*, *T. praecox* 2n = 28, 56; *T. algeriensis* 2n = 30, 56; *T. conzptus* 2n = 26, 52; *T. zygioides* 2n = 60, 90; *T. longedentatzls* 2n = 30, 90; *T. striatus* and *T. herba-barona* 2n = 28, 56, 84 (Giron et al., 2012; Federici et al., 2013; Tavan et al., 2015).

1. SYSTEMATIC CLASSIFICATION & MORPHOLOGY

The genus *Thymus* belongs to the monophyletic group of the subfamily Nepetoideae Kostel, the tribe Mentheae Dumort, and the subtribe Menthinae Endl (Lahlou et al., 2022). The four most closely related genera to the genus *Thymus* are *Origanum*, S*atureja*, *Micromeria* and *Thymbra*. Because of great morphological variability and chromosome number differences in this genus, there are more than one thousand species, with higher taxonomic synonyms (Bartolucci and Peruzzi, 2013).

Below, the systematic classification of the genus *Thymus* is listed:

Kingdom : Plantae
Subkingdom : Tracheobionta
Superdivision : Spermatophyta
Division : Magnoliophyta
Class : Magnoliopsida
Subclass : Asteridae
Order : Lamiales
Family : Lamiaceae
Subfamily : Nepetoideae
Tribe : Mentheae
Subtribe : Menthinae
Genus : *Thymus* L.
Species : each of 214 species i.e., *Thymus vulgaris* L.
Subspecies : T. species name, then subspecies name, i.e., *Thymus serpyllum* subsp. *serpyllum*

Other well-defined species other than *T. vulgare* are *T. zygis* L. (Spain thyme), *T. serpyllum* L. (wild thyme), and *T. pulegioides* L. (large thyme). These species provide the main commercial varieties in the world (Stahl-Biskup and Venskutonis, 2012). Species in the genus *Thymus* show great variation in geographic distribution, soil types, and climates. Many *Thymus* species do not require high soil fertility but do well in well drained soils, which can be calcareous, gypseous, rocky, or gravelly ground on rocky or stepped slopes, cold or Mediterranean climate (Figure 2).

Species of the genus *Thymus* could be divided into two groups, one of which contains little bushy plants, usually below 50 cm but ranges from creeping forms to 1 m, perennial herbs, or woody at the base stem. The second group contains creeping life-forms, common among the species belonging to the section *Serpyllum* or *Hyphodromi* (Stahl-Biskup and Saez, 2002).

Figure 2: General Appearance in Nature of Some *Thymus* Species Growing in Türkiye. Species at the upper left is *T. revolotus*, upper right is *T. sipyleus* subsp. *sipyleus*, lower right is *T. zygoides*, and lower right is *T. cilicicus*. The pictures in the figure were taken by Dr. S. Y. Elmasulu.

Species identification is usually based on the features of the habitus, leaf, stem, habitat, indumentum, inflorescences, bracts, bracteole, calyx, corolla, pollen along with some new features such as nutlet shape, distribution of trichomes and surface sculpture. For instance, a recently described species *Thymus baseri* Öztürk, Yaylacı, Koyuncu and Ocak has shrub habitus, cushion-forming dwarf shrub while *T. revolutus* has habitus of dwarf shrub with woody and slender (Ozturk et al., 2022).

As in most of the family Lamiaceae, species in the genus *Thymus* have quadrangular stems, erect to prostrate, sometimes caespititious and radicant. The hairs on the stems of plants can cover all four sides of the stem (holotrichous) or only two sides alternating in each internode (alelotrichous). The hairs can also be found only on the four ribs of the stems (goniotrichous). Examples include alelotrichous as *T. praecox*, goniotrichous as *T. pulegioides*, and holotrichous as *T. piperella*. Leaves of species are very usually ciliate at the margins, either at the whole margin or only at the base or on the petiole. The leaves form highly branched clumps that could rise to about 20 cm above the ground, are small (3 mm to 13 mm x 0.3 mm to 1.3 mm), linear, pubescent, entire, elliptic, frequently revolute, and form compacts (Lahlou et al., 2022; Ozturk et al., 2022).

Species of *Thymus* have inflorescences that are capitate, condensed, often spike-shaped, or interrupted panicle like (Lahlou et al., 2022), Corolla color ranges from lilac to purple, purple lilac, and white to lilac with a size of 4 mm to 8 mm (Ozturk et al., 2022). Flowering stem sizes vary among the species, ranging from 1 cm to 10 cm. Species of *Thymus* usually show gynodioecy; thus, some species produce two types of individuals, some with female flowers without stamens and others with hermaphrodite flowers. The fruits are nutlets, up to four per flower, but usually some of them abort during early development (Lahlou et al., 2022).

2. USE OF SPECIES IN THE GENUS *THYMUS*

Leaves, flowering parts, aerial parts, herbs, and dried flowers have been used for medicinal and aromatic purposes (Karaca et al., 2015). Although the essential oils of thyme are much more utilized and studied, the genus *Thymus* is rich in other nonvolatile secondary metabolites such as flavonoids, simple phenylpropanoids, lignans, tannins, organic acids, phytosterols, and benzoic acid derivatives. Volatile and nonvolatile secondary metabolites are responsible for the pharmacological utilization of *Thymus* plants. These volatile and nonvolatile secondary metabolites are utilized as preservatives for foods, and herbs are widely used as culinary ingredients in diverse regions of the world (Karaca et al., 2015). Volatile and secondary metabolites can contribute to extending the shelf-life of fresh foods and enhancing the safety of certain food products. On the other hand, extracts of *Thymus* genus plants have been widely used as environmentally friendly corrosion inhibitors for different metals in various acids (Li et al., 2019; Halat et al., 2022; Lahlou et al., 2022).

In addition to the use of volatile and nonvolatile compounds in industry, some species in the genus *Thymus* are grown as decorative, aromatic border, pathway, or rock garden plants. Although the species in the genus are well known for their medicinal and aromatic properties, they are useful sources of phytonutrients, minerals, vitamins, beta carotene, flavonoids, and antioxidants. For instance, the leaves of *T. vulgaris* have excellent sources of potassium, calcium, iron, manganese, magnesium, and selenium, as shown in Table 1 (Dauqan and Abdullah, 2017).

Table 1: The nutritional profile of *Thymus vulgaris* (Dauqan and Abdullah, 2017)

Nutritive components	Amount of mg per 100 g fresh leaves	Recommended daily allowance (%)
Vitamins		
Niacin	1.82	11
Pantothenic acid	0.41	8
Pyridoxine	0.35	27
Riboflavin	0.47	36
Thiamin	0.48	4
Vitamin A	4751 IU	158
Vitamin C	160.1	266
Minerals		
Sodium	9	0.5
Potassium	609	13
Calcium	405	40.5
Iron	17.5	218
Magnesium	160	40
Manganese	106	15
Zinc	1.81	16.5
Beta carotene	2851	-

3. CHEMICAL CONSTITUENTS OF *THYMUS*

Like many other genera in the mint family, the species in the genus *Thymus* produce incredibly diverse natural biomolecules with quite different structures. These biomolecules are commonly referred to as “secondary metabolites” as opposed to “primary metabolites”, which are nucleic acids, polysaccharides, lipids, and proteins that are essential for plant growth and development (Karaca and Ince, 2022a; b; Lahlou et al., 2022). Compared to the primary metabolites, the exact functions or roles of secondary metabolites are not fully understood. Chemical compounds in the genus *Thymus* can be grouped into essential oils (volatiles), nonvolatile secondary metabolites such as phenolic compounds, terpenoids, and others (Li et al., 2019). Although these substances are synthesized by all the plant organs, such as buds, flowers, leaves, stems, seeds, fruits, and roots, and are stored in secretory cells, cavities, canals, epidermal cells, or glandular trichomes, which are grouped as capitate or peltate glandular trichomes (Figure 3), the type and amount of these substances vary depending on the tissue, developmental stage, and species. Among the trichomes, capitate glandular trichomes are composed of a cell or two cells that sit at the terminal end of a stalk of one to several cells. On the other hand, peltate trichomes usually consist of several secretory head cells (up to 16), a wide, short stalk, and a basal epidermal cell (Stahl-Biskup and Saez, 2002; Feng et al., 2021).

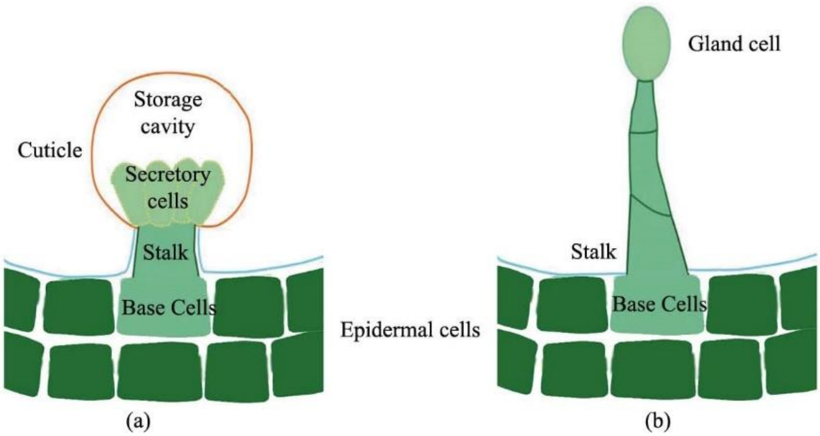


Figure 3: Anatomy of the Glandular Peltate Trichome Represented by *T. vulgaris* (adapted from Stahl-Biskup and Saez, 2002).

The types of chemical properties of plant species vary depending on the genotype, epigenotype, tissue, organ and development stages (Karaca and Ince, 2022a). Environmental abiotic factors such as temperature, moisture, chemical composition of soil also significantly influence chemical composition, along with the cultivation methods (Stahl-Biskup and Saez, 2002; Feng et al., 2021). These factors also influence the chemical composition of *Thymus* biomolecules. Nonetheless, these substances are defensive substances of plants, but they are widely used in cosmetology, medicine, food, and other fields. Many of these substances such as flavonoids, phenylpropanoids, organic acids, terpenoids, tannins, lignans, quinic acid and dotriacontane alcohol are biologically active as antioxidant, anti-inflammatory, anticancer, antibacterial, antifungal, anthelmintic, and antiviral (Nabavi et al., 2015; Salehi et al., 2019; Li et al., 2019; Halat et al., 2022).

4. VOLATILE SECONDARY METABOLITES

Thymus plants produce abundant volatile oils, which are the main secondary metabolites in this genus. They are volatile, low-molecular-weight terpenes, terpene alcohols, esters and phenolics easily isolated by steam distillation of plant material and have been widely used in medicine, cosmetology, health care, food, and other fields (Li et al., 2019; Halat et al., 2022). Volatile secondary metabolites can be synthesized by all plant organs, i.e., buds, flowers, leaves, stems, twigs, seeds, fruits, roots, wood, or bark, and are stored in secretory cells, cavities, canals, epidermal cells or glandular trichomes (Stahl-Biskup and Saez, 2002; Nabavi et al., 2015; Zarshenas and Krenn, 2015; Salehi et al., 2019; Lahlou et al., 2022).

Some volatiles of *Thymus* function as chemical signals, controlling their external environment. It was speculated that stresses such as pathogen infections or subterranean microbial communities can induce the particular emission of volatile compounds from plants. They attract insect pollinators and repel predators. Some of these signals are generated and emitted directly after the attacks of herbivores. The volatile substances released often serve as indirect defenses, attracting insects and mites. Additionally, some volatiles inhibit seed germination and help plants communicate with each other. Indeed, several previous scientific reports have shown that crops can perceive other volatile substances emitted by nearby crops under attack by herbivore insects. They respond to the information emitted by activating their defenses (Halat et al., 2022; Lahlou et al., 2022).

Volatile secondary metabolites are composed of monoterpenes, sesquiterpenes, and diterpenes. Volatiles are monoterpenes and sesquiterpenes. Camphor, carvacrol acetate, elemol, linalool terpinene-4-ol, α-terpinyl acetate, thymol, α-pinene, β-myrcene, and γ-terpinene are the main constituents of volatile secondary metabolites (commonly known as essential oils), extracted by hydro distillation, steam distillation, or microwave. The well-known terpenes such as thymol, carvacrol, linalool, and menthol show enhanced antimicrobial activities due to the presence of highly active functional groups, which delocalize electrons (Salehi et al., 2019; Li et al., 2019; Halat et al., 2022; Lahlou et al., 2022). Major volatiles of the genus *Thymus* grown in Türkiye are shown in Figure 4.

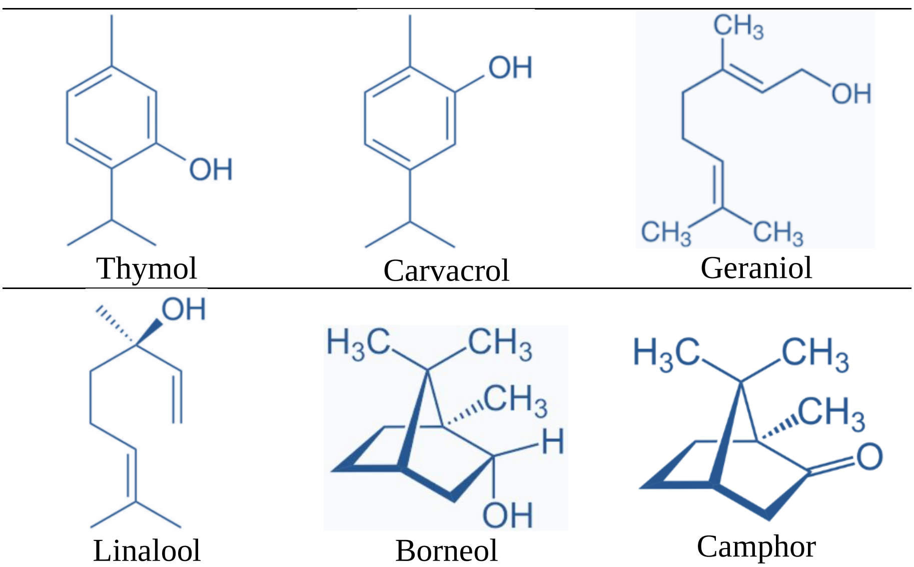


Figure 4: Chemical Structure of Essential Oil Types of *Thymus* Species Naturally Occurring in Türkiye

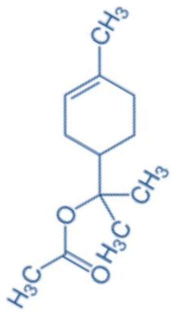
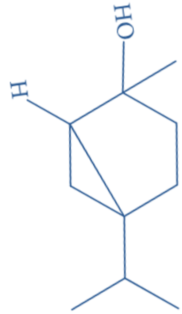
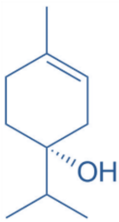
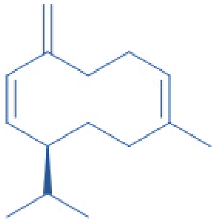
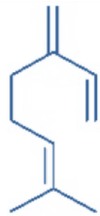
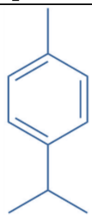
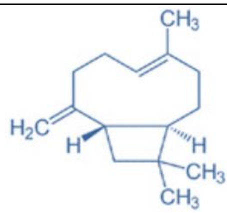
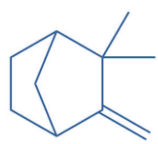
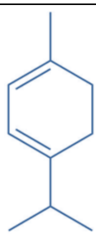
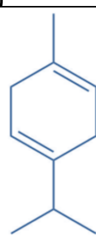
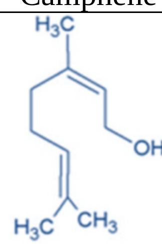
 α-terpinyl acetate	 1,8-Cineole	 Sabinene hydrate
 Terpine-4-ol	 Germacrene D	 β-Myrcene
 ρ-Cymene	 β-Caryophyllene	 Thujene
 α-Pinene	 β-Pinene	 Camphene
 α-Terpinene	 γ-Terpinene	 Nerol

Figure 4: (continued) Chemical Structure of Essential Oil Types of *Thymus* Species Naturally Occurring in Türkiye

Thymol and carvacrol are two well-known famous volatile secondary metabolites species of *Thymus*. These volatile secondary metabolites are used as food additives with no safety issues according to the World Health Organization food additive standard, and they contribute to the concentrated commercial interest because of their considerable amounts (Li et al., 2019). The whole dried herb of *Thymus* is supposed to contain volatile secondary metabolites up to 2.5%. However, the plant source, location and growing environment, harvesting season, and harvesting part, together with extraction methods, and analysis methods of volatile secondary metabolites play important impacts on the sorts and contents of some volatile and other components (Muller-Riebau et al., 1997; Varga et al., 2015). For instance, *T. zygioides* Griseb. var. *lycaonicus* consisted of thymol (45%) and beta-bisabolene (11%) in Tekirdağ, geraniol (77%) in Manisa, thymol (50%) in Kırklareli, thymol (58%) and ρ-cymene (11%) in Uşak (Tümen et al., 1995).

The major volatile secondary metabolites of the genus *Thymus* naturally occurring in Türkiye were listed in Table 2. As it can be seen in Table 2, the main volatile secondary metabolites of *Thymus* species mainly include thymol, carvacrol, linalool, α-terpinyl acetate, and geraniol. These volatile secondary metabolites range as high as 82.1% α-terpinyl acetate, 80% of linalool, 75.1% carvacrol, 70% thymol, and 68.8% geraniol (Table 2). However, some species of *Thymus* naturally occurring in Türkiye also include some other volatile secondary metabolites (essential oils).

Table 2: Major volatile secondary metabolites of thyme grown in Türkiye

Species	The major constituents (%)
*Thymus argae*us Boiss. & Balansa	linalyl acetate (45-66%), linalool (10.5%)
T. atticus Celak.	thymol (37.1-58.2%), β-cymene (9.0-12.9%), carvacrol (7.7-8.5%)
T. aznavourii Velen.	germacrene D (22.8%), (E)-P-farnesene (16.1%), α-pinene (11.1%)
T. bornmuelleri Velen.	thymol (45.0%), p-cymene (12.6%)
T. canoviridis Jalas	carvacrol (29.5%), geraniol (13.3%)
T. cariensis Hub.-Mor. and Jalas	borneol (13.4%), 1,8-cineole (12.7%), α-pinene (12.2%)
T. cherlerioides Vis.	thymol (60.0%)
T. cilicicus Boiss. et Bal.	α-terpineol (33.4%), α-pinene (16.7%)
T. convolutus Klokov	camphor (16.6%)
T. eigii (M. Zohary and P.H. Davis) Jalas	carvacrol (75.1%)
T. eriocalyx (Ronniger) Jalas	thymol (43.1%), linalool (11.1%), γ-terpinene (6.0%)
T. fallax Fisch. and Mey.	carvacrol (70.87%), ρ-Cymene (3.39-7.46%)
T. fedtschenkoi var. handelii (Ronn.) Jalas	linalool (17.2%), borneol (10.4%)
Thymus Integer Griseb	borneol (22%), p-cymene (10.1%)
T. haussknechtii Velen.	1,8-Cineole (21.5%) linalool (19.9%)
T. kotschyanus Boiss. and Hohen	carvacrol (40.74%), thymol (26.9%)
T. kotschyanus Boiss. and Hohen var. kotschyanus	thymol (26-47.5%), carvacrol (24.3%) and ρ-cymene (17.6%)
T. kotschyanus Boiss. and Hohen. var. glabrescens Boiss.	carvacrol (44.2%)

Table 2. (continued)

Species	**The major constituents (%)**
T. leucostomus Hausskn. and Velen. var. argillaceus Jalas	thymol (27.0%), carvacrol (22.0%)
T. leucostomus Hausskn. and Velen. var. gypsaceus Jalas	thymol (33.2%), borneol (22.2%)
T. leucostomus Hausskn. and Velen. var. leucostomus	carvacrol (21.6%), a-terpinyl acetate (23.8%), linalool (13.7%)
T. leucotrichus Halacsy	β-caryophyllene, elemol, germacrene D
T. longicaulis C. Presl ssp. *chaubardii* (Boiss. and Heldr. ex Reichb.fi1.) var. chaubardii Jalas	thymol (67%)
T. longicaulis C. Presl ssp. *chaubardi*i (Boiss. and Heldr. ex Reichb.fi1.) var. alternatus Jalas	thymol (70%)
T. longicaulis C. Presl ssp. *longicaulis* var. longicaulis	α-terpinyl acetate (82.1%), geraniol (68.8%), thymol (52.9%), linalool (80%)
T. longicaulis C. Presl ssp. *longicaulis*	geraniol (47.0%)
T. longicaulis C. Presl var. subisophyllus (Borbas) Jalas	thymol (21.7%), borneol (15.8%), ρ-cymene (15.4%)
T. migricus Klok. and Des.-Shost.	carvacrol (36.5%), thymol (36.3%)
Thymus nummularius M. Bieb	thymol (60.4%), α-terpinyl-acetate (10.49%)
Thymus pallasicus Hayek & Velen	thymol (55.5%), ρ-cymene (19.9%), γ-terpinene (7.2%)
T. pectinatus Fisch. and Mey. var. pectinatus	thymol (35.0%), borneol (17.7%), ρ-cymene (11.l%)
T. praecox Opiz ssp. *grossheimii* (Ronn.) Jalas var. grossheimii	thymol (26.6%), ρ-cymene (24.9%)

Table 2. (continued)

Species	**The major constituents (%)**
Thymus praecox subsp. *caucasicus* (Willd. ex Ronniger) Jalas	thymol (42.12%) carvacrol (40-50%) α-terpinyl acetate (31.4%)
T. praecox Opiz ssp. *skorpilii* (Velen.) Jalas var. laniger (Borb.) Jalas	thymol (17.8%), carvacrol (10.5%)
T. praecox Opiz ssp. *skorpilii* (Velen.) Jalas var. skorpilii	geraniol (24.2%), α-terpineol) and α-terpinyl acetate (25.06%)
T. pseudopulegioides Klokov and Des.-Shots	thymol (50.1%), carvacrol (10.7%), ρ-cymene (10.7%)
T. pubescens Boiss. and Kotschy var. crateriola Jalas	carvacrol (17.5%), ρ-cymene (16.4%), thymol (10.8%)
T. revolutus Celak.	α-terpineol (30.5%), linalool (22.5%)
T. roegneri C. Koch	thymol (58.2%), ρ-cymene (12.9%)
T. serpyllum L.	thymol (42.6%)
T. serpyllum L. ssp. *rosulans*	thymol (39-68%)
T. sibthorpii Benth.	thymol (34.8-50.0%)
T. *sipyleus* Boiss. ssp. *sipyleus* var. sipyleus	geranial (37.0%), neral (25.6%), linalool (21.8%)
T. sipyleus ssp. *sipyleus* var. davisianus	geranial (32.8%)
T. spathulifolius Hausskn. and Velen.	carvacrol (49.0%), thymol (17.8%), ρ-cymene (12.3%)
T. striatus Vahl var. interruptus Jalas	Geraniol (69%), β-caryophyllene (29.6%), carvacrol (20.6%)
T. subcollinus Klok.	germacrene D (31.9%), β-caryophyllene (17.6%)
T. syriacus Boiss.	thymol (49%), carvacrol (15.9%)
T. thracicus Velen. var. *longidens* (Velen.) Jalas	geraniol (15.7%), thymol (12.3%), ρ-cymene (12.2%)
T. transcaucasicus Ronniger	thymol (55.0%)
T. trautvetteri Klok.	geraniol (9.8-12.7%)

Table 2. (continued)

Species	**The major constituents (%)**
T. zygioides Griseb. var. *lycaonicus* (Celak.) Ronninger	geraniol (68.7%), carvacrol (48.1%)
T. zygioides Griseb. var. zygioides	linalool (33.7%), (e)-nerolidol (12.5%)
T. zygioides Griseb. var. lycaonicus	geraniol (77), thymol (50%), carvacrol (62%)
T. vulgaris L.	thymol (46.2%), γ-terpinene (14.1%), ρ-cymene (9.9%)

Although many of the compounds in Table 2 have been regarded as toxic waste products of plant metabolic processes with no practical value to the plant, today it is well known that they have significant properties that help the plant in repelling leaf-eating insects and in preventing microbial attack (El-Jalel et al., 2018).

4.1. Monoterpenes of *Thymus*

It is well-known that the biosynthesis of terpenoids in plants occurs via two main pathways: the mevalonate (MVA) pathway in the cytosol and the methylerythritol phosphate (MEP) pathway in the chloroplasts, which yields the five-carbon precursors isopentenyl pyrophosphate and dimethylallyl pyrophosphate (Lahlou et al., 2022).

Monoterpenes are the most common group contained in the *Thymus* genus, while sesquiterpenes tend to be less important. The dominant monoterpene components are thymol (10–64%), carvacrol (0.4–20.6%), p-cymene (9.1–22.2%), α-pinene (0.9–6.6%), linalool (2.2–

4.8%), 1,8-cineole (0.2–14.2%), γ-terpinene (5–10%), camphene, α-terpinene, β-pinene, and terpinen-4-ol. Among them, thymol (2-isopropyl-5-methylphenol), an isomer of carvacrol, is responsible for the typically strong and spicy thyme flavor. Both of them are monoterpene phenol derivatives of p-cymene (Halat et al., 2022; Lahlou et al., 2022).

Monoterpenes are formed by combining the two basic two-isoprene units (C10), and these terpenes function as major compounds (90%) of the volatiles of *Thymus*. They are formed in the chloroplasts, and the biosynthesis of them begins with the production of geranyl pyrophosphate, which contributes to the highly unstable intermediate α-terpenyl cation. Geranyl pyrophosphate can be later converted to specific monoterpenes, such as γ-terpinene, 1,8-cineole, or α-terpinene as a result of complex terpene synthases. Monoterpenes (C10) and sesquiterpenes (C15) are the major types of terpenes, and apart from that, the other types are hemiterpenes (C5), diterpenes (C20), triterpenes (C30), and tetraterpenes (C40) (Halat et al., 2022; Lahlou et al., 2022).

4.2. Sesquiterpenoids of *Thymus*

Sesquiterpenoids are diverse naturally occurring products of terpenoids, existing in a wide variety of forms, such as linear, monocyclic, bicyclic, and tricyclic frameworks. Sesquiterpenoids are synthesized from the 15-carbon precursor, farnesyl pyrophosphate. The genus *Thymus* include (+)-epi-bicyclosesquiphellandrene, allo-aromadendrene, cis-αbisabolene, elemol, epiglobulol, germacrene B, ledol, spathulenol, α-cadinol, α-copaene, α-humulene, β-caryophyllene, β-eudesmol, γ-cadinene, and γ-gurjunene (Halat et al., 2022; Lahlou et al., 2022).

4.3. Terpenoids of *Thymus*

Terpenes (pinene, myrcene, limonene, terpinene, p-cymene) are those compounds with simple hydrocarbons structures while terpenoids (oxygen-containing hydrocarbons) are modified class of terpenes with different functional groups and oxidized methyl groups moved or removed at various positions. In the literature, terpenoids and terpenes are often used to refer to the same compounds such as carvacrol, citronellal, geraniol, linalool, linalyl acetate, piperitone, menthol, and thymol. Both terpenes and terpenoids are synthesized by the mevalonic acid pathway in the cytosol and the 2C-methyl-d-erythritol-4-phosphate pathway in the plastid for the formation of precursors: isopentenyl pyrophosphate and dimethylallyl pyrophosphate (Stephane and Jule, 2020; Masyita et al., 2022)

The major terpenoids found in thyme are p-cymen-9-yl-glucopyranoside, 5-glucopyranosylthymoquinol, 2-glucopyranosylthymoquinol, 2,6-dihydroxy-4-isopropylphenyl-β-D-glucopyranoside, epirosmanol, carnosol, methyl carnosate, carnosic acid, oleanolic acid, ursolic acid, epifriedelinol, friedelinol, friedelin, daucosterol, sitosterol and (24S)-stigmasterol-4-en-3-one (Lahlou et al., 2022). Table 3 listed chemical structures of these terpenoids found in *Thymus* species (Li et al., 2019).

Table 3. Main terpenoids in *Thymus* species (adapted from Li et al., 2019)

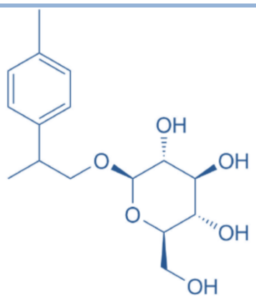
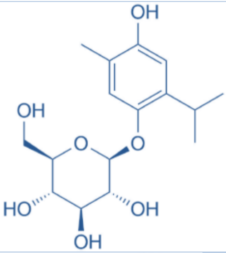
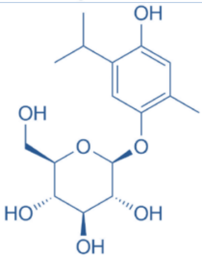
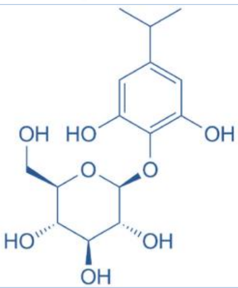
Structure	**Compound**	**Species isolated from**
	p-Cymen-9-yl-glucopyranoside	*T. vulgaris*
	5-Glucopyranosylthymoquinol	*T. vulgaris*
	2-Glucopyranosylthymoquinol	*T. vulgaris*
	2,6-Dihydroxy-4-isopropylphenyl-β-D-glucopyranoside	*T. quinquecostatus*

Table 3. (continued)

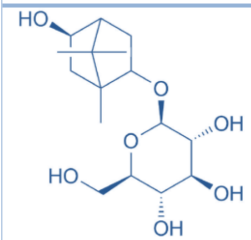
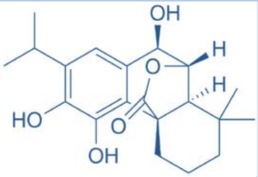
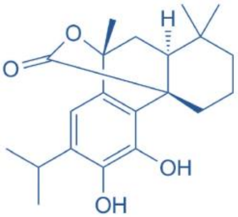
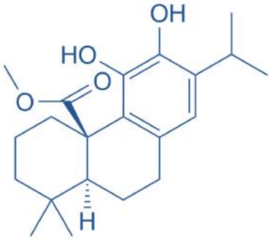
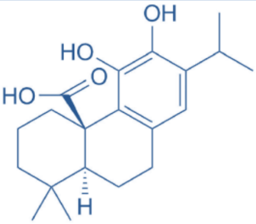
Structure	Compound	Species isolated from
	(-)-Angelicoidenol-2-O-β-D-glucopyranoside	*T. vulgaris*
	Epirosmanol	*T. vulgaris*
	Carnosol	*T. vulgaris*
	Methyl carnosate	*T. vulgaris*
	Carnosic acid	*T. vulgaris*

Table 3. (continued)

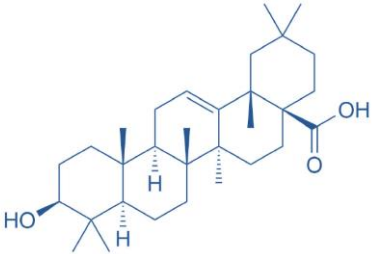
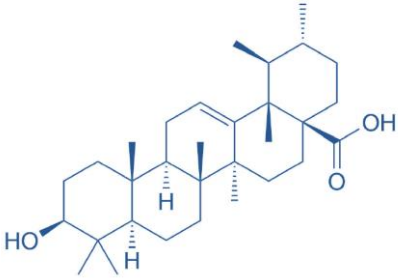
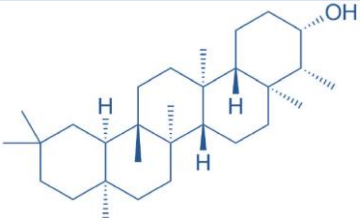
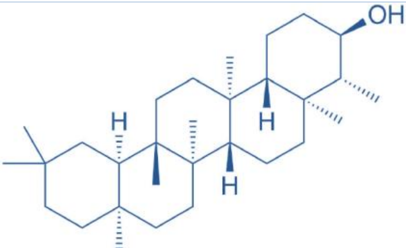
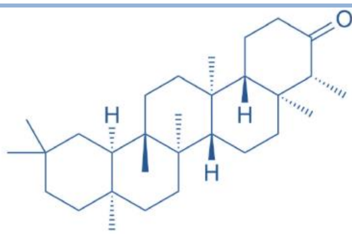
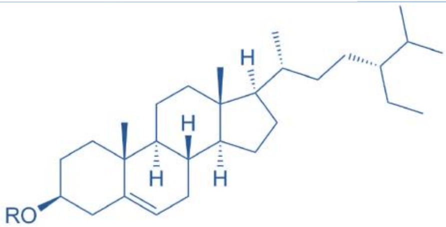
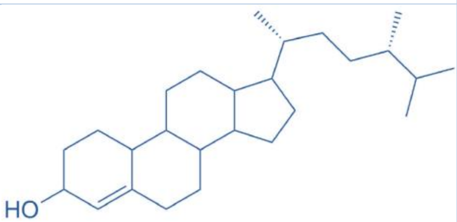
Structure	**Compound**	**Species isolated from**
	Oleanolic acid	*T. quinquecostatus ; T. vulgaris*
	Ursolic acid	T. *quinquecostatus*
	Epifriedelinol	T. *quinquecostatus*
	Friedelinol	*T. mongolicus*

Table 3. (continued)

Structure	Compound	Species isolated from
	Friedelin	*T. mongolicus*
 R = Glc = Daucosterol R = H = Sitosterol	Daucosterol	*T. quinquecostatus*
	Sitosterol	*T. quinquecostatus; T. mongolicus*
	(24S)-Stigmasterol-4-en-3-one	*T. quinquecostatus*

5. NONVOLATILE SECONDARY METABOLITES

Species of the genus *Thymus* are considered sources of nonvolatile secondary metabolites. Nonvolatile secondary metabolites include flavonoids, flavones, phenylpropanoids, benzoic acid, fatty acids and their esters, alcohols, acids, epoxides, aldehydes, ketones, amines, and sulfide derivatives. These nonvolatile secondary metabolites comprise similar structural mother nucleuses with different substituent groups and connection ways (Lahlou et al., 2022). Nonvolatile secondary metabolites are characterized by many structures and functions but possess an aromatic ring bearing one or more hydroxyl substituents. They are produced via the shikimic acid pathway. They are usually involved in plant adaptation to environmental stress conditions. Nonvolatile metabolites are usually referred to as phenolic compounds and are low in volatile secondary metabolites (Stankovic, 2020; Michel et al., 2020; Silva et al., 2020; Lahlou et al., 2022).

5.1. Flavonoids of *Thymus*

Flavonoids are hydroxylated polyphenolics with a benzo-γ-pyrone structure found in *Thymus* plants. These compounds are produced in the phenylpropanoid pathway, which also produces a range of other secondary metabolites, including lignins, lignans, and stilbenes (Li et al., 2019). Flavonoids are phenyl linked with chromones consisting of a 15-carbon basic skeleton (C6-C3-C6). The benzo ring A and the heterocyclic ring C form a chroman (C6-C3) nucleus, and the aromatic ring B usually substitutes the 2-position (Table 4).

To date, more than sixty flavonoids have been isolated and reported from *Thymus* genus plants (Li et al., 2019). There are several groups of flavonoids, such as flavones, flavanols, and dihydroflavonoids, shown in Table 4. Flavonoids function as UV filters, signaling molecules, allelopathic agents, frost, and drought protection agents, phytoalexins (Gavaric et al., 2015; Karaca and Ince, 2022a), detoxifiers, antimicrobials, and anti-herbivore factors (Lahlou et al., 2022). It is known that the C-3 position in ring C is linked with diverse groups, e.g., hydroxy, glucopyranosyl, rutinoside, and glucuronic acid (Table 4).

Rutin, quercetin, kaempferol, and their substitutes are major known flavonoids in the genus *Thymus* (Tohidi et al., 2017; Li et al., 2019).

Table 4. Main flavonoid compounds in *Thymus* species (adapted from Li et al., 2019)

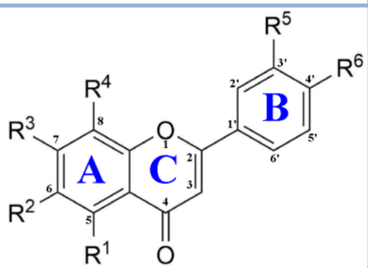
Structure	**Compound**	**Species isolated from**
 Mother nucleus of flavonoids R1 to R6 are covalently attached to one of functional groups such as oxygen (O), hydrogen (H), hydroxy (OH), methoxy (OCH_3), and glycosyl (O-β-D-Glc) to form any of thirty-three flavonoids listed in the second column. Please note Luteolin and apigenin are two main flavones in the genus *Thymus*	Luteolin	*T. vulgaris; T. quinquecostatus*
	Apigenin	*T. vulgaris; T. serpyllum*
	Baicalin	*T. vulgaris*
	Baicalein	*T. vulgaris*
	Chrysin	*T. vulgaris*
	Thymonin	*T. vulgaris*
	Thymusin	*T. vulgaris*
	Xanthomicrol	*T. vulgaris*
	Salvigenin	*T. vulgaris*
	Cirsimaritin	*T. vulgaris*
	Cirsilineol	*T. vulgaris*
	8-methoxycirsilineol	*T. vulgaris*
	Scutellarein	*T. quinquecostatus*
	Scutellarin	*T. quinquecostatus*
	Scutellarein 4'-methyl ether	*T. quinquecostatus*
	4'-Methoxyluteolin	*T. quinquecostatus*

Table 4. (continued)

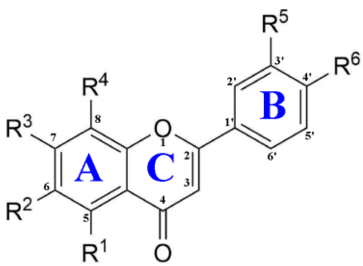
Structure	**Compound**	**Species isolated from**
	6-Hydroxyluteolin	*T. vulgaris*
	Luteolin-7-*O*-*beta*-D-glucoside	*T. quinquecostatus; T. vulgaris*
	Luteolin-7-rutinoside	*T. vulgaris*
	Luteolin-7,3’-diglucoside	*T. vulgaris*
	Luteolin-3’-O-β-D-glucuronide	*T. broussonetii*
	Luteolin-5-O-β-glucopyranoside	*T. sipyleus*
	Luteolin-7-O-glucuronide	*T. vulgaris*
	Apigenin-6,8-di-C-glucoside	*T. vulgaris*
	Apigenin-7-O-rutinoside	*T. vulgaris*
	Apigenin-7-O-glucoside	*T. serpyllum*
	Apigenin-7-O-glucuronide	*T. vulgaris; T. serpyllum*
	Genkwanin	*T. vulgaris*
	Hydroxygenkwanin	*T. vulgaris*
	5-Demethylnobiletin	*T. vulgaris*
	5-Desmethylsinensetin	*T. vulgaris; T. numidicus*
	Sideritoflavone	*T. vulgaris*
	Gardenin B	*T. vulgaris*

Table 4. (continued)

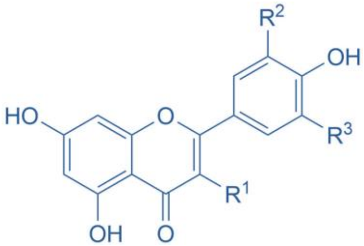
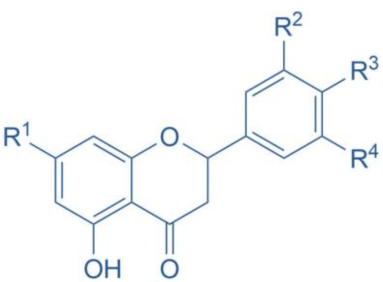
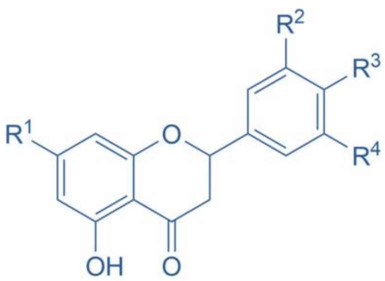
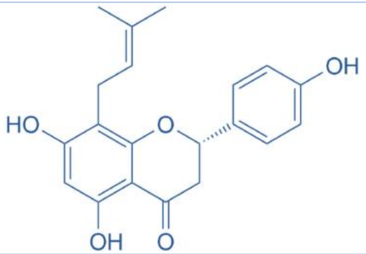
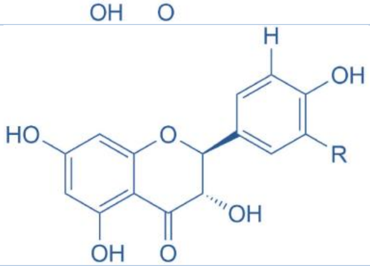
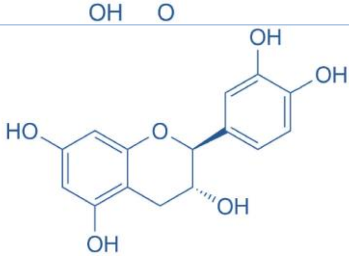
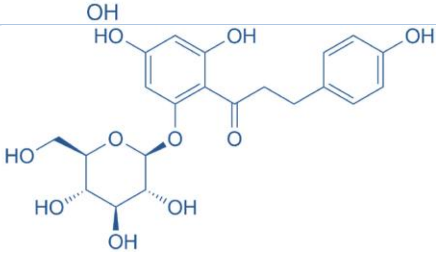
Structure	**Compound**	**Species isolated from**
R1 to R3 are covalently attached one of hydroxy, glucopyranosyl, rutinoside, and glucuronic acid etc. to form any of ten flavonoids listed in the column.	Rutin	*T. vulgaris; T. quinquecostatus*
	Isorhamnetin	*T. vulgaris*
	Isorhamnetin-3-O-glucoside	*T. vulgaris*
	Kaempferol	*T. vulgaris*
	Kaempferol-O-glucuronide	*T. vulgaris*
	Kaempferide-3-O-rutinoside	*T. vulgaris*
	Quercetin	*T. vulgaris; T. serpyllum*
	Quercetin-3-O-glucoside	*T. vulgaris*
	Quercetin-3-O-glucuronide	*T. vulgaris*
	Myricetin	*T. vulgaris*
R1 to R4 are covalently attached one of OH, H, OCH_3, O-β-D-GlcA, O-β-D-Glc or O-β-D-Glc-(6-1)-α-L-Rha molecules to form any of twelve flavonoids listed in the second column.	Naringenin	T. vulgaris; T. webbianus
	Naringin	T. vulgaris
	Sakuranetin	T. vulgaris
	Naringenin-7-O-glucoside	T. vulgaris
	Naringenin-7-O-rutinoside	T. vulgaris
	Hesperetin-7-O-rutinoside	T. vulgaris
	Eriodictyol	*T. vulgaris; T. serpyllum*
	Eriocitrin	*T. vulgaris*
	Eriodictyol-7-O-glucoside	*T. vulgaris*

Table 4. (continued)

Structure	**Compound**	**Species isolated from**
	Eriodictyol-7-glucuronide	*T. vulgaris*
	(2S)-5,7,3’,5’-Tetrahydroxy flavanone	*T. quinquecostatus*
	Hesperidin	*T. vulgaris*
	8-Prenylnaringenin	*T. serpyllum*
	Taxifolin	*T. serpyllum; T. quinquecostatus*
	Aromadendrin	*T. quinquecostatus; T. vulgaris*
	Catechin	*T. serpyllum*
	Phlorizin	*T. vulgaris*

5.2. Phenylpropanoids of *Thymus*

Thymus species are rich in phenylpropanoids, which are a diverse family of organic compounds that are synthesized by plants from the amino acids phenylalanine and tyrosine (Vogt, 2010; Barros et al., 2016; Li et al., 2019; Sampaio et al., 2021). The name of phenylpropanoid is derived from the six-carbon, aromatic phenyl group and the three-carbon propene tail of coumaric acid, which is the central intermediate in phenylpropanoid biosynthesis. The coumaroyl component is produced from cinnamic acid. Phenylpropanoids provide protection from ultraviolet light, defend against herbivores and pathogens, and also mediate plant-pollinator interactions as floral pigments and scent compounds (De Elguea-Culebras et al., 2022). Table 5 lists the main phenylpropanoids in *Thymus* species (Li et al., 2019; Lahlou et al., 2022).

Table 5. Main phenylpropanoids in *Thymus* species (adapted from Li et al., 2019)

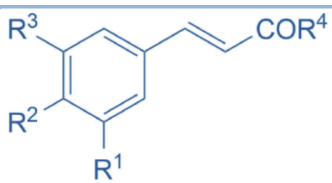
Structure	**Compound**	**Species isolated from**
 R1 to R4 are covalently attached one of OH, H, OCH_3, O-β-D-GlcA, O-β-D-Glc or $OC_{12}H_{25}$ to form any of eight phenylpropanoids listed in the second column.	Cinnamic acid	*T. vulgaris*
	Ferulic acid	*T. vulgaris; T. serpyllum*
	Ferulic acid dodecyl ester	*T. quinquecostatus*
	ρ-Coumaric acid	*T. serpyllum*
	Sinapic acid	*T. vulgaris*

Table 5. (continued)

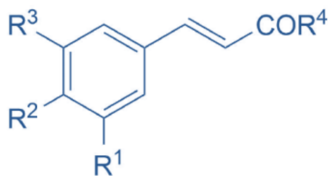
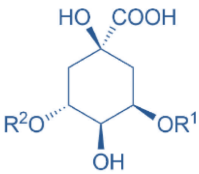
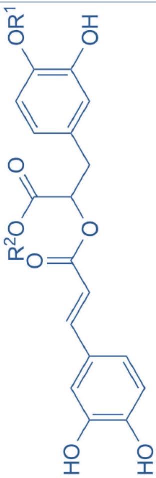
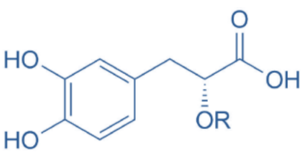
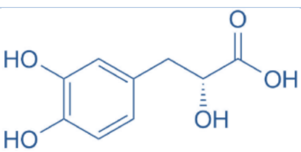
Structure	**Compound**	**Species isolated from**
	Caffeic acid	*T. vulgaris*
	Caffeic acid ethyl ester	*T. serpyllum*
	Caffeic acid glucoside	*T. vulgaris*
	Chlorogenic acid	*T. vulgaris; T. serpyllum*
	3,5-Dicaffeoylquinic acid	*T. vulgaris*
	Rosmarinic acid	*T. quinquecostatus*
	Rosmarinic acid glucoside	*T. vulgaris*
	Methyl rosmarinate	*T. vulgaris*
	Melitric acid A	*T. vulgaris*
	Isomelitric acid A	*T. vulgaris*
	Salvianolic acid K	*T. vulgaris*
	Danshensu	*T. quinquecostatus*

Table 5. (continued)

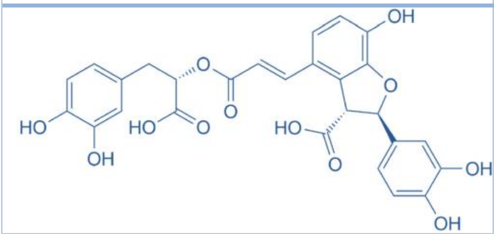
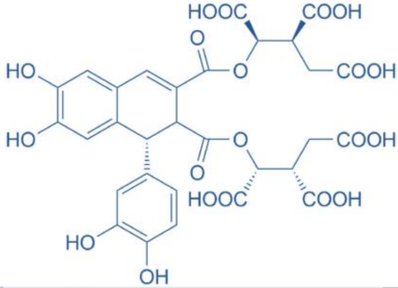
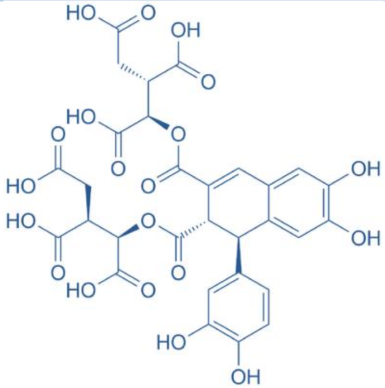
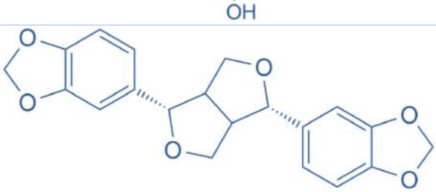
Structure	**Compound**	**Species isolated from**
	Lithospermic acid	*T. vulgaris*
	Caffeoylquinic acid derivative	*T. vulgaris*
	Sevanol	*T. armeniacus*
	Sesamin	*T. mongolicus*

Table 5. (continued)

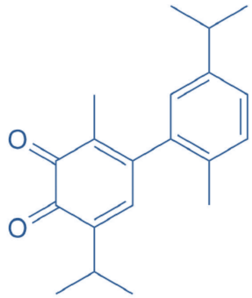
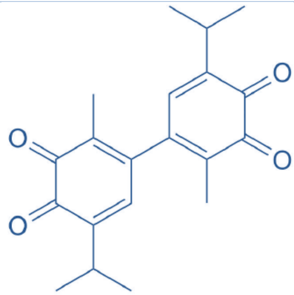
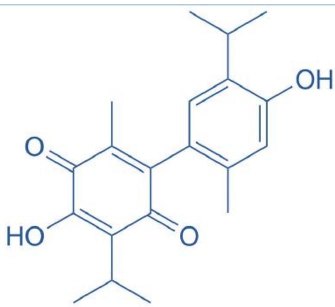
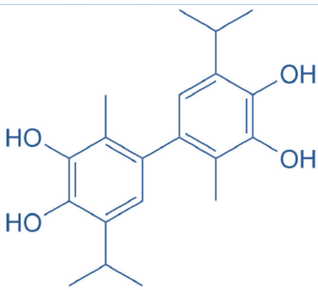
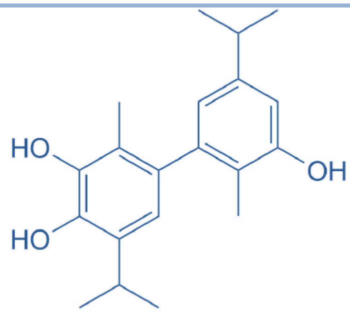
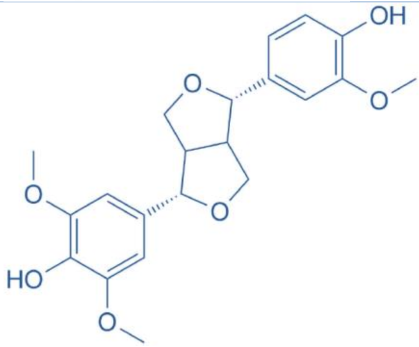
Structure	**Compound**	**Species isolated from**
	5,5’-Diisopropyl-2,2’-dimethyl-[1,1’-biphenyl]-3,4-dione	*T. vulgaris*
	5,5’-Diisopropyl-2,2’-dimethyl-[1,1’-bi(cyclohexane)]-1,1’,5,5’-tetraene-3,3’,4,4’-tetraone	*T. vulgaris*
	4,4’-Dihydroxy-3,5’-diisopropyl-2’,6-dimethyl-[1,1’-biphenyl]-2,5-dione	*T. vulgaris*
	p-Cymene-2,3-diol 6,6’-dimer	*T. vulgaris*

Table 5. (continued)

Structure	**Compound**	**Species isolated from**
	5,5’-Diisopropyl-2,2’-dimethyl-[1,1’-biphenyl]-3,3’,4-triol	*T. vulgaris*
	Medioresinol	*T. vulgaris*

5.3. Phenolic Acids of *Thymus*

A wide range of phenolic acids (benzoic and cinnamic acid series) was identified in species of *Thymus*. They are distinguished from other phenols by their acidic character. These compounds engage in various functions related to plant physiology, including nutrient uptake, protein synthesis, enzymatic activity, photosynthesis, structural components, and allelopathy. Phenolic acids are widely present in plant foods (e.g., fruits, vegetables, and cereals), which comprise a considerable proportion of the human diet. Phenolic acids can coexist in association with other structural molecules (cellulose, protein, and lignin), polyphenolic or terpene plant components, and smaller organic molecules (e.g., glucose, quinic, maleic, or tartaric acids).

Phenolic acids are, after flavonoids, the most investigated secondary plant metabolites due to their extensive presence in the diet and rapid metabolism in the human body. They are well known substances with protective antioxidant properties (Lahlou et al., 2022).

Depending on the constituent carbon frameworks, phenolic acids can be divided into two categories: benzoic acid derivatives (i.e., hydroxybenzoic acids) and cinnamic acid derivatives (i.e., hydroxycinnamic acids). Phenolic acids are characterized by 6- and 9-carbon skeletons containing a carboxyl group attached to the benzene ring with one or more hydroxyl or methoxyl groups attached. On the other hand, the cinnamic acids, in addition, have an unsaturated propionic acid side chain attached to the benzene ring (Lahlou et al., 2022).

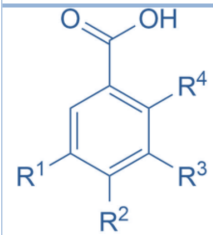
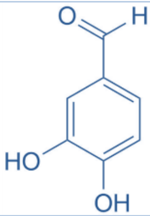
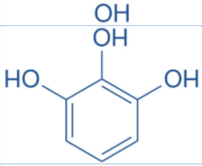
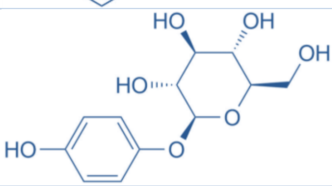
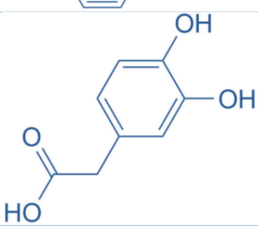
Most hydroxybenzoic acids include a C6-C1 backbone directly obtained from benzoic acid. A considerable number of *Thymus* species contain p-hydroxybenzoic acid, 2,5-dihydroxybenzoic acid, 3,4-dihydroxybenzoic acid, 2,3-dimethoxyben zoic acid, anisic, ellagic, methyl gallate, and salicylic acids. Studies revealed that the content of hydroxybenzoic acids (gallic acid, syringic acid, and vanillic acid) varies between species. However, this difference can also be related to the extraction method. The efficiency of an extraction technique depends on several critical parameters (Lahlou et al., 2022).

5.4. Organic Acids of *Thymus*

Main organic acids of the species *Thymus* were listed in Table 6. They include 12-hydroxyjasmonic acid 12-O-β-D-glucoside, 12-hydroxyjasmonic acid sulphate, 12-hydroxyjasmonic acid, 12-O-β-D-glucoside, 4-hydroxy phenyl acetic acid, caffeic acid, cinnamic acid, caffeoyl 3-hydroxy-3-methylglutaroyl, citric acid, ferulic acid, p-coumaric acid, fumaric acid, hydroxycinnamic acid, malic acid, pentacyclic triterpenoid (oleanolic acid), phenolic aldehyde (isovanillin), phloretic acid caffeoyl 3-hydroxy-3-methylglutaroyl, phloretic acid, phytosterols (β-sitosterol), quinic acid, rosmarinic acid, sagerinic acid, in the form of sagerinate, belongs to the cyclobutane lignans, salvianolic acid, schizotenuin F, stilbenoid (polydatin), tri-hydroxyoctadecedienoic acid, and tri-hydroxyoctadecedienoic acid isomer (Lahlou et al., 2022).

Some of these compounds exhibit multiple physiological functions and high pharmacological potential, which can be attributed to the presence of multiple hydroxyl groups in their chemical structure, making them suitable free radical scavengers (Li et al., 2019; Halat et al., 2022). Antioxidants inhibit the oxidation process, and antioxidant processes are known as free radical scavengers. Some of these free radical scavengers influence the course of a biochemical chemical reaction by ready combination with free radicals. Among other effects of free radical scavengers are the protection of pancreatic islets against damage by cytokines and the prevention of myocardial and pulmonary perfusion injuries.

Table 6. Main organic acids in *Thymus* species (adapted from Li et al., 2019)

Structure	**Compound**	**Species isolated from**
 R1 to R4 are covalently attached one of OH, H, OCH_3, O-β-D-GlcA, O-β-D-Glc molecules to form any of 7 organic acids listed in the second column	Protocatechuic acid	*T. quinquecostatus ; T. vulgaris*
	Gallic acid	*T. vulgaris*
	p-Hydroxybenzoic acid	*T. vulgaris; T. capitatus*
	Gentisic acid	*T. vulgaris*
	Syringic acid	*T. vulgaris*
	Vanillic acid	*T. vulgaris; T. quinquecostatus*
	p-Hydroxybenzoic acid-O-glucoside	*T. vulgaris; T. quinquecostatus*
	Protocatechuic aldehyde	*T. vulgaris; T. quinquecostatus*
	Pyrogallol	*T. vulgaris*
	Arbutin	T. vulgaris
	3,4-Dihydroxyphenylacetic acid	*T. vulgaris*

6. TERPENE GROUP OF *THYMUS* OF TÜRKİYE

The types of essential oils of *Thymus* have been classified by Stahl-Biskup based on three terpene groups (Stahl-Biskup and Saez, 2002). The first type of terpene group comprises nine terpenes, which are (1) thymol, (2) carvacrol, (3) linalool, (4) linalyl acetate, (5) borneol, (6) p-cymene, (7) 1,8 cineole, (8) gamma-terpinene, and (9) camphor. These nine volatile secondary metabolites of *Thymus* within this group have remarkably high concentrations in comparison to the other two groups (Stahl-Biskup and Saez, 2002).

The second chemical group of *Thymus* based on the terpenes, has eight volatile secondary metabolites. These terpenes include (1) geranyl acetate, (2) alfa-terpineol, (3) alfa-terpinyl acetate, (4) dihydrocarvon, (5) citronellol, (6) geranyl butyrate, (7) hedicaryol, and (8) carvon. The number of *Thymus* within this group is lower than the first group (Stahl-Biskup and Saez, 2002).

The third group of *Thymus* based on the terpenes comprises compounds that are typical minor components of volatile secondary metabolite. These terpenes are (1) terpinen-4-ol, (2) B-caryophyllene, (3) geraniol, (4) bornyl acetate, (5) trans-sabinene hydrate, (6) alfa-humulene, (7) caryophyllene epoxide, (8) B-bisabolene, (9) 1-octen-3-ol, (10) neryl acetate, (11) nerolidol, (12) carvacrol methyl ether, (13) thymol methyl ether, (14) germacrene D and (11) B-terpineol (Stahl-Biskup and Saez, 2002).

Based on the terpene information, it can be stated that *Thymus* species naturally occurring in Türkiye are in the first and third groups classified by Stahl-Biskup based on the three terpene groups. In comparison to the number of naturally growing species of *Thymus* in Türkiye, the number of studies related to the exact contents of volatile and nonvolatile metabolites is lower in other countries. We should also mention that the solvent, the nature of the material, the light, the duration of the extraction period, the pH, the temperature, the size of the material, the solvent/substrate ratio, and the liquid-liquid or solid-liquid ratio definitely influence the volatile and nonvolatile secondary metabolites of *Thymus*. Therefore, the selection of an optimal extraction method and the choice of a suitable technique for detecting and quantifying phenolic compounds have high relevance. By using advanced isolation technology and analytical methods, researchers can get more detailed information about the chemical compounds of this genus. Furthermore, more in-depth investigations associated with their mechanisms can also be provided via effective methods such as structure–activity relationships (Zarshenas and Krenn, 2015; Bhavaniramya et al., 2019; Cüce and Basançelebi, 2021; Halat et al., 2022; Lahlou et al., 2022).

7. FUTURE RESEARCH OF *THYMUS*

The *Thymus* genus is a famous functional food and folk medicine throughout the world, both before and now. The common thyme (*T. vulgaris* L.) is the most known species in the genus, and therefore, it has been used for a long history. Other species, including Spain thyme

(*T. zygis* L.), wild thyme (*T. serpyllum* L.), and large thyme (*T. pulegioides* L.), are also the main commercial varieties in the world. *Thymus* volatile and nonvolatile extracts are contributing to their traditional uses for the treatment of a series of respiratory and digestive system diseases, cardiovascular and renal diseases, and inflammation-related diseases, which could be derived from the activities of phenolic derivatives such as thymol, carvacrol, and rosmarinic acid (Lahlou et al., 2022). Further research is needed to further characterization of genomic features of this genus.

To date, the literature has revealed that all species of *Thymus* are rich in volatile and nonvolatile secondary compounds. These secondary metabolites are heterogeneously present on all parts of the plant, such as: flowers, buds, seeds, leaves, twigs, bark, herbs, wood, fruits, and roots, but they are also rich in minerals such as potassium, calcium, iron, manganese, magnesium, and selenium. Therefore, future research in the genus *Thymus* needs to further investigate its mineral and vitamin contents and utilization possibilities (Lahlou et al., 2022).

Economically important volatile oils of *Thymus* are essential oils which are a mixture of diverse different volatile secondary compounds with low molecular weights about below one thousand Da (usually three hundred Da). Among essential oils, some show significant antimicrobial activities against many microorganisms, including *Listeria monocytogenes*, *Escherichia coli*, *Bacillus thermosphacta*, and *Pseudomonas fluorescens* (Bhavaniramya et al., 2019) and acaricidal activities against *Tetranychus viennensis*. However, further research is needed to precisely show the exact roles of their inhibitory functions. Although their inhibiting activities on the growth of microorganisms are due to the damaging effects on the cell membrane and cell wall, increasing permeability, hydrolysis of ATP, electron flow change, coagulation of cell contents, and reduction of proton motive force (Bhavaniramya et al., 2019; Cüce and Basançelebi, 2021), their effects on humans should be explained in much more detailed and scientific manners.

The role of volatiles in plants themselves needs further investigations. Although there exists evidence that essential oils leached from the glandular trichomes contribute to the allelopathic effects on the ground, inhibiting the germination and growth of competitors, this evidence should be further revisited. One of the interesting speculations about the roles of volatiles states that oil vapors near the leaf surface may reduce water loss, and the oils in the flowers might release odors attractive to pollinating agents (Li et al., 2019; Halat et al., 2022; Lahlou et al., 2022).

Another interesting activity of volatile secondary metabolites is their role in plant distribution. It was speculated that volatile and nonvolatile secondary metabolites, along with dense and tomentose hairs of the genus *Thymus* supported the survival of the plant in dry, hot, and freezing conditions. Differing from nonvolatile secondary metabolites, volatile secondary metabolites are speculated to evaporate and produce a saturated atmosphere around the plant that makes the loss of water more difficult (Li et al., 2019; Halat et al., 2022; Lahlou et al., 2022). These speculations are needed for further evaluations.

Molecular and morphology-based species identifications in the species of *Thymus* have limitations (Karaca et al., 2015). Future studies should be focused on the taxonomy of *Thymus*, and the taxonomy should be revised through extensive sampling and analyses with different tools using next generation sequencing studies such as one of the genotyping by sequencing methods. Variability, morphology, and geographical distribution should be considered to define the natural units at the species level. Although DNA barcoding using the combination of *mat*K and *rbc*L sequences was initially suggested to help solve issues of taxonomical difficulties in plant genera, including (Federici et al., 2013), there exists a barcoding gap using DNA barcoding methods in *Thymus*.

CONCLUSIONS

In the literature there are wonderful reviews including book chapters highlighting the important application of thyme volatile secondary metabolites especially for essential oils in the food industry and their notable antimicrobial, antioxidant and antitumor activities *in vitro* and *in vivo* (Salehi et al., 2019), their bioactivity, toxicity, bioavailability, metabolism, and distribution in animals and humans (Salehi et al., 2018), overview of the phytochemical and pharmacological investigations (Zarshenas and Krenn, 2015), traditional uses, chemical constituents and biological activities (Li et al., 2019), biological, chemical, and therapeutic properties (Halat et al., 2022; Lahlou et al., 2022) and information on the cultivation of the genus *Thymus* (Nabavi et al., 2015).

In brief, this chapter on *Thymus* comprehensively summarizes important volatile and nonvolatile secondary metabolites of the *Thymus* genus. Volatile secondary metabolites (monoterpenes, sesquiterpenoids, and terpenoids) and nonvolatile secondary metabolites (phenylpropanoids, flavonoids, phenolic acids, and main organic acids) of *Thymus* species.

The types of essential oils of *Thymus* naturally grown in Türkiye were placed in the first and second terpene groups that were classified by Stahl-Biskup based on three terpene groups. The main essential oils of *Thymus* naturally grown in Türkiye were listed with their chemical formulas. We also briefly visited the taxonomy, systematic classification, and nutritional properties of the species *Thymus*.

Further research directions for the genus *Thymus* were discussed. We believe that more nutritional and pharmacological investigations should be considered for the dietic and clinical benefits of this legendary herb, *Thymus*. The requirements for alternative compounds as replacements for existing ones is due to increasing demands on food security and the severe acute respiratory syndrome coronavirus 2 (COVID-19) pandemic. The information presented herein may be helpful to create more interests and benefits for the *Thymus* genus in future research.

ACKNOWLEDGEMENTS

This chapter is dedicated to Dear Dr. Sukumar Saha, who was a teacher, advisor, and friend to the first author of this chapter, Mehmet Karaca, from 1994 to 2022, and forever.

REFERENCES

Barros, J., Serrani-Yarce, J. C., Chen, F., Baxter, D., Venables, B. J., & Dixon, R. A. (2016). Role of bifunctional ammonia-lyase in grass cell wall biosynthesis. Nature Plants, 2: 16050. https://doi.org/10.1038/nplants.2016.50

Bartolucci, F., & Peruzzi, L. (2013). *Thymus paronychioides* (Lamiaceae), a neglected species from Sicily belonging to the section Hypodromi. Folia Geobotanica, 49: 83-106. https://doi.org/10.1007/s12224-013-9156-2

Baser, K. H. C., Demirci, B., Kirimer, N., Satil, F., & Tumen, G. (2002). The essential oils of *Thymus migricus* and *T. fedtschenkoi* var. *handelii* from Turkey. Flavour and Fragrance Journal, 17: 41-45. https://doi.org/10.1002/ffj.1036

Bhavaniramya, S., Vishnupriya, S., Al-Aboody, M. S., Vijayakumar, R., & Baskaran, D. (2019). Role of essential oils in food safety: Antimicrobial and antioxidant applications. Grain & Oil Science and Technology, 2: 49-55. https://doi.org/10.1016/j.gaost.2019.03.001

Cumo, C. (Ed) (2013). Encyclopedia of cultivated plants: From Acacia to Zinnia, ABC-CLIO, Santa Barbara, California USA, 1: 532-533.

Cüce, M., & Basançelebi, O. (2021) Comparison of volatile constituents, antioxidant and antimicrobial activities of *Thymus leucotrichus* (Lamiaceae) stem and leaves essential oils from both natural resources and in vitro derived shoots. Journal of Essential Oil-Bearing Plants, 24: 1097-1112. https://doi.org/10.1080/0972060X.2021.2003256

Dauqan, E. M. A., & Abdullah, A. (2017). Medicinal and functional values of Thyme (*Thymus vulgaris* L.) herb. Journal of Applied Biology and Biotechnology, 5: 17-22. https://doi.org/10.7324/JABB.2017.50203

De Elguea-Culebras, G. O., Bravo, E. M., & Sanchez-Vioque, R. (2022) Potential sources and methodologies for the recovery of phenolic compounds from distillation residues of Mediterranean aromatic plants. An approach to the valuation of by-products of the essential oil market: A review. Industrial Crops and Products, 175: 114261. https://doi.org/10.1016/J.INDCROP.2021.114261

El-Jalel, L. F., Elkady, W. M., Gonaid, M. H., & El-Gareeb, K. A. (2018). Difference in chemical composition and antimicrobial activity of *Thymus capitatus* L. essential oil at different altitudes. Future Journal of Pharmaceutical Sciences, 4(2): 156-160. https://doi.org/10.1016/j.fjps.2017.12.004

Federici, S., Galimberti, A., Bartolucci, F., Bruni, I., De Mattia, F., Cortis, P., & Labra, M. (2013). DNA barcoding to analyze taxonomically complex groups in plants: the case of *Thymus* (Lamiaceae). Botanical Journal of the Linnean Society, 171: 687-699. https://doi.org/10.1111/boj.12034

Feng, Z., Bartholomew, E. S., Liu, Z., Cui, Y., Dong, Y., Li, S., Wu, H., Ren, H., & Liu, X. (2021). Glandular trichomes: new focus on horticultural crops. Horticulture Research, 8: 158. https://doi.org/10.1038/s41438-021-00592-1

Gavaric, N., Mozina, S. S., Kladar, N., & Bozin, B. (2015). Chemical profile, antioxidant and antibacterial activity of thyme and oregano essential oils, thymol and carvacrol and their possible synergism. Journal of Essential Oil-Bearing Plants, 18(4): 1013-1021. https://doi.org/10.1080/0972060X.2014.971069

Giron, V., Garnatje, T., Valles, J., Perez-Collazos, E., Catalan, P., & Valdes, B. (2012). Geographical distribution of diploid and tetraploid cytotypes of *Thymus* sect. *Mastichina* (Lamiaceae) in the Iberian Peninsula, genome size and evolutionary implications. Folia Geobotanica, 47: 441-460. https://doi.org/10.1007/s12224-012-9126-0

Halat, D. H., Krayem, M., Khaled, S., & Younes, S. A. (2022). Focused insight into Thyme: Biological, chemical, and therapeutic properties of an indigenous Mediterranean herb. Nutrients, 14: 2104. https://doi.org/10.3390/nu14102104

Harley, R. M., Atkinson, S., Budantsev, A. L., Cantino, P. D., Conn, B. J., Grayer, R., Harley, M. M., De Kok, R., Krestovskaja, T., Morales, R., Paton, A. J., Ryding, O., & Upson, T. (2004). Labiatae. In: J.W. Kadereit (ed.). The Families and Genera of Vascular Plants, Springer, Berlin, 7: 167-275.

Jalas, J. (1982) *Thymus*. In P.H. Davis (ed.), Flora of Turkey and the East Aegean Islands, Edinburgh, 7: 349-382.

Karaca, M., Ince, A. G., Aydin, A., Elmasulu, S. Y., & Turgut, K. (2015). Microsatellites for genetic and taxonomic research on Thyme (*Thymus* L.). Turkish Journal of Biology, 39: 147-159. https://doi.org/ 10.3906/biy-1406-20

Karaca, M., & Ince, A. G. (2022a). Grafting-induced seed gossypol levels by demethylation of (+)-delta-cadinene synthase genes in upland cotton. Plant Breeding, https://doi.org/10.1111/pbr.13066

Karaca, M., & Ince, A. G. (2022b). Grafting and rootstock effects on seed oil contents in tetraploid cotton species (*Gossypium* L.). Gesunde Pflanzen, https://doi.org/10.1007/s10343-022-00787-z

Lahlou, R. A., Samba, N., Soeiro, P., Alves, G., Gonçalves, A. C., Silva, L. R., Silvestre, S., Rodilla, J., & Ismael, M. I. (2022). *Thymus hirtus* Willd. ssp. *algeriensis* Boiss. and Reut: A Comprehensive Review on Phytochemistry, Bioactivities, and Health-Enhancing Effects. Foods, 11: 3195. https://doi.org/10.3390/foods11203195

Li, X., He, T., Wang, X., Shen, M., Yan, X., Fan, S., Wang, L., Wang, X., Xu, X., Sui, H., & She, G. (2019). Traditional uses, chemical constituents, and biological activities of plants from the genus *Thymus*. Chemistry & Biodiversity. 16(9): e1900254. https://doi.org/10.1002/cbdv.201900254

Masyita, A., Mustika Sari, R., Dwi Astuti, A., Yasir, B., Rahma Rumata, N., Emran, T. B., Nainu, F., & Simal-Gandara, J. (2022). Terpenes and terpenoids as main bioactive compounds of essential oils, their roles in human health and potential application as natural food preservatives. Food chemistry: X, 13: 100217. https://doi.org/10.1016/j.fochx.2022.100217

Michel, J., Abd Rani, N. Z., & Husain, K. (2020). A review on the potential use of medicinal plants from Asteraceae and Lamiaceae plant family in cardiovascular diseases. Frontiers in Pharmacology, 11: 852. https://doi.org/10.3389/FPHAR.2020.00852/BIBTEX

Morales, R. (2012). The History, botany, and taxonomy of the genus *Thymus*. In: Stahl-Biskup E. and Saez F. (ed.). Thyme The Genus *Thymus*. London: Taylor and Francis. 1: 1-43.

Muller-Riebau, F. J., Berger, B. M., Yegen, O., & Cakir, C. (1997). Seasonal variations in the chemical compositions of essential oils of selected aromatic plants growing wild in Turkey. Journal of Agricultural and Food Chemistry, 45: 4821-4825. https://doi.org/10.1021/jf970110y

Nabavi, S. M., Marchese, A., Izadi, M., Curti, V., Daglia, M., & Nabavi, S. F. (2015). Plants belonging to the genus *Thymus* as antibacterial agents: From farm to pharmacy. Food Chemistry, 173: 339-347. https://doi.org/10.1016/j.foodchem.2014.10.042

Nieto, G. (2017). Biological activities of three essential oils of the Lamiaceae family. Medicines, 4: 63. https://doi.org/10.3390/MEDICINES4030063

Ozturk, D., Yaylaci, O. K., Koyuncu, O., Sezer, O., Ozgisi, K., & Ocak, A. (2022). A new species of *Thymus* (Lamiaceae) from central Anatolia (Turkey). Pakistan Journal of Botany, 54(2): 453-459. http://dx.doi.org/10.30848/PJB2022-2(7)

Salehi, B., Mishra, A. P., Shukla, I., Sharifi-Rad, M., Contreras, M. D., Segura-Carretero, A., Fathi, H., Nasrabadi, N. N., Kobarfard, F., & Sharifi-Rad, J. (2018). Thymol, thyme, and other plant sources: Health and potential uses. Phytotherapy Research, 32, 1688-1706. https://doi.org/10.1002/ptr.6109

Salehi, B., Abu-Darwish, M. S., Tarawneh, A. H., Cabral, C., Gadetskaya, A. V., Salgueiro, L., Hosseinabadi, T., Rajabi, S., Chanda, W., Sharifi-Rad, M., et al. (2019). *Thymus* spp. plants – Food applications and phytopharmacy properties. Trends in Food Science & Technology, 85: 287-306. https://doi.org/ 10.1016/j.tifs.2019.01.020

Sampaio, L. A., Pina, L. T. S., Serafini, M. R., dos Santos Tavares, D., & Guimaraes, A. G. (2021). Antitumor effects of carvacrol and thymol: A systematic review. Frontiers in Pharmacology, 12: 1673. https://doi.org/10.3389/FPHAR.2021.702487/BIBTEX

Sevindik, H. G., Ozek, T., Yerdelen, K. O., Onal, M., Ozbek, H., Guvenalp, Z., & Demirezer, L. O. (2016). Chemical composition, antioxidant capacity, acetyl- and butyrylcholinesterase inhibitory activities of the essential oil of *Thymus haussknechtii* Velen. Records of Natural Products, 10(4): 503-507.

Silva, A. M., Martins-Gomes, C., Souto, E. B., Schafer, J., Santos, J. A., Bunzel, M., & Nunes, F. M. (2020). *Thymus zygis* subsp. *zygis* an endemic Portuguese plant: Phytochemical profiling, antioxidant, anti-proliferative and anti-inflammatory activities. Antioxidants, 9: 482. https://doi.org/10.3390/ANTIOX9060482

Stahl-Biskup, E., & Saez, F. (Eds.) (2002). Thyme: The genus *Thymus*. Taylor and Francis, Inc., London, 1: 1-346. https://doi.org/10.4324/9780203216859

Stahl-Biskup E., & Venskutonis, R. P. (Eds.) (2012). Handbook of herbs and spices (Second edition). Woodhead Publishing Series in Food Science, Technology and Nutrition, 1: 499-525.

Stankovic, M. (Ed.) (2020). Lamiaceae species: Biology, Ecology and Practical Uses; MDPI: Basel, Switzerland. https://doi.org/10.3390/books978-3-03928-419-1

Stephane F.F.Y., Jules B.K.J. In: Essential Oils - Bioactive Compounds, New Perspectives and Applications. Oliveira M.S.D., Costa W.A.D., Silva S.G., editors. IntechOpen; 2020. Terpenoids as Important Bioactive Constituents of Essential Oils.

Tavan, M., Mirjalil, M. H., & Karimzadeh, G. (2015). *In vitro* polyploidy induction: changes in morphological, anatomical, and phytochemical characteristics of *Thymus persicus* (Lamiaceae). Plant Cell Tissue and Organ Culture, 122: 573-583. https://doi.org/10.1007/s11240-015-0789-0

Tohidi, B., Rahimmalek, M., & Arzani, A. (2017). Essential oil composition, total phenolic, flavonoid contents, and antioxidant activity of *Thymus* species collected from different regions of Iran. Food Chemistry, 220: 153-161. https://doi.org/10.1016/j.foodchem.2016.09.203

Tümen, G., Kirimer N., & Baser, K. H. C. (1995). Composition of the essential oils of *Thymus* species growing in Turkey. Chemistry of Natural Compounds, 31: 42-47.

Tzima, K., Brunton, N. P., & Rai, D. K. (2018). Qualitative and quantitative analysis of polyphenols in Lamiaceae plants: A review. Plants, 7: 25. https://doi.org/10.3390/PLANTS7020025

Varga, E., Bardocz, A., Belak, A., Maraz, A., Boros, B., Felinger, A., Boszormenyi, A., & Horvath, G. (2015). Antimicrobial activity and chemical composition of thyme essential oils and the polyphenolic content of different *Thymus* extracts. Farmacia, 63: 357-361.

Vogt, T. (2010). Phenylpropanoid Biosynthesis. Molecular Plant, 3: 2-20. https://doi.org/10.1093/mp/ssp106. PMID 20035037

Zarshenas, M. M., & Krenn, L. (2015). A critical overview on *Thymus daenensis* Celak.: phytochemical and pharmacological investigations. Journal of Integrative Medicine, 13: 91-98. https://doi.org/10.1016/S2095-4964(15)60166-2

CHAPTER 2

GERMINATION AND CULTURE OF ENDEMIC *SALVIA HYPARGEIA* FISCH. & C. A. MEY. IN VITRO CONDITION

Cennet YAMAN[1]

[1]Yozgat Bozok University, Faculty of Agriculture, Department of Field Crops, Yozgat,Türkiye, e-mail: cennet.yaman@yobu.edu.tr
ORCID ID: 0000-0002-2364-8171

INTRODUCTION

The genus *Salvia*, belonging to the Lamiaceae (Labiatae) family, has more than 986 species with a remarkable diversity, distributed in both hemispheres of the world, especially in tropical and subtropical regions, Mediterranean and Central Europe. Türkiye, which has a rich flora as it is located at the intersection of three important phytogeographical regions: Europe-Siberia, Iran-Turan and the Mediterranean, is also the gene center of many medicinal aromatic plants. Türkiye ranks 13th in the world in terms of species richness of the genus *Salvia* (Arslan et al., 1995). Türkiye's flora is represented by 100 species and 107 taxa in the genus Salvia, and approximately 50% of these species are endemic (Yaman et al., 2022).

Salvia species have been used especially in the treatment of the most common diseases such as stomachache, cold, flu, sore throat, expectorant, analgesic, carminative, antiperspirant, sedative and externally wound healing for folk medicine (Baytop, 1994; Kintzios, 2000; Perry et al., 2003; Kamatou et al., 2008; Cardile et al., 2009). Therefore, *Salvia* species are mostly consumed as herbal tea among people, also they are used as a spice and sweetener, as well as, in many industries such as perfumery, pharmacology, and cosmetics colorants, dyes, and biocides (Delamare et al., 2007; Bağcı ve Koçak, 2008; Lubbea and Verpoorte, 2011). Additionally, *Salvia* species are used in gardens and landscape works due to their external appearance, as well as their healing power.

The therapeutic properties of *Salvia* species are due to the beneficial phytochemical ingredients found in the parts of the plant. According to previous research, they have especially rich essential oils, and their essential oils are is characterized by the predominance of monoterpene derivatives such as 1,8-cineole, camphor, α- thujone, β-thujone, borneol, bornyl acetate, α-pinene, β-pinene, camphene, and myrcene (Raal et al., 2007; Tahar et al., 2021; Talebi et al., 2021; Saffariha et al., 2021; Aćimović et al., 2022). The scientific research were reported polyphenolic compounds in methanolic or other solvent extracts from the aerial parts of *Salvia* species: phenolic acids (rosmarinic acid, salvianolic acids, caffeic, chlorogenic, p-coumaric, coumaric, protocatechuic, vanillic, syringic and ferulic), flavonoids (apigenin, luteolin, hesperidin, kaempferol), terpenoids (salvin, salvinorin, salvihispin, sclareol), tannins, and others (Dweck, 2005; Fan et al., 2018; Piątczak et al., 2021; Onder et al., 2022), which are important in many biological activities such as anticancer, antioxidant, antimicrobial, anti-inflammatory, hypolipidemic, hypoglycemic, antinociceptive, memory enhancing effects, and others (Sharifi-Rad et al., 2018; Baricevic and Bartol, 2005; Ghorbani and Esmaeilizadeh, 2017).

Therefore, many *Salvia* species are cultivated for their phytochemicals. *Salvia* species that are most economically important in the global world are *S. officinalis, S. sclarea* L. (clary sage), *S. fruticosa* Miller, *S. lavandulifolia* Vahl. (Spanish sage), *S. verbenaca* L., and *S. tomentosa* Miller. Among them, the essential oils of *S. officinalis, S. sclarea*, and

S. lavandulifolia were traded on the global market of essential oils with an estimated volume production ranging between 50 and 100 tonnes per year (Lubbea and Verpoorte, 2011). *S. miltiorrhiza*, ranked topmost levels in the Chinese medicinal market among all over-the-counter drugs, is the most popular Chinese medicinal product for treating heart disease and has a serious market value in the world (Jia et al., 2012). Approximately 400 *Salvia* species are used in traditional and modern medicine worldwide (Franz and Novak, 2010). Also, *Salvia* is prominently described as official drugs in the pharmacopeias of many countries throughout the world (Dweck, 2005).

Unfortunately, endemic and cosmopolitan taxa are at constant risk in the countries of the world with threats such as extreme drought, global warming, salinization, industrialization, urbanization, expanding agricultural areas, overgrazing, hydroelectric power construction, formation of artificial lakes, export, collections that endanger plant extinction, agricultural activities, pollution, and forest fires. The endemic species are in different risk categories according to "The red book of Turkish plants", and as their populations decrease, they pass into a higher category and face the danger of extinction (Çördük, 2012). With these threats, the habitat of some endemic taxa has decreased and some of them have gradually disappeared (Ekim et al., 2000). Again, wrong tourism activities and climate change threaten biodiversity (Tunçkol and Akkemik, 2013). Plant species should be protected with an appropriate strategy in order to transfer the biodiversity of our country to future generations and to prevent the loss of gene resources and wild forms of species (Acar Deniz and Çördük, 2016). Considering that the *Salvia* species found in the flora of Türkiye, which is one of the most important gene centers, will be extinct in the world, especially if endemic species become extinct, it is vital to protect them. Therefore, both the conservation of endemic species and the determination of their trade potential is a more essential issue.

In nature, it may take a long time for some plant species to reach maturity by blooming from seed, some cannot form seeds, or generative reproduction rates are very low due to low germination potential in seeds. However, some species have difficulties in vegetative reproduction in nature. Therefore, the promotion of rapid propagation techniques under controlled conditions with the help of specially developed artificial nutrient media and plant growth regulators for the propagation of species with high commercial value and/or endangered species has come to the fore. Thus, in vitro plant tissue and organ culture techniques have emerged as an ideal system for the rapid propagation of plant material.

Salvia hypargeia Fisch. & C.A.Mey. is one of the endemic species to Türkiye of the genus *Salvia*, which is distributed in Türkiye, and and there are no studies on its germination and reproducibility. Also, considering the potential of endemic plants to be a medicine due to the fact that they are the richness of our country, as well as their commercial use or effect on human health, the protection of these very valuable species is of serious importance. Therefore, in this study, germination and reproduction of *Salvia hypargeia* under in vitro conditions were investigated.

1. HERBAL PROPERTİES OF *SALVIA HYPARGEIA*

Salvia hypargeia Fisch. & C.A. Mey. belongs to the genus *Salvia* of the Lamiaceae family and is an endemic species for Türkiye. Also, it is categorized as least concern (LC) in the threat categories (Bingöl et al., 2019). *Salvia hypargeia*, perennial herb forming tufts to 60 cm diam. Stems erect, sturdy, 25-40(-60) cm, usually unbranched, eglandular arachnoid to lanate below, glandular pilose above (Figure 1). Leaves simple, linear to linear-oblong, mostly basal, green¬ish above, white lanate below, margins subentire, 4-8 x 0.5-1 cm, incl. indistinct petiole. Verticillasters 4-8-flowered, clearly distant. Bracts broadly ovate, c. 15 x 12 mm, lower surface lanate. Pedicels 2-3 mm, ± erect. Calyx tubular-ovate, c. 10 mm, to c. 12 mm in fruit, lanate and glandular; upper lip truncate. Corolla lavender to purplish-blue, c. 25 mm; tube straight, slightly ventricose above; upper lip falcate (Figure 2). Stamens B. Nutlets rounded trigonous, 3.5 x 2.5 mm. 2n = 22. Fl. 6-7. Limestone slopes and banks, with Pinus brutia, fallow fields, 800-2000 m (Davis, 1982).

Figure 1: The Natural View of *Salvia hypargeia* in Habitat (Yozgat)

Figure 2: The Flower Structure of *Salvia hypargeia* (Yozgat)

According to Türkiye's grid system, *Salvia hypargeia* is situated in the province of Adana, Ankara, Çankırı, Elazığ, Erzincan, Kahramanmaraş, Karabük, Karaman, Kastamonu, Kayseri, Kırşehir, Konya, İçel, Malatya, Nevşehir, Niğde, Sivas, Tunceli, Yozgat, Zonguldak and within A4, A5, B3, B4, B5, B6, B7, C4, C5 of the grid system (Figure 3) (Davis, 1982; Güner et al., 2012; Bingöl et al., 2019; Anonim, 2022).

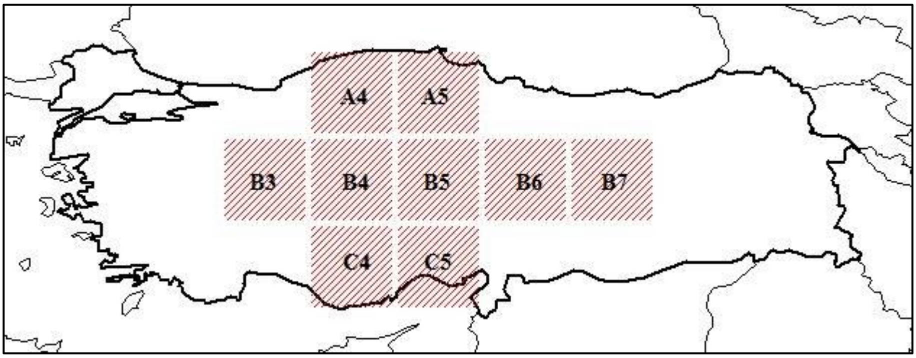


Figure 3: Distribution of Endemic *Salvia hypargeia* in Türkiye (Türkiye′s Grid System)

There are few studies on *Salvia hypargeia,* and these studies are mostly on its phytochemicals and biological activities. Ulubelen et al. (1988) investigated the diterpenoid compounds of *Salvia* species and identified cryptanol, horminone and hypargenins A, B, C, D, E, F compounds in the roots of *S. hypargeia.* Ulubelen et al. (1999) identified 10 diterpenes and 3 triterpene compounds in the roots of this species and emphasized that 6a-hydroxysalvinolone and taxodione among these compounds may have cytotoxic potential. Bakir et al. (2020) analyzed ethanol extracts of root, leaf, branch, flower and mixture in terms of diterpenoid, triterpenoid, steroid and flavonoid content, and found the extracts, especially root and leaf extracts, very rich in triterpenes such as lupenone and lupeol. Also, they noticed that all extracts, especially root extract contained high amounts of ferruginol, cryptanol, and sugiol as diterpenes.

Atas et al. (2011) examined the essential oil (EO) compounds of *S. hypargeia* aerial parts and identified 20 compounds (90.5%), the main components of which are β-pinene (22.3 %), β-ylangene (17.8%), α-pinene (15.9%), pulegone (13.5%). Erdoğan Eliuz (2021) identified approximately 90% with 22 compounds, and reported that β-pinene (49.99%), 1,8-cineole (9.50%), camphor (8.98%), α-pinene (8.26%) as the main components of the EO.

Phytochemical studies on this species indicate that *S. hypargeia* exhibit strong biological activity (antimicrobial, antioxidant, enzyme inhibitory, cytotoxic activities and management of diabetic wounds, due to being rich in both β-pinene in the EO and triterpenes, diterpenes in the extracts (Topcu et al., 2008; Atas et al., 2011; Bakir et al., 2020; Erdoğan Eliuz et al., 2021; Ozay et al., 2021).

2. IN VITRO GERMINATION OF *SALVIA HYPARGEIA*

Salvia species have generally low germination potential. The reason for this may be genetic, the physical structure as well as ecological conditions of the seed. Therefore, many scientists have tried different applications on germination of *Salvia* seeds (Yaman et al. 2022).

Among *Salvia* species, most of the germination studies have been on economically valuable chia (*Salvia hispanica* L.) seeds. In previous studies, germination parameters of chia seeds were investigated as temperature (Cabrera-Santos et al., 2021; Nadtochii et al., 2019), salt (Younis et al., 2021), hormone (Costa et al., 2021), light (Nadtochii et al., 2019), nem rejimi (Nadtochii et al., 2019) and others (Salgado et al., 2022). Many scientists have stated that seeds of chia other *Salvia* species secrete mucilage in germination experiments (Gorai et al., 2011; Geneve et al., 2017; Afshin et al., 2019; Cabrera-Santos et al., 2021; Bingul et al., 2021). Some scientists have notified that the mucilage structure formed on *Salvia* seeds, and they have recorded that it has a negative effect on germination (Western, 2012; Cabrera-Santos et al., 2021). On the contrary, some scientists have reported that it does not show any effect on germination (Geneve et al., 2017).

On the other hand, in vitro studies, it was observed that the germination rate increased when seed coat (testa) was removed from seed (Maliro and Kwapata., 2000; Estaji et al., 2012; Germanà et al., 2014). Yaman (2020) reported that embryos with the endosperm tissue from which were removed seed coats, displayed higher germination in vitro conditions and even *S. yosgadensis* Freyn & Bornm, *S. ceratophylla* L., *S. sclarea* L. species had 100% germination. In addition, Yaman (2020), at the end of the studies, emphasized that the seed coat has an inhibitory structure on the germination of *Salvia* species.

Remarkably, in this study, we found that the germination rate of *Salvia hypargeia* seeds was very low and its seed coat exhibited a negative effect on germination. In fact, in these in vitro experiments, it was observed that there was a difference in the germination of seeds with or without testa (Table 1). There is no germination of seeds with testa. However, seeds (embryos with the endosperm tissue) without testa showed a high rate of germination (%76.7) even on an agar-containing medium alone. The presence of macro-microelements, vitamins, sucrose and plant growth regulators (PGRs) in the nutrient medium showed positively different effects on seedling formation from embryos without testa, but did not show any effect on embryos with testa. The highest germination rate was obtained from Agar (%0.6) +MS+Sucrose (%3)+1.0 mg/L BAP application with 95% (Table1, Figure 4D).

Table 1: Effect of Different Medium on Germination of Seeds and Embryos of *Salvia hypargeia* in vitro Condition

Medium	Seed	Embryo
Agar (%0.6)	0	76.7±11.5
Agar (%0.6) +Sucrose (%3)	0	83.3±11.5
Agar (%0.6) +MS+Sucrose (%3)	0	93.3±11.5
Agar (%0.6) +MS+Sucrose (%3)+1.0 mg/L BAP	0	95.0±5.0

MS, Murashige & Skoog medium including vitamins (Murashige and Skoog, 1962). BAP, 6-Benzylaminopurine. ±standard deviation. Each application has three replications and each replication contains 10 seeds.

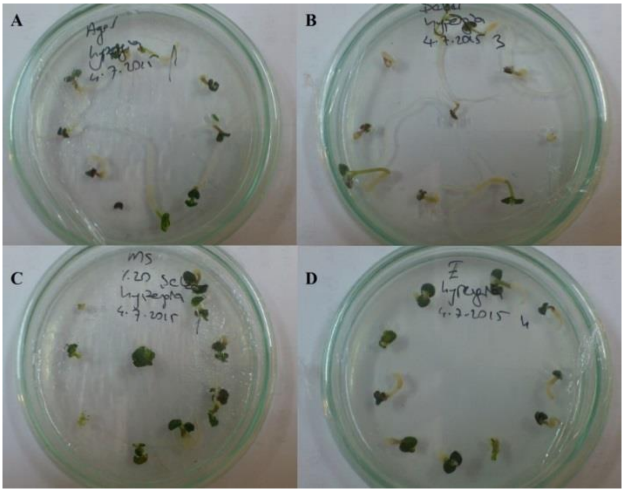


Figure 4: Germination on Different Medium of *Salvia hypargeia* Embryos in vitro Condition. A: Agar (%0.6), B: Agar (%0.6) +Sucrose (%3), C: Agar (%0.6) +MS+Sucrose (%3), D: Agar (%0.6) +MS+Sucrose (%3)+1.0 mg/L BAP.

3. IN VITRO CULTURE OF *SALVIA HYPARGEIA*

In previous studies, there is no enough information about tissue culture applications of *Salvia hypargeia*. In this study, it was found that this species has regeneration capacity such as shoot and root development and callus formation (Table 2, Table 3, Figure 5, Figure 6 and Figure 7).

As shown in Table 2, *S. hypargeia* can be micropropagated from its apical shoot parts. Also, sucrose concentration and PGR have an effect on the plant growth. As a result of culturing the apical shoot tip explants of *S. hypargeia* for one month, it was observed that strong and healthy seedlings developed in MS medium containing agar (0.6%) + sucrose (3%) + 1.0 mg/L BAP (Figure 5).

Table 2: Effect of Different Medium on Shoot Growth from Apical Shoot Tips of *Salvia hypargeia* in vitro Condition

Medium	Number of shoots	Shoot length
Agar (%0.6) +Sucrose (%2)	0.5	4.6
Agar (%0.6) +Sucrose (%3)	0.7	7.0
Agar (%0.6) +MS+Sucrose (%2)	0.8	4.1
Agar (%0.6) +MS+Sucrose (%3)	1.0	5.4
Agar (%0.6) +MS+Sucrose (%2)+1.0 mg/L BAP	0.7	3.7
Agar (%0.6) +MS+Sucrose (%3)+1.0 mg/L BAP	1.0	4.5
Average Sucrose (%2)	0.7	4.1
Average Sucrose (%3)	0.9	5.6

MS, Murashige & Skoog medium including vitamins (1962). BAP, 6-Benzylaminopurine. Each application has three replications and each replication contains 9 apical shoot tips

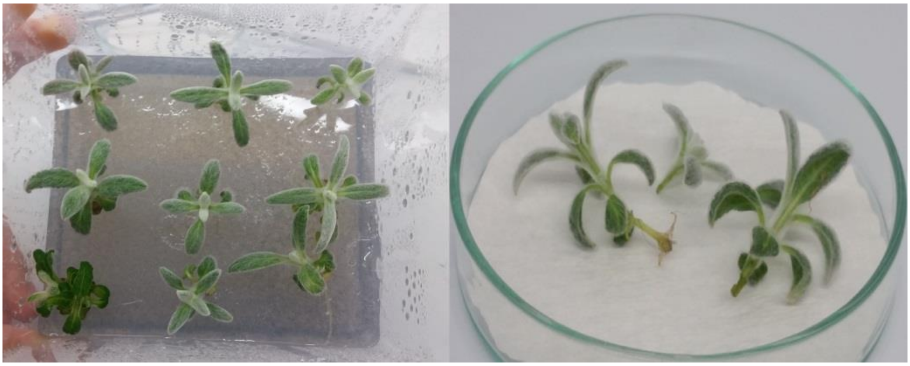


Figure 5: Shoot Growth from Apical Shoot Tips of *Salvia hypargeia* in vitro Condition [Agar (%0.6) +MS+Sucrose (%3)+1.0 mg/L BAP].

S. hypargeia has the root forming and elongation capacity from the apical shoot tip explants. Although the nutrient medium does not contain auxin PGRs, the apical shoot tip explants promotes root regeneration (Table 2). On the contrary, its root growth was further increased in MS medium containing agar (%0.6) and sucrose (%3) supplemented with 1.0 mg/L IAA, an auxin (Figure 6).

Table 2: Effect of Different Medium on Root Growth from apical shoot tips of *Salvia hypargeia* in vitro Condition

Medium	Number of roots	Root length (mm)
Agar (%0.6) +Sucrose (%2)	0.5	14.5
Agar (%0.6) +Sucrose (%3)	0.7	33.1
Agar (%0.6) +MS+Sucrose (%2)	0.8	7.7
Agar (%0.6) +MS+Sucrose (%3)	0.5	7.7
Agar (%0.6) +MS+Sucrose (%2)+1.0 mg/L BAP	0.7	10.6
Agar (%0.6) +MS+Sucrose (%3)+1.0 mg/L BAP	0.4	2.7
Average Sucrose (%2)	0.7	10.9
Average Sucrose (%3)	0.5	14.5

MS, Murashige & Skoog medium including vitamins (1962). BAP, 6-Benzylaminopurine. Each application has three replications and each replication contains 9 apical shoot tips.

Figure 6: The Root Growth from Apical Shoot Tips of *Salvia hypargeia* in vitro Condition [Agar (%0.6) +MS+Sucrose (%3)+1.0 mg/L IAA].

In addition to these, *S. hypargeia* can also show callus regeneration from leaf explants (Figure 7).

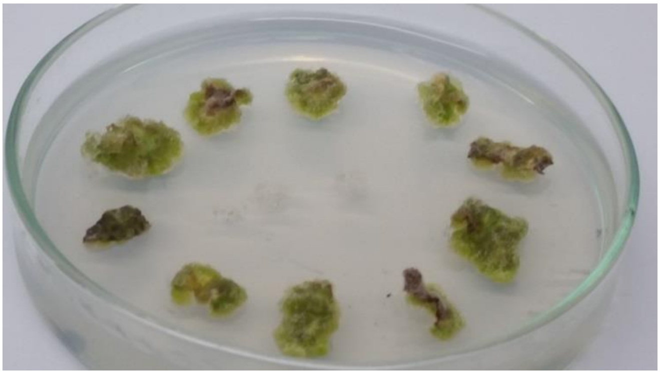


Figure 7: Callus Induction from Leaf Parts of *Salvia hypargeia* in vitro Condition [Agar (%0.6) +MS+Sucrose (%3)+0.5 BAP+ 1.0 Kinetin+1.0 mg/L IAA].

CONCLUSIONS

In this study, it has been highlighted that plant tissue culture applications can serve many purposes from an efficient tool to break the dormancy of seed to micropropagation and callus production for *Salvia hypargiea*. This study will shed light on future studies in terms of demonstrating the usability of tissue culture as an alternative propagation method of an endemic plant. In addition, it will be effective in the formation of the idea of producing the commercially valuable terpene group and other economically important compounds in the roots and leaves of the plant under in vitro conditions.

REFERENCES

Acar Deniz, Z., & Çördük, N. (2016). Climatic change of the areas where *Digitalis trojana* Ivanina, endemic plant of Kazdagi, spreads. International Geography Symposium, 13-14 October, pp. 230-237 (In Turkish).

Aćimović, M., Pezo, L., Čabarkapa, I., Trudić, A., Stanković Jeremić, J., Varga, A., ... & Tešević, V. (2022). Variation of *Salvia officinalis* L. essential oil and hydrolate composition and their antimicrobial activity. Processes, 10(8): 1608.

Afshin, S., Rashtbari, Y., Shirmardi, M., Vosoughi, M., & Hamzehzadeh, A. (2019). Adsorption of Basic Violet 16 dye from aqueous solution onto mucilaginous seeds of *Salvia sclarea*: kinetics and isotherms studies. Desalination and Water Treatment, 161: 365-375.

Anonim, (2022). Turkish Plants Data Service. (http://194.27.225.161/yasin /tubives/index.php?sayfa=1&tax_id=8080) (Accessed date: 24.10.2022)

Atas, A. D., Goze, I., Alim, A., Cetinus, S. A., Vural, N., Murat Goze, H., & Korkoca, H. (2011). Chemical composition, antioxidant, antimicrobial activities of the essential oil *of Salvia hypargeia* Fisch. & Mey. Journal of Essential Oil Bearing Plants, 14(3): 289-296.

Bağcı, E., Koçak, A. (2008). *Salvia palaestina* Bentham ve *S. tomentosa* Miller türlerinin uçucu yağ kompozisyonu, kemotaksonomik bir yaklasım. Fırat Üniversitesi Fen ve Mühendislik Bilim Dergisi, 20(1): 35-41.

Bakir, D., Akdeniz, M., Ertas, A., Yilmaz, M. A., Yener, I., Firat, M., & Kolak, U. (2020). A GC–MS method validation for quantitative investigation of some chemical markers in *Salvia hypargeia* Fisch. & CA Mey. of Türkiye: Enzyme inhibitory potential of ferruginol. Journal of Food Biochemistry, 44(9): e13350.

Baricevic, D., & Bartol, T. (2005). V. Pharmacology 11. The biological and pharmacological activity of the *Salvia* genus. Pp 143– 184. In: S. E. Kintzios (Editor) Sage the genus Salvia, Medicinal and aromatic plants-Industrial profiles. Hardwood Academic Publishers, The Netherlands.

Baytop, T. (1994). Turkish plant names dictionary. Turkish Language Association Publications. No: 578, Ankara, Türkiye.

Bingöl, M. U., Balpinar, N., Guney, K., Geven, F., Ketenoglu, O., Arslan, M., & Karakas, M. (2019). Evaluation of threat categories of the endemic plants of Deveci mountains (Yozgat-Tokat/Türkiye). Communications Faculty of Sciences University of Ankara Series C Biology, 28(1): 22-34.

Bingul, Z., & Adar, E. (2021). Usability of spent Salvia officinalis as a low-cost adsorbent in the removal of toxic dyes: waste assessment and circular economy. International Journal of Environmental Analytical Chemistry, 1-16.

Cabrera-Santos, D., Ordoñez-Salanueva, C. A., Sampayo-Maldonado, S., Campos, J. E., Orozco-Segovia, A., & Flores-Ortiz, C. M. (2021). Chia (*Salvia hispanica* L.) seed soaking, germination, and fatty acid behavior at different temperatures. Agriculture, 11:1–16.

Cardile, V., Russo, A., Formisano, C., Rigano, D., Senatore, F., Arnold, N. A., & Piozzi, F. (2009). Essential oils of Salvia bracteata and Salvia rubifolia from Lebanon: Chemical composition, antimicrobial activity and inhibitory effect on human melanoma cells. Journal of Ethnopharmacology, 126(2): 265-272.

Çördük, N. (2012). In vitro çoğaltılan ve doğal ortamda yayılış gösteren *Digitalis trojana* Ivan. türünde progesteron 5βreduktaz gen ifadesinin ve kardenolid üretiminin karşılaştırılması, Doktora Tezi. Çanakkale Onsekiz Mart Üniversitesi, ÇAnakkale, Türkiye (In Turkish).

Costa, A. A., Paiva, E. P., Torres, S. B., Souza Neta, M. L., Pereira, K. T. O., Leite, M. S., Sá, F. V. S., & Benedito, C. P. (2021). Osmoprotection in *Salvia hispanica* L. seeds under water stress attenuators. Brazilian Journal of Biology, 82.

Davis, P. H. (1982). Flora of Turkey and the east aegean island. Vol. 7, pp. 435-436, Edinburgh University Press, Edinburg.

Delamare, A. P. L., Moschen-Pistorello, I. T., Artico, L., Atti-Serafini, L., & Echeverrigaray, S. (2007). Antibacterial activity of the essential oils of *Salvia officinalis* L. and *Salvia triloba* L. cultivated in South Brazil. Food chemistry, 100(2): 603-608.

Dweck, A. C. (2005). Introduction. The folklore and cosmetic use of various *salvia species*. S.E. Kintzios (Ed.), Sage, the genus Salvia, Harwood Academic Publishers, Singapore.

Ekim, T., Koyuncu, M., Vural, M., Duman, H., Aytaç, Z., & Adıgüzel, N. (2000). Türkiye bitkileri kırmızı kitabı. Türkiye Tabiatını Koruma Derneği ve Van Yüzüncüyıl Üniversitesi Yayınları, Ankara (In Turkish).

Erdoğan Eliuz, E. A. (2021). Antimicrobial activity and mechanism of essential oil of endemic *Salvia hypargeia* Finc. & Mey. in Türkiye. Indian Journal of Microbiology, 61(3): 291-297.

Estaji, A., Hosseini, B., Dehghan, E., & Pirzad, A. (2012). Seed treatments to overcome dormancy of Nuruozak (*Salvia leriifolia* Bent.). IRJABS, 3: 2003-2008.

Fan, M., Zhu, Y., Zhang, Z. J., Du, R. N., Zhu, Q. F., Wu, X. D., & Zhao Q. S. (2018). Salvihispin A and its glycoside, two neo-clerodane diterpenoids with neurotrophic activities from Salvia hispanica L. Tetrahedron Letters, 59(2): 143-146.

Franz, C., & Novak, J. (2010). Sources of essential oils. Baser, K. H. C., Buchbauer, G. (Eds.), Handbook of Essential oils, Science, Technology, and Applications. Vol 994, CRC Press, Boca Raton, London, New York.

Geneve, R. L., Hildebrand, D. F., Phillips, T. D., AL-Amery, M., & Kester, S. T. (2017). Stress influences seed germination in mucilage-producing chia. Crop Science, 57(4): 2160-2169.

Germanà, M. A., Chiancone, B., Hammami, S., & Rapoport, H. F. (2014). Olive embryo in vitro germination potential: role of explant configuration and embryo structure among cultivars. Plant Cell, Tissue and Organ Culture (PCTOC), 118(3): 409-417.

Ghorbani, A., & Esmaeilizadeh, M. (2017). Pharmacological properties of *Salvia officinalis* and its components. Journal of Traditional and Complementary Medicine, 7(4): 433-440.

Gorai, M., Gasmi, H., & Neffati, M. (2011). Factors influencing seed germination of medicinal plant *Salvia aegyptiaca* L.(Lamiaceae). Saudi Journal of Biological Sciences, 18(3): 255-260.

Güner, A., Aslan, S., Ekim, T., Vural, M., & Babaç, M. T. (2012). Türkiye bitkileri listesi (Damarlı bitkiler). Nezehat Gökyiğit Botanik Bahçesi ve Flora Araştırmaları Derneği Yayını, sayfa 578, İstanbul (In Turkish).

Jia, Y., Huang, F., Zhang, S., Leung, S. (2012). Is danshen (*Salvia miltiorrhiza*) dripping pill more effective than isosorbide dinitrate in treating angina pectoris? A systematic review of randomized controlled trials. International Journal of Cardiology, 157: 330-340.

Kamatou, G. P., Makunga, N. P., Ramogola, W. P. N., & Viljoen, A. M. (2008). South African *Salvia* species: a review of biological activities and phytochemistry. Journal of Ethnopharmacology, 119(3): 664-672.

Kintzios, S. E. (Ed.). (2000). Sage: the genus Salvia. CRC Press.

Lubbea A., Verpoorte R. 2011. Cultivation of medicinal and aromatic plants for specialty industrial materials. Industrial Crops and Products, 34, 785-801.

Maliro, M. F. A., & Kwapata, M. B. (2000). Apomictic embryo development and survival in Uapaca kirkiana under in vitro and in vivo seed germination. Scientia Horticulturae, 83(2): 139-147.

Murashige, T., & Skoog, F. (1962). A revised medium for rapid growth and bioassays with tobacco cultures. Physiol Plant, 15: 473-497.

Nadtochii, L. A., Kuznetcova, D. V., Proskura, A. V., Apalko, A. D., Nazarova, V. V., & Srinivasan, M. (2019). Investigation of various factors on the germination of chia seeds sprouts (*Salvia hispanica* L.). Agronomy Research, 17(S2): 1390–1400

Onder, A., Izgi, M. N., Cinar, A. S., Zengin, G., & Yilmaz, M. A. (2022). The characterization of phenolic compounds via LC-ESI-MS/MS, antioxidant, enzyme inhibitory activities of *Salvia absconditiflora*, *Salvia sclarea*, and *Salvia palaestina*: A comparative analysis. South African Journal of Botany, 150: 313-322.

Ozay, Y., Guzel, S., Gokalp Ozkorkmaz, E., Kumas, M., Uzun, C., Yıldırım, Z., ... & Kahraman, A. (2021). Biochemical, histopathologic, and genotoxic effects of ethanol extract of *Salvia hypargeia* (Fisch. & Mey.) on incisional and excisional wounded diabetic rats. Journal of Investigative Surgery, 34(1): 7-19.

Perry, N. S., Bollen, C., Perry, E. K., & Ballard, C. (2003). Salvia for dementia therapy: review of pharmacological activity and pilot tolerability clinical trial. Pharmacology Biochemistry and Behavior, 75(3): 651-659.

Piątczak, E., Owczarek, A., Lisiecki, P., Gonciarz, W., Kozłowska, W., Szemraj, M., ... & Grzegorczyk-Karolak, I. (2021). Identification and quantification of phenolic compounds in Salvia cadmica Boiss. and their biological potential. Industrial Crops and Products, 160: 113113.

Raal, A., Orav, A., & Arak, E. (2007). Composition of the essential oil of *Salvia officinalis* L. from various European countries. Natural product research, 21(5): 406-411.

Saffariha, M., Azarnivand, H., Zare Chahouki, M. A., Tavili, A., Nejad Ebrahimi, S., Jahani, R., & Potter, D. (2021). Changes in the essential oil content and composition of *Salvia limbata* CA Mey at different growth stages and altitudes. Biomedical Chromatography, 35(8): e5127.

Salgado, V. D. S. C. N., Zago, L., Antunes, A. E. C., & Miyahira, R. F. (2022). Chia (*Salvia hispanica* L.) seed germination: A brief review. Plant Foods for Human Nutrition (Dordrecht, Netherlands).

Sharifi-Rad, M., Ozcelik, B., Altın, G., Daşkaya-Dikmen, C., Martorell, M., Ramírez-Alarcón, K., ... & Sharifi-Rad, J. (2018). *Salvia* spp. plants-from farm to food applications and phytopharmacotherapy. Trends in Food Science & Technology, 80: 242-263.

Tahar, S., Bendif, H., Zedam, A., Flamini, G., & Maggi, F. (2021). A new chemotype with high tricyclene content from the essential oil of *Salvia aegyptiaca* L. growing in Algerian Pre-Sahara. Natural Product Research, 1-6.

Talebi, S. M., Askary, M., Khalili, N., Matsyura, A., Ghorbanpour, M., & Kariman, K. (2021). Genetic structure and essential oil composition in wild populations of *Salvia multicaulis* Vahl. Biochemical Systematics and Ecology, 96: 104269.

Topcu, G., Turkmen, Z., Schilling, J. K., Kingston, D. G. I., Pezzuto, J. M., & Ulubelen, A. (2008). Cytotoxic activity of some Anatolian salvia. Extracts and isolated abietane diterpenoids. Pharmaceutical biology, 46(3): 180-184.

Tunçkol, B., & Akkemik, Ü. (2013). Endemic plants of Taşlıyayla and Kızık (Bolu-Seben) surrounding. Journal of the Faculty of Forestry, 63 (2): 1-10.

Ulubelen, A., Evren, N., Tuzlaci, E., & Johansson, C. (1988). Diterpenoids from the roots of *Salvia hypargeia*. Journal of Natural Products, 51(6): 1178-1183.

Ulubelen, A., Topçu, G., Chai, H. B., & Pezzuto, J. M. (1999). Cytotoxic activity of diterpenoids isolated from *Salvia hypargeia*. Pharmaceutical biology, 37(2): 148-151.

Western, T. (2012). The sticky tale of seed coat mucilages: production, genetics, and role in seed germination and dispersal. Seed Science Research, 22: 1–25.

Yaman, C., Khalid, P. S., & Bakhsh, A. (2022). Dormancy and germination of *Salvia* species: an overview. New Development on Medicinal and Aromatic Plants-II, pp. 321.

Younis, M. E., Rizwan, M., & Tourky, S. (2021). Assessment of early physiological and biochemical responses in Chia (*Salvia hispanica* L.) sprouts under salt stress. Acta Physiologiae Plantarum, 43: 1–10.

CHAPTER 3

POPPY (*Papaver somniferum* L.) THE MISCELLANOUS INDUSTRIAL CROP

Ebru ERDEM[1]
Ahmet GÜMÜŞÇÜ[2]

[1] Eskişehir Osmangazi University, Faculty of Agriculture, Department of Field Crops, Eskişehir, Türkiye, e-mail:medreurbe@gmail.com
ORCID ID: 0000-0002-6030-2436
[2] Eskişehir Osmangazi University, Faculty of Agriculture, Department of Field Crops, Eskişehir, Türkiye, e-mail:ahmet.gumuscu@ogu.edu.tr
ORCID ID: 0000-0002-3452-3307

INTRODUCTION

Poppy is belonging to the family Papaveraceae, genus Papaver and species *Papaver somniferum* L. The species in the family Papaveraceae are mostly spread mild and subtropical regions of the northern hemisphere (Seçmen et al., 1995; Parmaksız et al., 2009). There are 28 genus and about 250 species in the family *Papaveraceae*. Seven genus belonging to this family are there in Türkiye. In the last studies is reported totally 58 *Papaver* taxa including 15 endemic of 36 species, 22 sub-species and varieties (Güner et al., 2012). The varieties in poppy cultivating countries are well known such as album (white flower), nigrum (violet flower), setigerum (dark violet flower) and glabrum (red-violet flower). The white and violet flowered varieties of *Papaver somniferum* L. subsp. *Anatolicum* are sown mostly in Türkiye (Tanker and Tanker, 1990).

Papaver is meaning in Latin “corn-poppy” and *somniferum* is “dream” and “soporific” (Gümüşçü and Arslan, 1999, Facchini et al.., 2007). When injured superficially the immature poppy capsules, the latex get dark brown vaporizing a little and then the alkaloid concentrate. This material called opium (Bernáth, 1998). The poppy is a miscellaneous plant which synthesize narcotic analgesic benzylisoquinoline alkaloids such as morphine and codeine; benefit from their seed and oil; also be used medicinal and ornamental plant (Gümüşçü and Arslan, 1999; Facchini et al., 2007). The poppy production is under control for economic importance and be permitted to grow definite provinces.

There are both winter and spring type but the winter type is preferred for higher yield.

The poppy cultivation is brought under control firstly in 1933 in Türkiye and continued to cultivation by the laws and regulations introduced time to time. Türkiye is participated to studies relating to bring control opium smuggling around the world, and the new law was introduced in 1959 for regulating poppy cultivation. The limited production was started in 1961. Türkiye started to reduce area sown poppy delivering comminments of UN and permitted cultivation and production in 42 provinces in the season 1962-1963 (Arslan et al., 1986). The poppy cultivation was banned in Türkiye by 2654 bylaw in 1971. The production was released again in 1974. The cultivation was unbanned limited to 7 provinces and poppy production started again. But the capsule injure was banned and permitted only morphine production from dry capsules in Bolvadin Opium Alkaloids Factory established from Turkish Grain Board (TGB). This factory has processing capacity dry poppy capsules 20.000 tonnes per year and can serve the purpose 35% of the world annual need (Erdurmuş, 1989).

1. REGISTRATED VARIETIES

The variety Emiral-84 was first registrated by Prof. Dr. Şükrü Emiroğlu from Ege University, Agricultural Faculty in Türkiye. This variety has red flower and grey-darkgreen seed and no seed production.

The actual registrated varieties are TMO1, Ömürcan, Hüseyinbey, Çelikoğlu, Seyitgazi, Ofis Nm, Ofis 1 and Ofis 2.

Some poppy varieties developed by Turkish Grain Board (TGB);

TMO 1 was registrated by TGB at April 7th 2005 and developed by crossing. Petals are white in color, seed color is yellowish-brown, in the variety description document are seed yield, capsule yield, morphine ratio and thebaine ratio, 136-190 kg/da, 123-189 kg/da, 0.65-0.92%, 0.01%, respectively.

Ofis NM was registrated by TGB at April 8th 2014 and developed by selection. It is spring type and its morphine, thebaine, noscapine ratio are 0.958%, 0.186% and 1.376%, respectively. Its seed color is grey, petal color is light violet, and its habit is early flowered.

Ofis 1 was registrated by TGB in 2016 and developed by crossing. Its seed color is bluish, petals color are violet and blotched. The capsule longitudinal section shape is wide elliptical, stigma disc shape is wide umbellate. It is winter type and its habit is late flowered. Morphine ratio is 1.902% and thebaine ratio is 0.084%.

Ofis 2 was registrated by TGB in 2016 and developed by crossing. Seed and petals are white in color, the capsule longitudinal section shape is wide elliptical, stigma disc shape is wide umbellate. It is winter type and its habit is late flowered. Morphine ratio is 1.659% and thebaine ratio is 0.048%.

Poppy varieties developed by Eskişehir-Anadolu Agricultural Research Institute (AARI);

Hüseyinbey was registrated by AARI at April 8th 2014 and developed by selection. Its petal and seed color are white, capsule base shape is hollow. It is winter type and its capsule yield, seed yield and morphine ratio are 110.3 kg/da, 125.3 kg/da and 0.613%, respectively, at the area sown.

Çelikoğlu was registrated by AARI at April 8th 2014 and developed by selection. Its seeds are yellowish in color, petals are white in color, capsule base shape is hollow. It is winter type and its capsule yield, seed yield and morphine ratio are 117.7 kg/da, 137.6 kg/da and 0.591%, respectively, at the area sown.

Ömürcan was registrated by AARI in 2011. Its petals are violet in color, seeds are khaki in color and capsule is round shape. It is winter type and its capsule yield, seed yield and morphine ratio are 60-115 kg/da, 70-134 kg/da and 0.5-0.7%, respectively, at the area sown.

Seyitgazi was registrated by AARI at April 8th 2014 and developed by selection. Its petals are violet in color, seeds are bluish in color, capsule base shape is hollow, longitudinal section is straight. It is winter type and its capsule yield, seed yield and morphine ratio are 112 kg/da, 124 kg/da and 0.68%, respectively, at the area sown.

2. NUTRITIONAL VALUE

Poppy is an important medicinal plant because the alkaloids obtained from capsules are used medicinal purposes (Er, 1994). The most important ones of these alkaloids are morphine, codeine, thebaine and papaverine (Baytop, 1963). The oil content of seeds is 40–50% and its important oil acids are linoleic acid and oleic acid.

In the seed oil, linoleic acid (Omega 6), oleic acid (Omega 9), palmitic acid, stearic acid and linolenic acid contents are 62% (Küçük, 1996), 13-24%, 12- 18%, 2-4% and 0.1-0.4%, respectively (Özcan and Atalay, 2006). Also, seed protein content is 20-30%. The morphine content is very important because it is obtained from directly capsule. The morphine ratio in capsule processing in factory is forseen 0.5%. But, the morphine ratio in previous years reduced to 0.3% (Yazıcıoğlu and Karaali, 1983).

2.1. Capsule Content

The medicinally important 80 alkaloids were determined in poppy capsules. The most important alkaloids are morphine, codeine, thebaine, noscapine, oripavine vand papaverine. Morphine, codeine and thebaine are under international control because they are phenanthrene alkaloids (Çelik, 2011; Mishra et al., 2013; Marciano et al., 2018).

Thebaine content at different developing stage is 0.002% the lowest at rosette stage and 1.01% the highest at ripening stage. Noscapine content is 0.01% the lowest at rosette stage and 1.17% the highest at ripening stage.

It was recorded that the dominant alkaloid in whole plant is morphine (38.5%), following noscapine (32.8%) (Alaca, 2015), and the morphine content in roots is 0.03% (Gessner, 1974).

It was stated that *P. somniferum* L. has the highest morphine content 2-3 weeks after flowering. When the capsules harvested before this time, thebaine and codeine were the dominant alkaloids, while the morhine decomposed delaying harvest (Al- Hussiany, 2011).

2.2. Opium Content

The morphine content in opium 7-20%, codeine is monomethyl ether of morphine and 0.3-6% in opium. Thebaine is derivate of codeinone and 0.2-1% in opium. Noscapine is 2-12% and the highest amount followed morphine. Oripavine is 0.1-0.2% and papaverine 0.5-3.0% (Kapoor, 1995; Blaschek et al., 2006; Bracher et al, 2010).

2.3. Areas of Usage

- For the first time, humankind used the poppy plant by mixing the sap into foods to help babies sleep well (İncekara, 1964).
- There are two important products, seeds and capsule shells.
- Also, the young seedlings are used as salad and the stems of harvest residue are used as fuel (Balcı et al., 2007).
- Some seeds cultivated in Türkiye spare to next cultivation and the rest is for trading in the free market (Lo and Chua, 1992).
- Poppy seed is commonly used traditional food and cake preparation in Slovakia and The Czech Republic (Hayes et al., 1987).
- Poppy seed and its oil are used in the kitchen and food industry (Yazıcıoğlu and Karaali, 1983).
- Its oil is recommended for some diets because of rich for unsaturated fatty acids (İncekara, 1964).

- The cake after defatted seeds is rich for protein, oil and nitrogen free essential substances and used for animal fodder (Özer, 2004).
- Codeine and morphine in opium are analgesic, papaverine is vasodilator, noscapine is antitussive and anticancer, sanguinarine is antimicrobial and cholesterol lowering, also tubocrine is relaxative (Peter, 2001; Ünver et al., 2010).
- Opium and its alkaloids are commonly used calmative and analgesic in medicine.
- The capsules can be used ornamental (Büyükgöçmen, 1994).
- The seed oil can be used dyeing and soap industry because of semi-siccative oil (İncekara 1964).
- It is used analgesic and antitussive in modern medicine (Peter, 2001; Ünver et al., 2010).
- The stems of poppy is used making mat and fuel material (Büyükgöçmen, 1994).

2.4. Poppy Straw

Poppy straw obtained from harvested plants when they came whole maturity or drought mechanically and took seeds. The dry leaves, stems and capsule shells were used for producing morphine and other alkaloid derivated drugs, therefore, poppy straw was obtained first separating seeds, then concentrate was made from poppy straw (Bernáth, 1998).

Nowadays, poppy straw concentrate is basic source of a lot of opiate and other alkaloids. It is source of 90 % of legal morphine around the world (for medicinal and scientific uses) and illegal morphine source convertible to heroin in some countries.

The first commercial process obtaining opiates from poppy straw was invented by János Kabay in Hungary. This process called “poppy straw method” is valid at the present time, too. János Kabay applied his new process when the capsules were fresh between flowering and maturity periods on the poppy fields. There were some disadvantages and the most important one is not to harvest immature seeds, therefore not only was the seed product lost, but also the poppy seed oil could not be obtained. After a while later, he found out that the process could be applied to the residues of the poppy straw after harvesting seeds and thus be eliminated these disadvantages (Bayer, 1961; Bayer, 1987).

2.5. Trace of Illegal Drugs

The poppy straw is a raw material which can be produce illegal heroin. The alkaloid profiles of poppy straw and opium are similar, but some researches show that can be partially distinguished by their alkaloids. In terms of consisting of oripavine in some poppy cultivars, it was asserted that the illegal heroin captured in Australia was produced from poppy stems which were stolen in Tasmania few years ago (Odell et al., 2008). Therefore, selling and processing phases of poppy are registered. This records around the world are pursued regularly.

2.6. Single Convention on Narcotic Drugs

The cultivation, production, import and export of the drugs around the world are arranged according to UN 1961 Single Convention on Narcotic Drugs signed by Türkiye and to the protocol 1972 related to modulate. Single convention on narcotic drugs signed in New York on March 30th 1961 bring provision running one-handed drug dealing in countries and agree on visitorial power of narcotic drugs of UN.

Single convention on narcotic drugs was approved law number 812 on December 27th 1966 and Türkiye was joined on Februar 14th 1967. The parties signed convention accepted that narcotic uses were mandatory for medicinal purposes taking care of people's illnesses and spiritual health and that measures were need to be taken to ensure that the narcotics were available for this reason and that drug addicition was a disaster for persons and that was a political and social danger for mankind.

It was aimed that production, trade, smuggling and use should be hit rock bottom amounts increasing day by day of illegal narcotic drugs. The sanction power on countries signed this convention was considered, which were legal producer.

A sample of this sanction power was applied on Türkiye in 1971. Due to be accused by one of illegal drug source, Turkish government banned the cultivation of poppy by the cabinet decree the number of 7/2654 and date of 06/26/1971.

The 3-years-cultivation-ban in Türkiye not caused a shrink on world narcotic drug market, on the contrary it showed a big increase. It was impossible that a country increase the opium production without an UN verdict.

The area sown and production of poppy in Türkiye differ over the years. The area sown for poppy was showed in Table 1, the production was showed in Table 2.

Table 1: Area sown over the years in Türkiye (da)

	2016	2017	2018	2019	2020
Poppy	-	237.314	451.226	677.369	461.252

Source: Anonymous, 2022

Table 2: Production between 2012-2020 in Türkiye (ton)

	2012	2013	2014	2015	2016	2017	2018	2019	2020
Poppy	3.844	19.244	16.223	30.730	18.205	15.244	26.991	27.288	20.542

Source: Anonymous, 2022

2.7. The Geographical Distribution of Poppy Agriculture in Türkiye

The poppy cultivation is generally transition zones of coastal and central regions, which are hot and middle rain in summer (Darkot, 1968). It can grow everywhere except high grounds of east Anatolia. The coastal regions due to excessive rainfall and humidity and high grounds of east Anatolia due to inadequate temperatures were not appropriate for poppy agriculture.

The poppy agriculture in Türkiye was affected from human and economical factors, such as permit and pricing policy of government, competition of other products, knowledge and skill level of poppy farmer, also natural factors, such as rainfall, humidity, temperature, elevation and water.

Poppy is cultivated Afyonkarahisar, Amasya, Balıkesir, Burdur, Çorum, Denizli, Eskişehir, Isparta, Konya, Kütahya, Manisa, Tokat and Uşak provinces in Türkiye. These areas are transition zones adjacent to Central Anatolia Region. There is an optimum temperatures in these areas and elevation is generally around 1000-1200 m. Türkiye is the country among most and most quality growing poppy countries for a long time (Gümüşçü and Gümüşçü, 1997).

2.7.1. Rotation

Poppy tire not the soil and is counted semi-fallow. The cereals can be sown after poppy because it is harvested early. Due to an industrial crop sould be hoed poppy and therefore it leave a clean and without weeds field the successor crop.

It is possible to grow poppy successive in the same field, but has some drawbacks. Some of these drawbacks are increasing diseases and pests in successive years, variety mixing due to falling seeds onto field, etc. (Erdurmuş and Öneş, 1990).

It is favourable that poppy sould be in rotation with other crops for bountiful harvest and healthy product. It is recommended sowing poppy after fallow or hoed crops. Poppy gives enough yield after barley or wheat fertilized sufficient. Poppy is sown mostly on fallow land in non-irrigated regions in Türkiye and one of cereals comes after harvesting poppy (Gümüşçü ve Gümüşçü, 1997).

2.7.2. Harvest

The spring type poppy varieties ripen 6 months, winter type poppy varieties ripen 9 months. Poppy harvest when aerial parts of plants dried, capsules get yellow in color and seeds in capsule sound when shaking (Arslan et al., 2016). Poppy harvest generally in July- August. The seeds on carpel walls fall on the bottom of capsules when they dry. The whole capsules on a plant or on the field ripen not same time. Due to the capsules underside of plant ripen latest, it sould be check these capsules to decide harvesting.

The being open or closed capsules is a variety feature and extremely dried capsules can open sometimes. Therefore, the harvest should not retard because of seed fall and product lost. The rainfall in harvest time can cause opening and darkening capsules, seed fall and decreasing the germination. This induce the value of capsule and seed.

The harvest process is done different ways in the world. The harvest in Afghanistan, India and Pakistan is done being injured the capsules. In Australia, Romania, Hungary and Austria is harvest done by machine. In Afghanistan, China and India collect opium with special tools when the capsules are green. Then, tha capsules collected by hand and fill in the sacks (Hacıyusufoğlu, 2013). In Türkiye, the harvest is done by breaking the capsules with hands. The capsules collect by breaking the nodes jointed by the stem harvesting by hand. The collected capsules are stored in the big sacks.

2.7.3. The ost-harvest works

The collected capsules are passed through tha capsule crushing machine or broken with wooden clasps. The capsule crushing machine used after harvest in Turkey are usually driven by the tractor power-take-off or started by the electrical engine. The capacity of these machines is about 2 ton/h. The capsules filled by the hand into the material feeding entrance are conveyed to chopping chamber and then chopped the capsules. The seeds and broken capsules falled on to the sieve are elected. The splitted seeds and capsules are filled separately in the sacks. The hole diameter of top sieve is 3-5 mm and of bottom sieve is 2-3 mm on average.The bottom sieve should split the parts of capsule and stem well, otherwise the flavor of edible seeds get of poor quality bittering (Özarslan et al., 2018).

2.7.4. Blending unit

The stem parts should be in the clear when the capsules break with stem in the stage of capsule chopping and split. It is important that the proper chopping unit should use breaking capsules stemmed of the cut the specific length on the purpose of overcome this problem. In the preliminary tests are presented that the stemmed capsules chop on the nod point and the stems generally desert the unit in a single piece (Özarslan et al., 2018).

2.7.5. Drying and storage

The drying time changes according to drying temperature and method. The optimal drying method is lyophilisation at the temperature of 105 minutes in view of maximal content of anthocyanins. It is required to dry at the temperature of 45 °C for 210 minutes under vacuum condition not to change of color. The best result at the oven drying was obtained at the temperature of 55 °C for 180 minutes (Karasu et al., 2015).

The poppy seeds should check regularly, store at the sensitive conditions and transport. At the proper storage and conditions should conserve to prevent many disease formation and deterioration.

2.8. Important Breeding Aims of Poppy

Yield Criterions

- Increasing seed yield (Németh et al., 2002).
- Earliness
- Resistance to diseases
- Resistance to lodging and short plant length (Singh et al., 2003).
- Developing winter types

Quality Criterions

- Increasing oil ratio
- Increasing linoleic acid ratio in oil
- Enhancing seed color, especially blue
- Developing the oil type varieties as low morphine ratio types

- High morphine, noscapine, codeine and thebaine ratio containg varieties for pharmaceutical industry (Balcı et al., 2007).

The breeding situation in Türkiye

The public enterprises and universities in Türkiye registrated many poppy varieties through breeding studies as part of their collaboration. The alkaloid contents (morphine, thebaine, noscapine, oripavine, codeine, papaverine) are nominal, and yields of seed and capsule are not up to the mark.

The morphine ration in capsule is about 2-2,5% in the countries which grow commercial poppy and produce morphine and derivatives in the world. These countries decrease production costs to production more morphine from capsule and have advantages on international competition (Arıoğlu, 2016). The high alkaloid content having, seed and capsule yielded varieties should breed for competition to obtain more products from unit area.

The producer can earn through increasing seed and capsule yield on unit area. On the other hand, farmers will prosper sowing high morphine having varieties with contract production model (Arıoğlu, 2016).

Main qualifications to be considered in breeding

- Big conical and camous capsules in terms of high seed and opium yield
- Multi-capsule forms
- Bowl and hollow bowl forming stigmas

- Flat-surfaced capsules for injuring and picking opium
- Because increasing morphine and other alkaloid contents is the aim in breeding, bright green, unwaxed and thin capsule shell in technical ripening for high morhine content and opium yield
- White and yellow seeds for high oil content
- Grey seeded varieties for pastry and bread making
- Resistance to winter conditions for more yield sown in autumn than sown in spring to ensure sowing in autumn (Valizadeh and Arslan, 2013).

2.9. Breeding Methods

2.9.1. Selection

Selection is to select proper plants among non-uniform individuals.

Bhandari (1990) found that the morphine ratio in capsules of 171 lines were between 0.32-0.82%, and stated that tall, thick stemmed, multi-capsule and multi-stigma plants should be selected in a selection study for seed yield and morphine ratio together. He proposed as criterion minimized capsule number and capsule volume for higher opium yield through the selection.

The ideal plant type consisting of to be ensured genetic sources is determined for poppy. (Dubedout, 1993; Singh et al., 1995). Sharma et al. (1981) proposed short (resistant to lodging), early flowering and big capsule having plants for preferred plant type in their study on a large collection collected from different geographical regions in India.

The election for alkaloid content may be with selections under natural conditions. Noscapine and codeine ratios were not determined or at the low level under low temperature and light conditions. The election under these conditions helps to determine high genetic potential having types and to synthesis high alkaloid content (Bernáth et al. 1988). The election in resistance and endurance breeding is done preferably under adverse conditions (Bhandari, 1990).

2.9.2. Crossing

The crossing is done to gather in a variety presented and preferred characteristics in two or more lines, varieties or species and to increase variation.

It is thought that the autogamy is dominant in *P. somniferum* L. besides the allogamy can be various level according to the variety and environment conditions (Patra et al., 1992). The allogamy ratios can increase on some varieties depending anatomical or physiological characteristics.

Khanna and Shukla (1986) obtained 3 black seeded and low morphine ratio having lines from selection by crossing between low morphine ratio having and black seeded Soma variety with high yielded non-domestic lines. It is achieved no result if thebaine is favoured main alkaloid, self-pollination and selection were done accordingly. Because high morphine ratio having plants had chromosome number by 2n=23, 2n=24 or 2n=36. Then, they were transformed to high morphine ratio types when over chromosomes were eliminated to obtain 2n=22 number.

Some white seeded lines yielded less 25% than Soma variety, while their fatty oil ratio was increased that they are obtained from selection by crossing Soma variety with white seeded non-domestic lines. If the paper or linen bags were not taken in a few days after crossing, hindered development of the capsules.

Instead of these bags, it is better the big petals should be assemble with a wire paper-clip or closed by roping. These petals prevent the allogamy because they remain firmly attached for 5-10 days upon the stigma, even though they broke from the bottom, while the ovary develops. The selected individuals get homozygocıty when they are continuously subjected to isolation for a long-time and then they can accept to performance tests (Valizadeh and Arslan, 2013).

2.9.3. Mutation

Mutation is sudden and persistent changing in genetic structure of living creature,

In mutation breeding practices, in the studies to be done in order to obtain new varieties, variations that are either found in nature or that will be revealed by different methods are used. Crossing, mutation and polyploidy practices were done in order to create variation. Mutants which are spontaneous and stimulated by mutagens were notified in *P. somniferum* L.

These mutants can be used as a cultural variety directly. The variety Soma is a spontaneous mutant of the variety Indra (Nyman, 1978). The mutants are used mostly as parent in breeding program (Chauhan, 1993). The spontaneous mutants that have low morphine or high thebaine ratio were isolated by Nyman and Hall (1976).

Some characters such as male sterility, rising morphine content, increasing capsule number, short plant and early flowering were obtained by chemical mutagens or radiation (Khanna and Singh, 1975; Nigam et al., 1990). Thebaine and oripavine accumulation is determined in mutants and it is defined that their biosynthesis transform to codeine and morphine (Millgate et al., 2004).

High morphine, noscapine, codeine and thebaine having poppy varieties were obtained by mutation for pharmaceutical industry (Bernáth and Nemeth, 2005; Millgate et al., 2004). Mutation is encouraging for developing agricultural characters of plant and this was achieved in various plants. The secondary metabolites content or yield were increased in several plant species (Mears, 1980). The tetraploid and triploid plants of *P. somniferum* L. have high morphine content and it is found that diploid individuals obtained from these plants have high capsule yield per plant. Triploid individuals were developed for these characters (Andreev, 1963). Poliploid plants flowered late. The seed formation was poor in triploid plants especially. For this reason, it is occurred that polyploidy use too little to obtain high seed yield and can be considered in order to rise morphine yield (Valizadeh and Arslan, 2013).

2.10. Yield

The long term annual mean poppy capsule yield is about 50-60 kg/da, because poppy cultivate mostly on barren land and non-irrigated area in Türkiye (Arslan et al., 2016). Seed yield is higher than capsule yield. But, it is presented by studies, that the seed and capsule yields are more than 100 kg/da with modern applications on fertile lands and irrigated area. Seed and capsule yields under irrigation conditions can be obtained 150 kg/da and 120-130 kg/da, respectively. These values are ranged between 30-100 kg/da under non-irrigation conditions (Camcı et al., 2008).

2.11. Poppy Production in The World

Poppy is one of important crops in world commerce. Poppy production conduct under control in the world. There are six big legal poppy producing country, Türkiye, India, Austria, France, Spain and Hungary. The world commercial values is showed on Table 3. According to the table, it can not see regular increasing or decreasing.

Table 3: Poppy commercial values in the world between 1965-2020 ($)

Year	Value	Year	Value
1965	52.802	2005	147.269
1970	47.741	2010	182.710
1980	70.637	2015	189.662
1990	56.331	2020	43.525
2000	86.190		

2.12. Import and Export

Poppy import and export for many years in Türkiye. The export values are higher in comparison of import and export amounts and values. The amounts and values changed in every passing year. The import and export values were given in Table 4 and Table 5. According to the tables, Türkiye not imported in 2016, but exported in every year. There is not the regular increasing at the export values in Türkiye. It is possible that Türkiye export more ensuring to rise poppy production areas and yield in order to compete easy other countries.

Table 4: Poppy seed import between years 2015-2019 in Türkiye

2015		2016		2017		2018		2019	
Amount (ton)	Value ($)	Amount (ton)	Value ($)	Amount (ton)	Value ($)	Amount (ton)	Value ($)	Amount (ton)	Value ($)
1	3	-	-	20	55	46	125	30	132

Table 5: Poppy seed export between years 2015-2019 in Türkiye

2015		2016		2017		2018		2019	
Amount (ton)	Value ($)	Amount (ton)	Value ($)	Amount (ton)	Value ($)	Amount (ton)	Value ($)	Amount (ton)	Value ($)
12.125	37.688	20.429	56.510	3.773	10.996	26.132	76.844	25.194	90.480

CONCLUSIONS

Poppy is a plant that can grow in extreme conditions and has rich of usage area. Thanks to its nutritional content, it should be consumed. The increasing of conscious and experienced farmers is required for the cultivation. The studies related to breeding of variety, rising of production area and yield shoul be increased both usage and essential plant for health. The cultivation should be done on the larger area and under control. The plant can misuse and this restrict production. Required controls should be increased. The breeding studies are insufficient in Türkiye. Required breeding scopes should be determined and the studies should be directed to these scopes.

REFERENCES

Alaca, F. (2015). Farklı Haşhaş Tiplerinde Alkaloidler Yönünden Morfolojik ve Ontogenetik Varyabilite. Ankara Ün. Fen Bil. Enst., Doktora Tezi, Ankara.

Al-Hussiany, G.A. (2011). Chemistry of natural drug products. Pharmacognosy. University of Babylon, Lecture, (8).

Andreev, V.S. (1963). The increase of morphine content in polyploids of opium poppy (*Papaver somniferum* L.). Dokl. Akad. Nauk. SSSR, 148: 206-208.

Anonymous, 2022. Bitkisel Üretim İstatistikleri. TUİK, www.tuik.com (Erişim Tarihi: 08.10.2022).

Arıoğlu, H. (2016). Oil Seeds and Crude Oil Production in Turkey, Problems and Solutions. Tarla Bitkileri Merkez Araştırma Enstitüsü Dergisi, 25(Special Issue): 357-368. (In Turkish).

Arslan, N., Er, C., & Camcı, H. (1986). Haşhaş Ekimi Yasağının Kaldırılmasından Beri Haşhaş Tarımı ve Problemleri. VI. Bitkisel İlaç Hammaddeleri Toplantısı. Bildiri Kitabı (Ed: B. Şener). 16-19 Mayıs, Ankara. S: 99-118.

Arslan, N., Yılmaz, G., Özgen, Y., & Yazıcı, L. (2016). Ankara ve Tokat Koşullarında Yetiştirilen Tescilli Bazı Haşhaş (*Papaver somniferum* L.) Çeşitlerinin Morfin ve Diğer Alkaloidler Yönünden Karşılaştırılması. III. Tıbbi ve Aromatik Bitkiler Sempozyumu, 4-6 Ekim, Antalya.

Balcı, A., Camcı, H., & Çelikoğlu, F. (2007). A research for thebaine and morphine contents of opium poppy lines selected and evaluated in Ankara conditions. Abstracts of the 1st International Medicinal and Aromatic Plants Conference on Culinary Herbs, Apr. 29-May 4. Antalya, Turkey, p. 24

Baytop, T. (1963). Türkiye'nin Tıbbı ve Zehirli Bitkileri. İstanbul Üniversitesi. S 499.

Bayer, İ. (1961). Macaristan'daki haşhaş bitkisinden alkaloid üretimi. Narkotik Bülteni. 13 (1): 21–28.

Bayer, İ. (1987). "[János Kabay ve haşhaş sapı işlemi. Ölümünün 50. yıldönümünü anma]". Acta Pharmaceutica Hungarica. 57 (3–4): 105–10. PMID 3314338.

Bernáth, J., Danos, B., Veres, T., Szánto, J., & Tétény, P. (1988). Variation in alkaloid production in poppy ecotypes: responses to different environments. Biochemical Systematics and Ecology,16(2):171-178.

Bernáth, J. (1998). Poppy cinsi *Papaver*. Amsterdam, Hollanda: Harwood Academic Publishers. s. vii. ISBN 978-0-203-30418-1.

Bernáth, J., & Nemeth, E. (2005). Stability and variability of alkaloid accumulation in poppy (*Papaver somniferum* L.) induced by crossing. Acta Hort. 675: 179-185.

Büyükgöçmen, R. (1994). Farklı Yörelerden Temin Edilen Yerli ve Yabancı Haşhaş (*Papaver somniferum* L.) Populasyonlarının Bazı Bitkisel Özellikleri. Master Thesis, Ankara University Graduate School of Natural and Applied Sciences, Ankara.

Bhandari, M.M. (1990). Out-crossing in opium poppy *Papaver somniferum* L. Euphytica, 48(2):167-169.

Blaschek, W., Ebel, S., Hackenthal, E., Holzgrabe, U., Keller, K., Reichling, J., & Schulz, V. (2006). Hager ROM 2006. Hagers handbuch der drogen und arzneistoffe. Springer Medizin Verlag, Heidelberg.

Bracher, F., Heisig, P., Langguth, P., Mutschler, E., Rücker, G., Scriba, G., Stahl-Biskup, E., & Troschütz, R. (2010). Kommentar zum europäischen arzneibuch Commentary to the Pharmacopoeia Europaea, Wissenschaftliche Verlagsgesellschaft, Stuttgart, Germany.

Camcı, H., Balcı, A., & Coşar, F. C. (2008). Haşhaş Tarımı. Ege Tarımsal Araştırma Enstitüsü Müdürlüğü Tarımsal Araştırma Yayım Eğitim ve Koordinasyon (TAYEK) 2008 Yılı Tarla Bitkileri Grubu Bilgi Alışveriş Toplantısı Bildirileri, Menemen- İzmir.

Chauhan, S.P., & Patra, N.K. (1993). Mutagenic effects of combined and single doses EMS in opium poppy. Plant Breeding, 110(4):342–345.

Çelik, İ. (2011). Development of SSR Markers in Poppy (*Papaver somniferum* L.). Master of Science in Molecular Biology and Genetics, İzmir.

Darkot, B. (1968). Türkiye İktisadî Coğrafyası. İstanbul Üniv. Coğrafya Enst. Yay. No: 51, İstanbul.

Dubedout, M. (1993). Analysis of Progenies From a Circular Plan of Crosses in Poppy (*Papaver somniferum* L.). PhD. Thesis, Univ. Of Paris, Orsay, 101.

Erdurmuş, A. (1989). Haşhaş (*Papaver somniferum* L.) Hatlarında Fenolojik ve Morfolojik Karakterlerin Morfin ve Tohum Verimleriyle İlişkileri. Ankara Üniversitesi Fen Bilimleri Enstitüsü, Doktora Tezi, Ankara.

Erdurmuş, A., & Öneş, Y. (1990). Haşhaş, TMO-Al-kasan Yayınlan, 1-24, Ankara.

Er, C. (1994). Tütün, İlaç ve Baharat Bitkileri Ankara Üniversitesi Ziraat Fakültesi Yayın No:1359.

Facchini, P. J., Hagel, M., Liscombe, K., Loukanina, N., MacLeod, P., Samanani, N., & Zulak, K. G. (2007). Opium poppy: blueprint for an alkaloid factory. Phytochem Rev., 6: 97-124.

Gessner, O. (1974). Poisonous and medicinal plants of central Europe. ISBN: 3533023729

Gümüşçü, A., & Gümüşçü, O. (1997). Türkiye'de haşhaş ve haşhaş tarımının coğrafi dağılışı. Ankara Üniversitesi Türkiye Coğrafyası Araştırma ve Uygulama Merkezi Dergisi, 6: 123-148.

Gümüşçü, A., & Arslan, N. (1999). Comparing yield and yield components of some selected poppy (*Papaver somniferum* L.) lines. Turkish Journal of Agriculture and Forestry, 23(supp 4): 991-997. (In Turkish).

Güner, A., Aslan, S., Ekim, T., Vural, M., & Babaç, M.T. (Eds.). (2012). Türkiye Bitkileri Listesi (Damarlı Bitkiler). Nezahat Gökyiğit Bahçesi ve Flora Araştırmaları Derneği Yayını. İstanbul

Hacıyusufoğlu, A.F. (2013). The Development of a Harvest System for Capsules of Opium Under Laboratuary Conditions. PhD Thesis, Adnan Menderes University Graduate School of Natural and Applied Sciences, Aydın.

Hayes, L. W., Krasselt, W.G., & Mueggler, P.A. (1987). Concentrations of morphine and codeine in serum and urine after ingestion of poppy seeds. Clinical Chemistry, 33(6): 806-808.

İncekara, F. (1964). Yağ Bitkileri. Ege Üniversitesi Yayınları, No:83, İzmir.

Kapoor, L. D. (1995). Opium Poppy: Botany, Chemistry and Pharmacology. New York: Food Products Press.

Karasu, S., Kılıçlı, M., Baslar, M., Arıcı, M., Sağdıç, O., & Karaağaçlı, M. (2015). Dehydration kinetics and changes of bioactive compounds of tulip and poppy petals as a natural colorant under vacuum and oven conditions. Journal of Food Processing and Preservation, 39(6): 2096-2106.

Khanna, K.R., & Singh, U.P. (1975). Correlation studies in (*Papaver somniferum* L.) and their bearing on yield improvement. Planta Medica, 28(5): 92-96.

Khanna, K.R., & Shukla, S. (1986). HPLC investigation of the inheritance of major opium alkaloids. Planta Med., 77(2):157–158.

Küçük, Y. (1996). Türkiye'nin Çeşitli Yörelerinde Yetiştirilen Haşhaş Bitkilerinden Alkaloidlerin Esktraksiyonu ve Ekstraktların Susuz Ortamlarda Özelliklerinin İncelenmesi. Basılmamış Doktora Tezi, Ankara Üniversitesi Fen Bilimleri Enstitüsü, Ankara. (https://dspace.ankara.edu.tr/xmlui/handle/20.500.12575/34876).

Lo, D.S.T., & Chua, T.H. (1992). Poppy seeds: implication of consumption. Medicine Science and the Law, 32(4): 296-302.

Marciano, M.A., Panicker, S.X., Liddil, G.D., Lindgren, D., & Sweder, K.S. (2018). Development of a method to extract opium poppy (*Papaver somniferum* L.) DNA from heroin. Scientific Reports, 8: 2590.

Mears, J.A. (1980). Chemistry of polyploids: A summary with comments on Parthenium (*Astraceae ambrosiinae*). In: Lewis, W.H. ed., Polyploidy-biological relevance. Basic Life Science, 13, Plenum Press, New York, N.Y. 77-101.

Millgate, A.G., Pogson, B. J., Wilson, I.A., Kutchan, T.M., Zenk, M.H., Gerlach, W.L., Fist, A.J., & Larkin, P.J. (2004). Morphine-pathway block in top1 poppies. Nature, 431: 413-414.

Mishra, B.K., Rastogi, A., Siddiqui, A., Srivastava, M., Verma, N., Pandey, R., Sharma, N.C., & Shukla, S. (2013). Opium poppy: Genetic upgradation through intervention of plant breeding techniques. 10.5772/53132.

Németh, E., Bernath, J., Sztefanov, A., & Petheo, F. (2002). New results of poppy (*Papaver somniferum* L.) breeding for low alkaloid content in Hungary. Acta Hort. 576: 151-158.

Nigam, K. B., Kandalkar, V. S., & Dhumale, D. B. (1990). Induced mutants in opium poppy (*Papaver somniferum*). Indian Journal of Agricultural Sciences, 60(4): 267-268.

Nyman, V., & Hall, O. (1976). Some varieties of *P. somniferum* L. with changed morphine alkaloid. Hereditas, 84: 69-76.

Nyman, V. (1978). Selection for high thebaine/low morphine content in poppy (*P. Somniferum* L.). Hereditas, 89: 43.

Odell, L.R., Skopec, J., & McCluskey, A. 2008. Isolation and identification of unique marker compounds from the Tasmanian poppy *Papaver somniferum* N. Implications for the identification of illicit heroin of Tasmanian origin. Forensic Science International, 175: 202-208.

Özarslan, C., Saraçoğlu, T., & Hacıyusufoğlu, A. F. (2018). Development of Poppy Harvester. Bilge International Journal of Science and Technology Research. 2(Special Issue): 82-91.

Özcan, M.M., & Atalay, Ç. (2006). Determination of seed and oil properties of some poppy (*Papaver somniferum* L.) varieties. Grasas Y. Aceites, 57(2): 169-174.

Özer, M. (2004). Tabiat Eczanesi. Şifalı Bitkiler Ansiklopedisi. Bürde Yayınları.

Parmaksız, İ., Önen, H., Yıldırım, A., Gümüşcü, A., İpek, A., & Arslan, N. (2009). Türkiye Doğal Florasında Yetişen *Papaver* Cinsi *Oxytona* Seksiyonuna Ait Gen Havuzunun RAPD ve SSR Teknikleriyle Genetik Karakterizasyonu, Morfolojik ve Alkaloit Kompozisyonlarının Kromozom Sayılarıyla İlişkilendirilmesi. Ankara. TÜBİTAK 105 O 501 nolu proje sonuç raporu.

Patra, N.K., Ram, R.S., Chauhan, S.P., & Singh, A.K. (1992). Quantitative studies on the mating system of opium poppy (*Papaver somniferum* L.). Theoretical and Applied Genetics, 84(3):299-302.

Peter, K. V. (2001). Handbook of Herbs and Spices, vol. 1. Woodhead Publishing, Cambridge, UK.

Seçmen, Ö., Gemici, Y., Görk, G., Bekat, L., & Leblebici, E. (1995). Tohumlu Bitkiler Sistematiği (Ders Kitabı). 4. baskı. Ege Ünv. Fen Fak. Ders Kitapları Serisi No: 116. İzmir.

Sharma, J.R., Mishra, H.O., Nair, R.V., Srivastava, R.K., Singh, O.P., & Srivastava, D.P. (1981). Phonological distribution of latex yield and plant type concept in opium poppy (*P. somniferum* L.) Indian Drugs, 19(2): 64-69.

Singh, S.P., Shukla, S., & Khanna, K.R. (1995). Opium poppy. In: Adv. In Horticulture, Medicinal and Aromatic Plants. Vol. 11, Eds. Chadha, K.L. and Gupta, R. Malhotra Pub. New Delhi, India, 535-574.

Singh, H.B., Singh, A., Priya, S., Srivastava, S., & Shukla, S. (2003). Evaluation of germplasm of opium poppy for resistance to downy mildew. Indian Journal of Agricultural Science, 73(7): 391-394.

Tanker, M., & Tanker, N. (1990). Farmakognozi Cilt II. Ankara Üniversitesi, Eczacılık Fak., Yayınları No, 65. Ankara.

Ünver, T., Parmaksız, İ., & Dündar, E. (2010). Identification of conserved micro-RNAs and their target transcripts in opium poppy. Plant Cell Reports, 29(7): 757-769.

Valizadeh, N., & Arslan, N. (2013). Popy Breeding. Turkish Journal of Scientific Reviews, 6(2): 86-92. (In Turkish)

Yazıcıoğlu, T., & Karaali, A. (1983). Türk Bitkisel Yağların Yağ asitleri Bileşimi. TUBİTAK, Marmara ve Bilimsel ve Endüstriyel Araştırma Enstitüsü Yayınları. 102.

CHAPTER 4

EVENING PRIMROSE (*Oenothera biennis* L.): A REVIEW OF PHYTOCHEMISTRY AND MEDICINAL USES

Sadiye Ayşe ÇELİK[1]

[1] Selçuk University, Faculty of Agriculture, Department of Field Crops, Konya, Türkiye. e-mail: sacelik@selcuk. edu.tr, ORCID ID: 0000-0002-0765-645X

INDRODUCTION

From the past to the present, people have utilised plants for nutrition, shelter, heating, healing their wounds and treating their diseases. In 5000 BC, it was determined that there were 250 plants that people used in treatments. Many civilisations that existed in the past, such as Egypt, have been treated with plants for years. However, over time, the use of medicinal plants started to decrease due to the production of drugs and the development of pharmacy. After the 1950s, with the emergence of the side effects of synthetic drugs due to the use of synthetic drugs, the demand for medicinal and aromatic plants and natural products has increased. The increase in chronic diseases and the lack of complete success in the prevention and treatment of these diseases have led patients and health professionals to various searches. For these reasons, "phytotherapy", which is one of the alternative medicine applications, in other words, the subject of treatment with plants is gaining a very important dimension scientifically today. The term "Phytotherapy; phytos = plant, therapy = treatment", which can be explained as an approach to treating patients by using plants traditionally very widely in China and India, was first named by Henri Lenclerc, a French physician who lived between 1870 and 1953, in the journal La Presce Medical. Since the history of mankind until today, treatment with plants continues and many herbal preparations and supplements are used by people due to the high demand for herbal products. One of these plants is Oenothera biennis L., which has become popular in the last 10 years and its use is increasing day by day in our country. It is widely used especially in gynecological diseases, rheumatism, cardiovascular diseases. However, the fact that there are almost no studies on this plant in our country is a deficiency. Studies should be carried out on this plant in the fields of medicine, pharmacy, food and agriculture, and extensive research should be carried out on its use.

As can be seen, many of today's medicines are obtained directly or indirectly from plants. Due to the gamma linoleic acid found in the seed of primrose, seed oil is consumed directly or in capsule form by the public. With this review, general information is given and its usage areas are mentioned.

1. MORPHOLOGICAL PROPERTIES AND DISTRIBUTION

Evening primrose (*Oenothera biennis*) is a biennial plant from the Onagraceae family, and is commercially produced in over thirty countries. The Onagraceae family is a family that spreads out of North Africa and is represented by 4 genera and 26 species in Anatolia. It grows in light sandy and gravelly soils. It likes barren lands and arid places. Primrose can grow in all climatic conditions, sandy-loam soils, roadsides, pastures and open areas.

Oenothera biennis is a plant native to North America, cultivated in Europe, and naturalized in many parts of the world. Evening primrose was first used by Native Americans to relieve swelling on the body. It became a popular folk medicine in Europe in the 17th century and took the name of the king's cure all (Bionity, 2010). One of the main factors in the widespread availability of the plant in the world is the ability of its seeds and itself to tolerate drought. In Turkey, it naturally spreads in the Edirne region.

The flowers of the biennial, 1.25 m tall ornamental plant are yellow and fragrant and open at night. The seeds are brown to red in color. Also, other names for evening primrose are wild primrose, fire plant, night moxibustion, kings' antidote, donkey grass, and broad bellflower. The flower is robust and develops upwards. The leaves are lanceolate, their upper parts are sharp, and the leaf length is in the range of 3-15 cm. Stem leaves are 8-12 cm long and 2-3 cm wide in simple structure. (Koç, 2016; NTP 2009; Tanker et al., 2014; Kaya, 2010; TÜBİVES 2022; Akkemik , 2020).

Figure 1: Evening Primrose Flower, Seed and Capsules

2. CONTENTS OF EVENING PRIMROSE

The primary use of the evening primrose plant is the oil found in its seeds. The oil obtained from the seeds of the evening primrose (*O. biennis*) plant, whose all parts can be eaten, is also valuable. Evening primrose oil is an antioxidant, anti-inflammatory, anticoagulant and immunomodulatory oil containing gamma linoleic acid. Evening primrose oil is obtained from the seeds of the evening primrose plant (*Oenothera biennis*) by cold pressing or solvent extraction (Blumenthal et al., 2003). It has a high antioxidant capacity due to the tocopherols found in unprocessed evening primrose oil. Tocopherols are separated in the distillation step (Jennifer et al., 2001). The reason why the evening primrose is important is the oil obtained from its seed. The main components of its oil are linoleic acid (65-80%), gamma linolenic acid (8-14%), oleic acid (6-11%) and palmitic acid (7-10%) (Gruenwald et al., 2004). Due to the gamma linolenic acid in the composition of evening primrose oil, the consumption of capsules containing oil has become widespread in recent years.

Aboveground parts tannins, organic acids; leaves contain flavonoids. In recent years, the fixed oil obtained from its seeds has become known and gained importance under the name of Evening Primrose Oil (EPO). Gamma linoleic acid, one of the fatty acids in the composition of this oil, is converted to prostaglandin E1 in the body, which is anti-inflammatory and has a dilating effect on blood vessels. In addition, fixed oil is used in atopic eczema, rheumatoid arthritis and menstrual irregularities. (Tanker et al., 2014). It has also been stated to be used in cough, asthma, and skin diseases. China leads the way in the production of Evening Primrose oil, which is obtained by using cold press, solvent extraction or supercritical carbon dioxide extraction methods (NTP, 2009; Kaya, 2010; Jennifer et al., 2001; Favati et al., 1991; Birch et al., 2001; İsmail et al., 2008; Riaz et al., 2009; Hederos and Ber, 1996; Ammar et al., 2000).

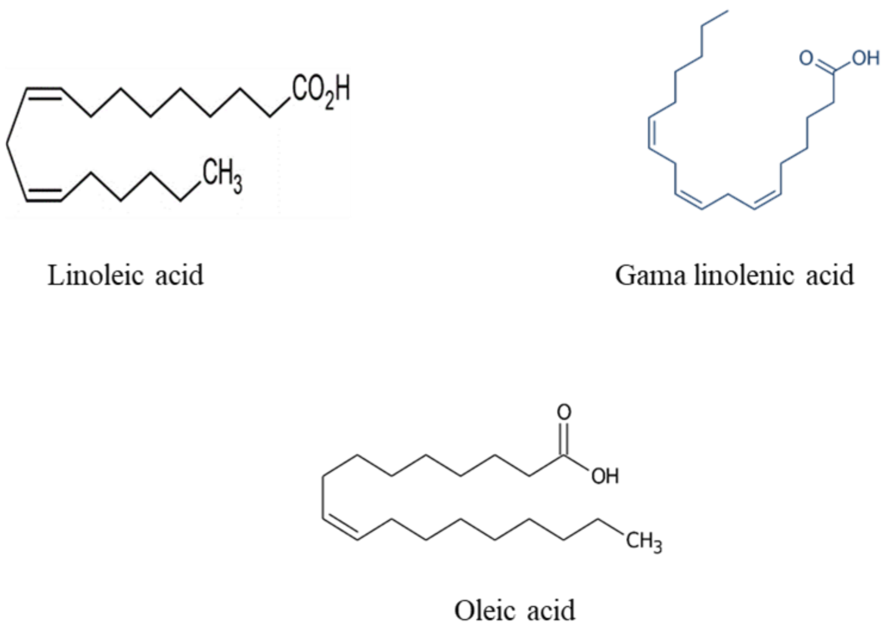


Figure 2: Fatty acids of EPO

3. MEDICINAL USES

The medicinal part of the primrose plant is the fresh plant before the beginning of flowering. Its root is consumed as a vegetable abroad and its taste is peppery (Barnes et al., 2007). However, the oil obtained from the seed has its uses. In the world and in our country in recent years, the oil of this plant is widely used, especially by women. Evening primrose seed fatty acids have an important role in the production of prostaglandins. Gamma linoleic acid, a component of evening primrose oil, is converted to dihomo gamma linoleic acid and then to prostagladin E1 by the enzyme delta-6-desaturase in vivo. Since prostaglandin E1 has a therapeutic effect, EPO has an important place in phytotherapy and traditional medicine (Gruenwald et al., 2004). The healing effect of evening primrose oil is related to the effect of its fatty acid components on the immune system. At the same time, prostaglandin and cytokine synthesis also play a role in this healing effect. (Fan and Chapkin, 1998; Vassilopoulos et al., 1997). Prostaglandins are involved in metabolizing cholesterol as well as dilating blood vessels.

Primrose Oil and Gamma Linoleic Acid

As it is known, gamma linoleic acid (GLA) is one of the essential fatty acids and is also known as Omega 6. Essential fatty acids refer to fatty acids that are not found in our body but must be taken from outside. Its chemical formula is C18:3, and its nomenclature according to IUPAC is all-cis-6,9,12-octadecatrienoic acid. Its molecular formula is $C_{18}H_{30}O_2$ and its molecular weight is 278.43 g/mol.

It is also an alpha linoleic acid isomer. GLA was first isolated from Evening Primrose seed oil. In 1919, Heiduschka and Luft obtained oil from evening primrose seeds and described another linolenic acid, which they named γ-. Later, its exact chemical structure was characterized by Riley. There are alpha and gamma forms of linolenic acid but no beta form (Yung-Sheng et al., 2001; Belch and Hill, 2000).

Apart from evening primrose seed oil, GLA is found in blackcurrant seed oil, borage oil, hemp oil, spirulina, and cyanobacteria. The reason why evening primrose seed oil has gained popularity in recent years is the GLA it contains.

Another name for evening primrose seed oil is primrose oil. Different brands offer it to consumers in capsule form as primrose oil. Primrose oil is used to alleviate premenstrual syndrome and to relieve menopausal symptoms, especially in women in our country. It is also used in diabetes, lowering cholesterol, and relieving symptoms in rheumatism and rheumatoid arthritis. Apart from these, it has been stated in recent years that oil has been used as an aid in weight loss in diets (Barnes et al., 2007). In Germany, it was determined that 500 mg Primrose oil should be in each capsule, and this ratio corresponds to 9% GLA in commercially produced capsules. In England, the amount in the capsule is adjusted according to gamma linoleic acid and it is desired to be 8% (Gruenwald et al., 2004; Briggs, 1986). Although there is not enough study in our country about the daily consumption amount, it is written as 2 capsules for adults and 1 capsule for children according to different brands. Especially companies such as solgar, balen, venatura, nature's bounty commercially sell evening primrose oil capsules in our country.

Evening primrose oil is also used topically, especially in eczema, in the world and in our country. It is also used to stop the formation of acne on the skin (Supplement Ansiklopedisi, 2022). In other sources, it has been stated that Primrose oil is also used in asthma, regulation of blood pressure, and digestive problems (NDHealthFacts, 2022).

Figure 3: Evening Primrose Oil of Some Trade Marks

CONCLUSIONS

Evening primrose oil has been reported to be used in many conditions such as mastalgia, atopic eczema, psoriasis, acne, ulceration, osteoporosis, multiple sclerosis, cancer, hypercholesterolaemia, coronary heart disease, alcoholism, alzeimer's disease, schizophrenia, chronic fatigue syndrome, asthma, diabetic neuropathy, neurodermatitis, myalgia, depression, allergy, inflammation, autoimmune disorders, obesity and hyperactivity in children (NTP, 2009). It has been popular in our country in the last 10 years and is used among the people especially for gynaecological diseases, rheumatic disorders and cholesterol lowering etc. effects. However, since this plant is not cultivated in our country, its oil is imported from abroad. In addition, it is seen that there is not enough research on the use of evening primrose in our country. For this reason, more emphasis should be placed on the commercial production of this plant and research.

REFERENCES

Akkemik, E. (2020). Çuha Çiçeği (*Oenothera biennis*) ve Tatlı Badem (*Prunus dulcis* Mill) Yağlarının Anti-enzim Aktivitelerinin Araştırılması, Avrupa Bilim ve Teknoloji Dergisi Sayı 18, S. 583-590 (In Turkısh).

Ammar, N.M., Soroor, K.H.A. & Mohammed, D.A. (2000). Impact of natural oils supplements on disease activity and antioxidant state of Egyptian patients with rheumatoid arthritis. MJIAS, 13, 161-171.

Anonymous, (2022). Evening Primrose Oil (Çuha Çiçeği Yağı) Nedir? https://supplementansiklopedisi.com/evening-primrose-oil-cuha-cicegi-yagi-nedir/ (Accessed date:06.12.2022) (In Turkısh).

Barnes, J., Anderson, A.L. & Philipson, J.D. (2007). Herbal Medicines Book, Pharmaceutical Press,710 pg. London.

Belch, J.J. & Hill, A. (2000). "Evening primrose oil and borage oil in rheumatologic conditions". Am. J. Clin. Nutr. 71 (1).

Bionity (2022). Gamma-Linolenic acid. https://www.bionity.com/en/encyclopedia/ Gamma-Linolenic_acid.html#_note-Huang/ (Accessed date: 30.12.2022).

Birch, A.E., Fenner, G.P., Watkins, R. & Boyd, L.C. (2001). Antioxidant properties of evening primrose seed extracts. J Agric Food Chem, 49, 4502- 4507.

Blumenthal, M., Brinckmann, J. & Wollschlaeger, B. (2003). The ABC Clinical Guide to Herbs. Austin. Tex. American Botanical Council.

Briggs, C.J. (1986). Evening primrose. Rev Pharm Can; 119: 249–254.

Fan, Y.Y. & Chapkin, R.S. (1998). Importance of dietary gamma-linolenic acid in human health and nutrition, J Nutr,128, 9, 1411-1414.

Favati, F., King, J.W. & Mazzati, M. (1991). Supercritical carbon dioxide extraction of evening primrose oil. JAOCS, 68, 422-427.

Gruenwald, J., Brendler, T., & Jaenıcke, C. (2004). PDR for Herbal Medicines. 3rd Ed. Montvale, NJ: Thomson Healthcare, pp. 566-569.

Hederos, C.A. & Ber, A. (1996). Epogam evening primrose oil treatment in atopic dermatitis and asthma. Arch Dis Child, 75, 494-497.

Ismail, M.F., EL-Maraghy, S.A. & Sadik, N.A.H. (2008). Study of the immunomodulatory and anti-inflammatory effects of evening primrose oil in adjuvant arthritis. AJBR, 2, 74-80.

Jennifer, M., Moody, W. & Heywood, J.S. (2001). Pollination limitation to reproductive success in the missouri evening primrose, *Oenothera macrocarpa* (Onagraceae). Am J Bot, 88, 1615-1622.

Kaya, Z. (2010). Arsenikle lipid peroksidasyon oluşturulan ratlarda çuha çiçeği yağının etkileri, EÜ SBE Yüksek lisans tezi, 64 pg. (In Turkısh).

Koç, İ. (2016). Çuha Çiçeği (*Qenothera biennis*) Yağının Diabetik Ratlarda Bazı Hormon ve Biyokimyasal Parametreler Üzerine Etkisi, YYÜ SBE Yüksek lisans tezi, 67 pg. (In Turkısh).

NDHealthFacts (2022). *Oenothera biennis*. https://www.ndhealthfacts.org/wiki/Oenothera_biennis (Accessed:06.12.2022).

NTP (2009). Chemical information review document for evening primrose oil (*Oenothera biennis* L.) [CAS No. 90028-66-3] https://ntp.niehs.nih.gov/ntp/noms/support_docs/evening_primrose_nov2009.pdf (Accessed date: 22.11.2022).

Riaz, A., Khan, R.A. & Ahmed, S.P. (2009). Assessment of anticoagulant effect of evening primrose oil. Pak J Pharm Sci, 22, 355-359.

Tanker, N., Koyuncu, M. & Coşkun, M. (2014). Farmasötik Botanik kitabı, 1-424, A.Ü. Eczacılık Fak. Yayınları No:105 (In Turkısh).

TÜBİVES (2022). *Oenothera biennis* L. http://194.27.225.161/yasin/tubives/index.php?sayfa=1&tax_id=3868 (Accessed date: 26.11.2022).

Vassilopoulos, D, Zurier, R.B., Rossetti, R.G. & Tsokos, G.C. (1997). Gamma linolenic acid and dihomo gamma linolenic acid suppress the CD3-mediated signal transduction pathway in human T cells. Clin Immunol Immunopathol, 83(3): 237-244.

Yung-Sheng, Huang. & Vincent, A. Z. (2001). Gamma-Linolenic Acid: Recent Advances in Biotechnology and Clinical Applications. AOCS Press, 259. ISBN 1893997170.

CHAPTER 5

EFFECT OF DIFFERENT SOLVENTS ON TOTAL PHENOLIC CONTENT AND ANTIOXIDANT ACTIVITY OF ELDERBERRY (*Sambucus nigra* L.) FLOWERS

Ferda SARI[1]

[1] Sivas Cumhuriyet University, Vocational School of Technical Sciences, Department of Crop and Animal Production, Sivas, Türkiye
e-mail:fesari@cumhuriyet.edu.tr, ORCID ID: 0000-0002-2249-3489

INTRODUCTION

Sambucus nigra L., which is also called elderberry and belonging to the Adoxaceae family, is a shrub-shaped (Ho et al., 2016) herb with small dark colored fruits and white flowers that matures in late summer, native to Europe, Asia and North Africa (Mandrone et al., 2014). Its creamy white flowers are used in the production of soft drinks in England, Sweden and Denmark with their distinctive scent (Ho et al., 2016). The productive parts of elderberry are the fruit and flower extract (Młynarczyk et al., 2018). Elderberry (*Sambucus nigra* L.) is a rich source of biologically active polyphenols, especially phenolic acids, flavonols and anthocyanins (Sidor and Gramza-Michałowska, 2015). These polyphenols are found in the leaves, fruits and flowers of elderberry (Veberic vd. 2009, Mandrone vd. 2014, Sidor and Gramza-Michałowska 2015). Therefore, a diet containing elderberry fruit, leaf and flower constitutes a potential protective agent against the negative effects of oxidative stress in the human body (Sidor and Gramza-Michałowska, 2015). Elderberry flowers are used in traditional medicine to treat inflammation, joint pains, skin disorders, diuretic, colds, fever and other respiratory disturbances. It has been stated in studies that elderberry flowers have pharmacological effects such as blood sugar regulator, diuretic, antibacterial, antifungal, antiviral, immunomodulation, anti-inflammatory, antioxidative (Ho et al., 2016).

Phenolic compounds are secondary metabolites in plants that can inhibit the reactive free radicals produced by lipid oxidation and chelate redox active metal ions (Rezaie et al., 2015). Phenolic compounds are the main antioxidant components and their total contents are directly proportional to their antioxidant activity (Do et al., 2014).

Oxidation processes are very important for the living organism. The uncontrolled production of free oxygen radicals and unbalanced mechanism of antioxidant protection cause the onset of many diseases and accelerate aging (Dawidowicz et al., 2006). Antioxidants are considered protective agents that reduce oxidative damage to the human body (Dawidowicz et al., 2006; Do et al., 2014). In recent years, many plants, especially medicinal and aromatic plants, have been intensively studied due to their antioxidant activities. It is believed that the intake of food rich in natural antioxidants is associated with the prevention of degenerative diseases due to oxidative stress, especially cardiovascular diseases and cancer (Pe´rez-Jime´nez et al., 2008; Rezaie et al., 2014). Studies are being carried out on medicinal and aromatic or derived antioxidants from other plants to develop natural antioxidant formulations to replace synthetic antioxidants (Rezaie et al., 2014), that are suspected to have potentially toxic effects for food, cosmetics and other applications (Miliauskas et al., 2004).

The solubility of phenolic compounds are affected by many factors such as the type of solvent used, the degree of polymerization of phenolic compounds, interactions between phenolics and other plant components, and the structure of insoluble complexes. Therefore, there is no universal method suitable for the extraction of all plant phenolics (Rezaie et al., 2015).

There is no detailed study on the effect of different solvents on TFC and antioxidant activity of elderberry flower (*S. nigra* L.). Therefore, this study was planned to determine the effects of different extraction solvents on the total phenolic content and antioxidant activity of elderberry flower (*S. nigra* L.).

1. MATERIALS AND METHODS

1.1. Material

Elderberry (*S.nigra* L.) flowers were collected at Sivas Cumhuriyet University Campus. The collected elderberry flowers were dried in the shade. Then, after the samples were ground in a coffee grinder (SİNBO), they were passed through sieves (RETSCH) with 300 µm and 150 µm aperture sizes, and samples in this range were used in the analyses. The samples stored at + 4^{o}C before experiments.

1.2. Chemicals

The solvents used in the extraction in the study acetone, methanol and ethanol were purchased from Riedel-de Haën. Folin–Ciocalteu’s reagent and sodium carbonate were purchased from Merck (Darmstadt-Germany), DPPH (2,2-diphenyl-1-icryhydrazil) from Sigma Chemical Co. (St. Louis, MO, USA).

1.3. Extraction of Samples

Water and three different concentrations (50%, 80% and 80%) of methanol, ethanol and acetone were used in the extraction of the samples. 0.2 g sample was extracted with 10 ml of distilled water and solvents for 1 h on a horizontal shaker (250 rpm). After extraction, the samples were filtered through filter paper. Extraction was carried out in triplicate. The extracts were diluted five times with distilled water to obtain appropriate absorbance values. extracts were stored at -18 °C until analysis.

1.4. Total Phenolic Content

The total phenolic content (TPC) of the samples was determined using the ISO (14502-:2005) method. 0.5 ml of extract was mixed with 2.5 ml of Folin-Ciocalteu (10%, v/v) reagent. 0.5 mL of extract or pure water (as a blank) was mixed with 2.5 mL of Folin-Ciocalteu rea-gent (10%, v/v). 2 mL sodium carbonate solution (7.5% w/v) is added to the mixture after 5 min and shaken thoroughly. The mixture was allowed to stand for 60 min and blue color formed was measured at 765 nm against blank using a spectrophotometer (Optima SP3000). The results were calculated from the regression equation of the calibration curve [y(absorbance)=0.0116 x (gallic acid concentration), R^2 =0.999] obtained with the gallic acid working solutions prepared at different concentrations (5-50 µg/ml) and expressed as mg Gallic acid equivalent (GAE)/g dry matter (DM).

1.5. Antioxidant Activity

Antioxidant activity was determined by using DPPH method of Turkmen et al., 2009). In this method, 50 µl of extract (2 mg/ml) was mixed with 1950 µl of DPPH radical ($6x10^{-5}$ M, prepared in methanol).

In the control sample, distilled water was used instead of the extract. The mixture was vortex-mixed and let to stand at room temperature in the dark for 60 min. After absorbance at 517 nm was measured using a spectrophotometer using methanol as a blank. Antioxidant activity (inhibition %) was determined by the following equation (Yen and Duh, 1994).

$$Antioxidant\ activity\ (\text{Inhibition }\%) = \frac{Abs_{Control} - Abs_{\text{Sample}}}{Abs_{Control}} x100$$

Abs control is the absorbance of the DPPH solution without sample and *Abs sample* is the absorbance of the test sample.

1.6. Statistical Analysis

Statistical analyzes were performed with variance analysis using one-way ANOVA in the MINITAB 18 program. Results are given as the mean ± standard deviation of triplicate measurements. Means were compared by using Tukey’s multiple comparison test ($p<0.05$).

2. RESULTS AND DISCUSSION

2.1. Total Phenolic Content

TPC of elderberry flowers is examined and presented in Table 1. The results indicated that TPC of *S. nigra* L. varied in the range of 3.31-59.71 mg GAE /g DM. Mikulic-Petkovsek et al., (2016) found the TPC of 40.14 mg GAE /g DM in elderberry flowers after extraction with methanol containing 3% (v/v) formic acid in an ultrasonic bath for 1 hour. They found it higher than the amount of TPC in this study (32.03 mg GAE /g DM). The TPC found by the researchers is higher than the TPC (32.03 mg GAE /g DM) obtained from 100 % methanol extraction in this study.

Table 1: Effect of different solvents on TPC (mg GAE/g DM) and antioxidant activity (inhibition %) of elderberry flowers

Solvents	TFC	Inhibition %
Water	35.54 ± 0.29	47.25 ± 0.15
Methanol		
50 %	51.89 ± 1.47[a]	74.44 ± 0.14[a]
80 %	48.43 ± 0.17[b]	73.55 ± 0.15[b]
100 %	32.03 ± 1.46[c]	35.51 ± 0.39[c]
Ethanol		
50 %	53.58 ± 0.37[a]	78.60 ± 1.04[a]
80 %	47.68 ± 0.34[b]	71.57 ± 0.48[b]
100 %	9.83 ± 0.17[c]	31.65 ± 1.27[c]
Acetone		
50 %	59.71 ± 0.39[a]	85.74 ± 0.45[a]
80 %	55.40 ± 0.35[b]	80.88 ± 0.52[b]
100 %	3.31 ± 0.47[c]	24.47 ± 0.76[c]

*: For each organic solvent, values in the same column bearing different letters are significantly different at $p<0.05$.

This difference is thought to be due to the formic acid added to the methanol solution and the extraction method. Viapiana and Wesolowski (2017) found the TPC of 15.23-35.57 mg GAE /g DM after 15 minutes extraction with boiling water in elderberry flowers from different regions. In this study, the of TPC (35.54 mg GAE / g DM) found as a result of the extraction with water is among these values. Pavlović et al., (2013) determined the of TPC after the extraction with water at 95 ^{o}C for 15 minutes, as 42.67 mg GAE/g DM, higher than the extraction with water in this study. The reason for this difference is thought to be due to the extraction temperature and time. The temperature of the water used in the extraction is very effective in the extraction of phenolic compounds (Yang et al., 2007).

Extracting solvent significantly affected TPC of elderberry flowers extracts ($p<0.05$). All extracts prepared with 50% solvents contained highest level of TPC and followed by those with 80% and 100% solvents, respectively. The highest TPC (59.71 mg GAE /g DM) was found in 50% acetone extract. The lowest amounts of TPC were obtained with 100% acetone (3.31 mg GAE /g DM) and 100% ethanol (9.83 mg GAE /g DM) extract, respectively. The results show that with the increase in the polarity of the solvent used, more TPC is obtained. These results are in agreement with studies (Türkmen et al., 2006; Sultana et al., 2009; Bhebbe et al., 2016) showing that the aqueous forms of the solutions used in the extraction extract higher TPC.

In general, the extractability of phenolic compounds depends on the solvents used in the extraction, the solute-solvent ratio, and the polarity of the solvent (Nguyen et al., 2022). In addition, the solubility of phenolic compounds in extraction solvents is also effective on the recovery of certain phenolic compounds. Extraction efficiency also depends on the polarity of certain phenolic compounds. Not all phenolic compounds can be extracted efficiently with organic solvents. The solubility trend is associated with the stereochemistry (the polar and the nonpolar fragment within their molecules) of phenolics and the intermolecular strength of hydrogen bonds that occur between phenolic compounds and solvents (Lopez-Perea et al., 2019). Soluble phenolic compounds are mainly distributed in cell vacuoles, while most lignin, flavonoids and insoluble phenolic compounds are found in the cell wall together with proteins and polysaccharides throughthe hydrogen bond and hydrophobic bond (Fan et al., 2015). The addition of water in solvents generates a medium polarity that facilitates the extraction (Lopez-Perea et al., 2019). Low concentration of organic solvents can reach the cells, but high concentration causes protein denaturation, preventing the dissolution of polyphenols and thus the passage of phenolic substances into the extraction solution (Chen et al. 2013).

2.2. Antioxidant Activity

DPPH is a stable organic nitrogen radical (Saha et al., 2016). DPPH react with phenols through two different mechanismis. The first is the direct separation of the H atom from the phenol, and the second is by electron transfer. Both of these pathways depends on the nature of the solvent and/or the redox potential (Saha et al., 2016; Vladimir-Knežević et al., 2011). Antioxidants that react with DPPH neutralize the free radical (Saha et al., 2016). The color of the reaction mixture changes from purple to yellow. The degree of the discoloration measures the potential of antioxidant activity (Vladimir-Knežević et al., 2011). Phenolic compounds are strong hydrogen donors to the DPPH radical due to their ideal chemical structure (Von Gadov and Hansman, 1997; Rice-Evans and Paganga, 1997). The DPPH method is widely used to determine the antioxidant activity of plant extracts (Türkmen et al., 2006; Do et al., 2014; Saha et al., 2017; Nguyen et al., 2020). Antioxidant activity of elderberry flowers is examined and presented in Table 1. The results indicated that antioxidant activity of elderberry flowers varied in the range of 24.47%-85.74%. Extracting solvent significantly affected antioxidant activity of elderberry flowers extracts ($p<0.05$). All extracts prepared with 50% solvents contained highest level of antioxidant activity and followed by those with 80% and 100% solvents, respectively. The highest antioxidant activity (85.74%) was found in 50% acetone extract. The lowest amounts of antioxidant activity were obtained with 100% acetone (24.47%) and 100% ethanol (31.65%) extract, respectively. Antioxidant activities of samples with high TPC were also high (Table 1). It has also been shown in previous studies that there is a strong relationship between TPC and antioxidant activity (Velioglu et al. 1998; Türkmen et al., 2006; Kim and Chin 2016). A high correlation was found between TPC and antioxidant activity in elderberry flowers (Figure 1). This has proven that phenolic compounds contribute to antioxidant activity.

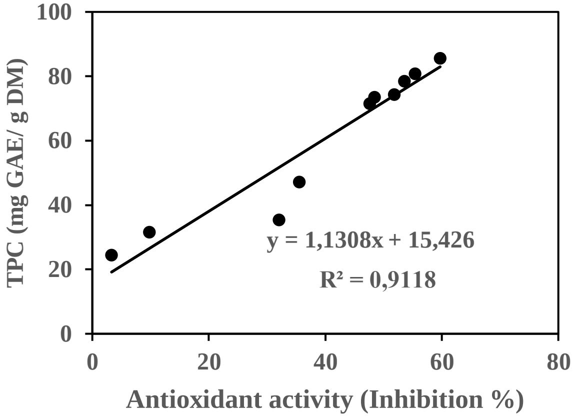


Figure 1: Correlation Between TPC Substance and Antioxidant Activity in Elderberry Flowers (*Sambucus nigra* L.)

CONCLUSIONS

In this study, the effects of different solvents on TPC and antioxidant activity of elderberry flowers (*Sambucus nigra* L.) were investigated. Extraction solvent significantly affected TPC and antioxidant activity of elderberry flowers extracts. Rankings in the TPC of extracts varied depending on the concentration of solvent. The most effective solvents for TPC extraction were 50% extracts of all solvents. These extracts also showed the highest antioxidant activity. A high correlation was obtained between the TPC of elderberry flowers extracts and their antioxidant activities. This study showed that elderberry flowers is an important source of phytochemicals with natural antioxidant properties when extracted with a suitable solvent. This study showed that elderberry flowers are an important source of phytochemicals with natural antioxidant properties when extracted with a suitable solvent.

REFERENCES

Bhebhe, M., Füller, T. N., Chipurura, B., & Muchuweti, M. (2016). Effect of solvent type on total phenolic content and free radical scavenging activity of black tea and herbal infusions. Food Analytical Methods, 9(4): 1060-1067.

Chen, X. X., Wu, X. B., Chai, W. M., Feng, H. L., Shi, Y., Zhou, H. T., & Chen, Q. X. (2013). Optimization of extraction of phenolics from leaves of *Ficus virens*. Journal of Zhejiang university science B, 14(10): 903-915.

Dawidowicz, A. L., Wianowska, D., & Baraniak, B. (2006). The antioxidant properties of alcoholic extracts from *Sambucus nigra* L.(antioxidant properties of extracts). LWT-Food Science and Technology, 39(3): 308-315.

Do, Q. D., Angkawijaya, A. E., Tran-Nguyen, P. L., Huynh, L. H., Soetaredjo, F. E., Ismadji, S., & Ju, Y. H. (2014). Effect of extraction solvent on total phenol content, total flavonoid content, and antioxidant activity of *Limnophila aromatica*. Journal of Food and Drug Analysis, 22(3): 296-302.

Fan, R., Yuan, F., Wang, N., Gao, Y., & Huang, Y. (2015). Extraction and analysis of antioxidant compounds from the residues of *Asparagus officinalis* L. Journal of Food Science and Technology, 52(5): 2690-2700.

Ho, G. T. T., Zou, Y. F., Aslaksen, T. H., Wangensteen, H., & Barsett, H. (2016). Structural characterization of bioactive pectic polysaccharides from elderflowers (Sambuci flos). Carbohydrate Polymers, 135: 128-137.

Kim, H.S. and Chin, K.B., 2016. Evaluation of different drying temperatures on physico-chemical and antioxidant properties of water-soluble tomato powders and on their use in pork patties. Journal of the Science of Food and Agriculture, 96(3): 742-750.

López-Perea, P., Guzmán-Ortiz, F. A., Román-Gutiérrez, A. D., Castro-Rosas, J., Gómez-Aldapa, C. A., Rodríguez-Marín, M. L., ... & Torruco-Uco, J. G. (2019). Bioactive compounds and antioxidant activity of wheat bran and barley husk in the extracts with different polarity. International Journal of Food Properties, 22(1): 646-658.

Mandrone, M., Lorenzi, B., Maggio, A., La Mantia, T., Scordino, M., Bruno, M., & Poli, F. (2014). Polyphenols pattern and correlation with antioxidant activities of berries extracts from four different populations of Sicilian Sambucus nigra L. Natural Product Research, 28(16): 1246-1253.

Młynarczyk, K., Walkowiak-Tomczak, D., & Łysiak, G. P. (2018). Bioactive properties of Sambucus nigra L. as a functional ingredient for food and pharmaceutical industry. Journal of Functional Foods, 40: 377-390.

Mikulic-Petkovsek, M., Ivancic, A., Schmitzer, V., Veberic, R., & Stampar, F. (2016). Comparison of major taste compounds and antioxidative properties of fruits and flowers of different Sambucus species and interspecific hybrids. Food Chemistry, 200: 134-140.

Miliauskas G, Venskutonis PR, & Van Beek TA. (2004). Screening of radical scavenging activity of some medicinal and aromatic plant extracts. Food Chem, 85:231e7.

Nguyen, N. V., Duong, N. T., Nguyen, K. N. H., Bui, N. T., Pham, T. L., Nguyen, K. T., ... & Kim, K. H. (2022). Effect of extraction solvent on total phenol, flavonoid content, and antioxidant activity of *Avicennia officinalis*. Biointerface Research in Applied Chemistry, 12(2): 2678-2690.

Pavlović, J.N.V.A.N., Tošıć, S.S.M.S.B., Kalıčanın, G.S.S.B.M., Stojkovıć, D.M.S.M.B., & Brcanovıć, M.N.M.J.M. (2013). Evaluation of individual phenolic compounds and antioxidant properties of black, green, herbal and fruit tea infusions consumed in Serbia: spectrophotometrical and electrochemical approaches. Journal of Food and Nutrition Research, 52(1): 12-24.

Pérez-Jiménez, J., Arranz, S., Tabernero, M., Díaz-Rubio, M. E., Serrano, J., Goñi, I., & Saura-Calixto, F. (2008). Updated methodology to determine antioxidant capacity in plant foods, oils and beverages: Extraction, measurement and expression of results. Food Research International, 41(3): 274-285.

Rezaie, M., Farhoosh, R., Iranshahi, M., Sharif, A., & Golmohamadzadeh, S. (2015). Ultrasonic-assisted extraction of antioxidative compounds from Bene

(*Pistacia atlantica* subsp. *mutica*) hull using various solvents of different physicochemical properties. Food Chemistry, 173: 577-583.

Rice-Evans, C. A., Miller, N. J., & Paganga, G. (1997). Antioxidant properties of phenolic compounds. Trends in Plant Science, 2: 152–159.

Saha, S., Barua, B., & Sikdar, D. (2017). Phytochemical screening, phenolic content and antioxidant activity of wild date palm (*Phoenix sylvestris* Roxb.) fruit extracted with different solvents. International Food Research Journal, 24(6).

Sidor, A., & Gramza-Michałowska, A. (2015). Advanced research on the antioxidant and health benefit of elderberry (*Sambucus nigra*) in food–a review. Journal of Functional Foods, 18: 941-958.

Sultana, B., Anwar, F., & Ashraf, M. (2009). Effect of extraction solvent/technique on the antioxidant activity of selected medicinal plant extracts. Molecules, 14(6): 2167-2180.

Türkmen Erol N., Sari F., Çalikoğlu E. and Velioğlu Y.S., 2009. Green and roasted mate: Phenolic profile and antioxidant activity. Turkish Journal of Agriculture and Forestry, 33: 353–362.

Turkmen, N., Sari, F., & Velioglu, Y. S. (2006). Effects of extraction solvents on concentration and antioxidant activity of black and black mate tea polyphenols determined by ferrous tartrate and Folin–Ciocalteu methods. Food chemistry, 99(4): 835-841.

Veberic, R., Jakopic, J., Stampar, F., & Schmitzer, V. (2009). European elderberry (*Sambucus nigra* L.) rich in sugars, organic acids, anthocyanins and selected polyphenols. Food Chemistry, 114(2): 511-515.

Velioglu, Y.S., Mazza, G., Gao, L. & Oomah, B.D., 1998. Antioxidant activity and total phenolics in selected fruits, vegetables, and grain products. Journal of Agricultural and Food Chemistry, 46(10): 4113-4117.

Viapiana, A., & Wesolowski, M. (2017). The phenolic contents and antioxidant activities of infusions of *Sambucus nigra* L. Plant foods for human nutrition, 72(1): 82-87.

Vladimir-Knežević, S., Blažeković, B., Štefan, M. B., Alegro, A., Kőszegi, T., & Petrik, J. (2011). Antioxidant activities and polyphenolic contents of three selected Micromeria species from Croatia. Molecules, 16(2): 1454-1470.

Von Gadow, A., Joubert, E., & Hansmann, C. F. (1997). Comparison of the antioxidant activity of rooibos tea (Aspalathus linearis) with green, oolong and black tea. Food Chemistry, 60: 73–77.

Yang, D. J., Hwang, L. S., & Lin, J. T. (2007). Effects of different steeping methods and storage on caffeine, catechins and gallic acid in bag tea infusions. Journal of Chromatography A, 1156(1-2): 312-320.

Yen, G. C., & Duh, P. D. (1994). Scavenging effect of methanolic extracts of peanut hulls on free-radical and active oxygen species. Journal of Agricultural and Food Chemistry, 42: 629-632.

CHAPTER 6

DISTRIBUTION OF *ALCHEMILLA* SPECIES IN RIZE AND THEIR USAGE IN FOLK MEDICINE

Haydar KÜPLEMEZ[1]
Aysel ÖZCAN AYKUTLU[2]
Emine YURTERİ[3]
Fatih SEYİS[4]

[1] Recep Tayyip Erdogan University, Faculty of Agriculture, Department of Field Crops, Rize, Türkiye. e-mail; haydar.kuplemez@erdogan.edu.tr,
ORCHID ID: 0000-0003-4094-1318
[2] Recep Tayyip Erdogan University, Faculty of Agriculture, Department of Field Crops, Rize, Türkiye. e-mail: aysel.ozcan@erdogan.edu.tr,
ORCHID ID: 0000-0001-5210-7617,
[3] Recep Tayyip Erdogan University, Faculty of Agriculture, Department of Field Crops, Rize, Türkiye. e-mail: emine.yurteri@ erdogan.edu.tr,
ORCHID ID: 0000-0002-3770-2714
[4] Recep Tayyip Erdogan University, Faculty of Agriculture, Department of Field Crops, Rize, Türkiye, fatih.seyis@erdogan.edu.tr,
ORCHID ID: 000-0001-9714-370X

INTRODUCTION

Lady's mantle (*Alchemilla* L.) is a perennial herbaceous plant belonging to the Rosaceae family, which contains medicinally important species. It has the feature of being one of the richest genera of the Rosaceae family, as it has close to 1000 species in the world and 74 species in Türkiye. The genus *Alchemilla,* which is represented by more than 1000 species, generally shows a holarctic distribution, but is found in the regions of Madagascar, South India, Ceylon and Java, from the Cape of Good Hope in Ethiopia to the East African Mountains (Izmailow, 1981). The Eurasian taxa of *Alchemilla* species were divided into two sections by Rothmaler. These sections are *Pentaphyllon Rothm*. and *Brevicaulon Rothm*. According to the same researcher, some of their taxa are widely distributed, while others are endemic (Rothmaler, 1937). According to the records in the flora of Türkiye, all of the *Alchemilla* species distributed in Türkiye belong to the *Alchemilla* section. This section is divided into 3 subsections (*Chirophyllum Rothm*, *Heliodrosium Rothm* and *Calycanthum Rothm*) and 6 series (*Saxatiles Bus, Sericeae Bus*, *Pubescentes Bus, Vulgares Bus*, *Elatae Rothmn* and *Calycinae Bus*) (Hatırlıoğlu and Beyazoğlu, 1997).

There are also species that can grow naturally in the Flora of Türkiye. Some of these are endemic for our country (Murathan, 2018). Lady's mantles genera (*Alchemilla* L.) can be easily distinguished from other morphologically closely related genera (Pawlowski and Walters, 1972; Türk et al., 2011). On the other hand, Lady's mantle species (*Alchemilla* spp.) are very similar to each other and cannot be distinguished from each other without microscopic identification (Türk et al., 2011). It has been reported that many species in Türkiye are native to Türkiye and they are mostly found in the Eastern Black Sea Region. These species have been named by local people as aslanpençesi, aslanayağı, fındıkotu, yeditepe and dokuztepe (Baytop, 1997; Türk et al., 2011). In the flora of Türkiye, the genus Lady's mantle (*Alchemilla* L.) is represented by approximately 50 species (Pawlowski and Walters, 1972; Hatırlıoğlu-Ayaz and Inceer, 2009). Most of them are in the North-Eastern Anatolia Region (Hatırlıoğlu-Ayaz and Inceer, 2009). In Rize province, the most common *A. sericea*, *A. rizensis*, *A. erytropoda*, *A.pseudocartalinica*, *A. transcaucasica*, A. *retinervis* and *A. ellenbergiana* species are found (Kalheber, 1994). There are not enough chemical characterization studies on our region's flora about the *Alchemilla* species, which are used by the people of the region for their diuretic, antiseptic, wound healing properties. There are still species in these areas that have not yet been identified.

1. GENERAL CHARACTERISTICS OF *Alchemilla* SPECIES

The genus *Alchemilla* L., is a perennial herbaceous plant, has woody rhizomes. The leaf feature consists of palmate or lobed structures. According to the region and conditions, there may be differences in leaf shape and feathering in growth after shearing and grazing. Therefore, during the diagnosis, the angle or space between the mature and basal leaves for the leaf and the two basal lobes for the sinus is evaluated. The inflorescence is compound chyme. Flower rings are 4-5 pieces. In the form of hypanthium test; is urceolate. Epicalyx is present, stamens have form of 4-5. Fruit single, achene, completely or partially covered by thin, dry hypanthium. Most of the species grown in Europe reproduce asexually. Pollen is largely undeveloped (Davis, 1982).

Figure 1: General view of *Alchemilla* spp.

Alchemilla SPECIES IN RIZE FLORA

Rize is one of the provinces with the richest plant species diversity in the Eastern Black Sea Region. Guner et al. (1987) reported that there are a total of 1430 plant species diversity in Rize, 15 of which are new records for the flora of Türkiye, 4 plant taxa are new to the scientific world, and 110 taxa are endemic plants of Türkiye. As stated by the researchers, the Eastern Black Sea Region has a very important place in terms of plant species. The presence of medicinal and high commercial value species among these plants requires attention to the region's plants (Yurteri, 2018).

The fact that almost every region of Türkiye has different climatic conditions causes the diversity of medicinal and aromatic plants. The climatic features of Rize province, which is located on the borders of the Eastern Black Sea Region, have led to the formation of a flora rich in medicinal plants. It has been reported that a significant contribution can be made to the Turkish economy by evaluating this plant richness. As a result of the studies to be carried out in the region, the determination of the species of medicinal plants with economic value is an important issue. Raw materials or synthesis products obtained from these plants can have significant returns in the domestic and foreign markets (Gül, 2014).

Lady's mantle species (*Alchemilla* spp.) establishes a natural dominance in Türkiye and the Eastern Black Sea Region. As seen in Table 1, 39.8% of the 74 known species grow spontaneously in Rize and 41.37% of these species are endemic. There are 29 species in Rize; As seen in Table 1; *A. sericea* Willd., *A. rizensis* B. Pawl., *A. caucasica* Buser, *A. erythropoda* Juz., A. aff. surculosa, A. aff. plicatissima Fröhner, *A. stevenii* Buser, *A. compactilis* Juz., *A. compactilis* Juz., *A. pseudocartalinica* Juz., *A. ziganadagensis*, *A. hirtipedicellata* Juz, *A. mollis* (Buser) Rothm, *A. aff. oriturcica*, *A. barbatiflora* Juz., *A. stricta* Rothm, *A. transcaucasica* Rothm, *A. retinervis* Buser, *A. ellenbergiana* Rothm., *A. hemsinica* Kalheber, *A. elevitensis* Kalheber, *A. cimilensis* Kalheber, A.Pawl.sis B., *A. ikizdereensis* Kalheber, *A. kackarensis* Kalheber, *A. ancerensis* Kalheber, *A. venosa* Juz., *A. chlorosericea* (Buser) Juz. apud Grossh., *A. ayderensis* Kalheber and *A. ovitensis*.

While 5 of the 12 species (*A. rizensis* B. Pawl., *A. ziganadagensis*, *A. aff. oriturcica*, *A. ayderensis* Kalheber and *A. ovitensis*) are endemic plants of Rize are in the danger class in nature.

Table 1: The Used Parts of Alchemilla Species Found in the Rize Flora, Usage and Purpose of Usage

No	Taxon	Danger Situation	Endemism	Parts used and method of use	Purpose of usage
1	*A.* aff. *oriturcica*	VU	Endemic	Herba- Tea	Painkiller- Inflammation Remover, Diuretic
2	*A. rizensis* B. Pawl.	VU	Endemic	Herba- Tea	Painkiller- Inflammation Remover, Diuretic
3	*A. ziganadagensis*	VU	Endemic	Herba- Tea	Painkiller- Inflammation Remover, Diuretic
4	*A. ayderensis* Kalheber	VU	Endemic	Herba- Tea	Painkiller- Inflammation Remover, Diuretic
5	*A. ovitensis*	VU	Endemic	Herba- Tea	Painkiller- Inflammation Remover, Diuretic
6	*A. hemsinica* Kalheber	EN	Endemic	Herba- Tea	Painkiller- Inflammation Remover, Diuretic
7	*A. elevitensis* Kalheber	EN	Endemic	Herba- Tea	Painkiller- Inflammation Remover, Diuretic
8	*A. cimilensis*Kalheber	EN	Endemic	Herba- Tea	Painkiller- Inflammation Remover, Diuretic
9	*A.cimilensis* B.Pawl.	EN	Endemic	Herba- Tea	Painkiller- Inflammation Remover, Diuretic
10	*A. ikizdereensis* Kalheber	EN	Endemic	Herba- Tea	Painkiller- Inflammation Remover, Diuretic
11	*A. kackarensis* Kalheber	EN	Endemic	Herba- Tea	Painkiller- Inflammation Remover, Diuretic
12	*A. ancerensis* Kalheber	EN	Endemic	Herba- Tea	Painkiller- Inflammation Remover, Diuretic
13	*A. sericea* Willd.			Herba, Leaf, Tea, Infusion	Painkiller- Anti-Inflammation, Diuretic, Tonic, Food
14	*A. caucasica* Buser			Leaf , Tea, infusion	Painkiller- Anti-Inflammation, Diuretic, Tonic, Food
15	*A. erythropoda* Juz.			Leaf , Tea, infusion	Ornamental plant, Painkiller, Diuretic, Curative for gynecological diseases
16	*A.* aff. *surculosa*			Herba, Leaf, Tea, Infusion	Menstrual pain reliever, anti-inflammatory,
17	*A.* aff. *plicatissima* Fröhner			Herba- Tea	Painkiller, Relief of Wound Fever, Relief of menstrual pain

Table 1: (Continued)

No	Taxon	Danger Situation	Endemism	Parts used and method of use	Purpose of usage
18	*A. stevenii* Buser			Herba- Tea	Treatment of intestinal and stomach ailments
19	*A. compactilis* Juz.			Root-leaf, infusion	Tonic, relief of menstrual pain
20	*A. pseudocartalinica* Juz.				No literature
21	*A. hirtipedicellata* Juz.				No literature
22	*A. mollis* (Buser) Rothm.			Herba- Tea	Painkiller, Relief of Wound Fever, Relief of menstrual pain
23	*A. barbatiflora* Juz.				No literature
24	*A. stricta* Rothm.			Herba-Root-Tea, infusion	Treatment of intestinal and stomach ailments
25	*A. transcaucasica* Rothm.			Herba-Root-Tea, infusion	Treatment of intestinal and stomach ailments
26	*A. retinervis* Buser			Herba-Infusion	Ornamental plant, Tonic
27	*A. ellenbergiana* Rothm.				No literature
28	*A. venosa* Juz.			Herba-Root-Tea, infusion	Menstrual pain reliever, anti-inflammatory,
29	*A. chlorosericea* (Buser) Juz. apud Grossh.				No literature

***EN:**Endangered), ***VU**:Vulnerable.
Source: (Davis, 1982; Ekim, et al., 2000; Falchero, et al., 2008; ESCOP Monographs, et al., 2013).

2. CHEMICAL CONTENT OF *Alchemilla* SPECIES

The main active ingredients in the drug of the Alchemilla plant; Orientin (luteolin-8-O-glucoside), vitexin (Apigenin-8-O-glucoside), Rutin (quurcetin-3-O-rutinoside), Hyperoside (quercetin-3-O-galactoside), Isoquercetin (quercetin-3- rammoside), micuelianine (quercetin-3-O-β-D-glucorinide), trifolin (kaempferol-3-O-β-D-glucoside) and Guaiaverin (quercetin-3-O- β-D-arabinoside). At the beginning of flowering, the plant is collected with all its parts or only as leaves, dried and used in this way (Kaya et al., 2012).

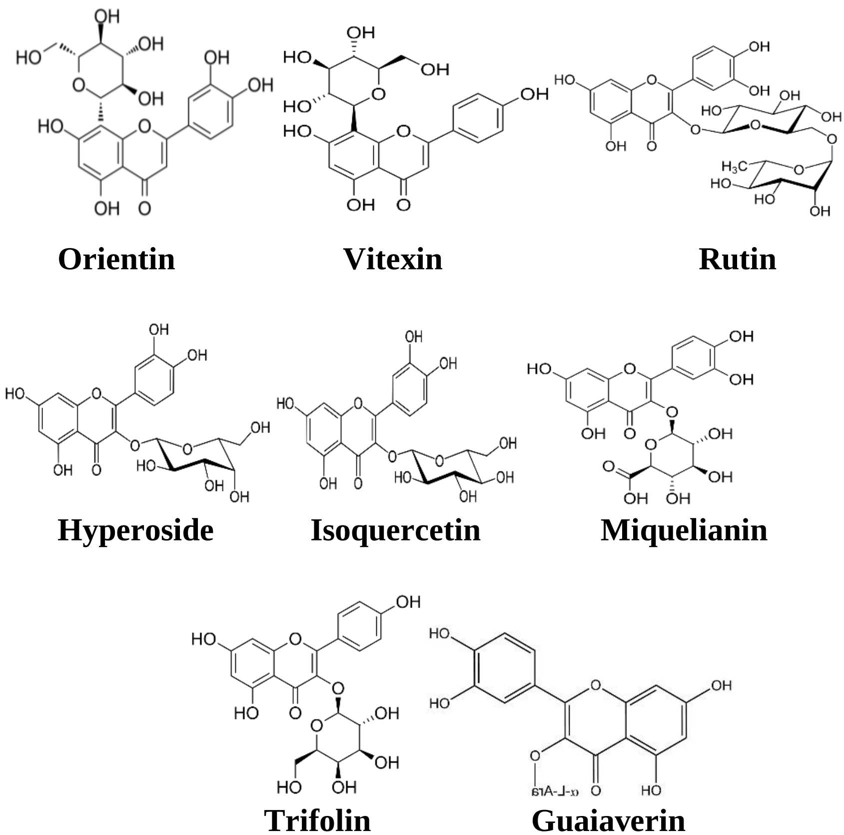


Figure 2: Chemical structures of phenolic compounds in *Alchemilla* spp.

It is one of the plants defined in the European Pharmacopoeia. The use of the plant in non-specific diarrhea has been approved by Commission E under the Ministry of Health in Germany (Commission E, 1986). Its use in nonspecific diarrhea, gastrointestinal complaints and dysmenorrhea has been approved in ESCOP monographs based on clinical studies and long-term use (ESCOP Monographs, 2013).

Bioactivity studies on *Alchemilla* species show that plants have angioprotective, anticarcinogenic, antioxidant, wound-healing, antimicrobial, antiviral activities (Condrat et al., 2009; Kupeli et al., 2015). The aerial parts of *Alchemilla* species used as drugs have a rich content in terms of phytochemical compounds. Phytochemical studies show that *Alchemilla* species contain tannin, flavonoside, proanthocyanidin, triterpene and phenolic compounds (Condrat et al., 2009; Makau et al., 2013; Kupeli et al., 2015).

The commercial preparation known as Herba Alchemilla containing *A.mollis* is used in Europe as an astringent, diuretic, antispasmodic in traditional treatment and in the treatment of severe menstruation and wound treatment. β-phenylpyruvic acid, salicylic acid, trans-cinnamic acid, vanillic acid, gentisic acid, protocatechic acid, syringic acid, p-coumaric acid, caffeic acid, sinapic acid in both bound and free form; benzoic acid, m-hydroxybenzoic acid, p-hydroxybenzoic acid, β-resorsilicic acid, mandelic acid, gallic acid, 3,4,5-trimethoxymandelic acid were detected only in bound form (Trendafilova et al., 2011; Nikolova et al., 2012; Makau et al., 2013).

As major components in the essential oil composition of the above-ground parts of *A. alpina* L. em. Buser; α-terpineol, linalool, (Z)-3-hexenol, 2-phenylethanol, benzyl alcohol, nonanal, dillapiol, β-pinene were detected (Falchero et al.,2008).). In the essential oil composition of Rothm *A. xanthochlora*. cis-3-hexenol, linalool, oct-1-en-3-ol, nonanal, mirtenol, hexadecanoic acid, cis-3-hexenyl acetate and α-terpineol compounds were found as components (Falchero et al., 2009). From the above-ground parts of the plant *A. faeroensis*; ursolic acid, 2α-hydroxyursolic acid, 2α,19α-dihydroxyursolic acid (tormentic acid), 2α,3α,19α-trihydroxyurs-12-en-28-oic acid (euscopic acid), and oleanolic acid have been isolated (Olafsdottir et al., 2001).

Figure 3: *A. mollis (*Buser*)* Rothm. and *A. caucasica* Buser

3. THE IMPORTANCE OF LADY'S MANTLE (*Alchemilla* spp.) SPECIES IN FOLK MEDICINE

Lady's mantle (*Alchemilla* spp.) species are plants that are widely used for medicinal purposes among the people. In addition to its microbial activities, dermatologically they contain substances that are effective in the treatment of inflamed tissues, healing of eczema and wounds, they are defined as pharmacopoeia. Due to the flavonoid content, its use in medicine has become widespread. Lady's mantle is used in folk medicine in the treatment of gynecological diseases. It has been named after the Virgin Mary since the beginning of Christianity. In addition to its menstrual regulator, uterine discharge, treatment of uterine complaints and its relaxing effects in menopause, when used with yarrow during the transition to puberty, it also regulates menstrual irregularity (Gruenwald et al. 2004; Eggensperger et al., 2006; Murathan, 2018).

Moreover, it is used in the treatment of abscessed wounds, boils and heart diseases. Due to its analgesic, therapeutic and sedative properties, Lady's mantle is effective in treatment of many painful diseases. It is also used in the treatment of anemia, muscle and organ fatigue. Furthermore, lady's mantle has many positive effects on the uterus. It helps women who are at risk of miscarriage to keep the child in the cervix, thereby minimizing the danger. Again, lady's mantle is among the plants that are very effective in birth injuries and fatigue of the uterus muscles. It also has positive effects such as anti-diarrheal stomach and intestinal regulator. It has therapeutic properties on the liver and kidneys. In recent studies, it is said to play an effective role in the treatment of cancer cells (Shrivastava et al., 2009).

CONCLUSIONS

Due to the flavonoids they contain, the dried leaves of the lady's mantle species (*Alchemilla* spp.) is evaluated as a pharmaceutical drug in the medical field and is used to relieve pain related to menopause. In addition, it is used effectively in the improvement of different gynecological problems, the treatment of menstrual pain, the elimination of gastrointestinal system disorders, and the resolution of inflammations. In recent years, studies on the mechanism of action of species on these cells have gained momentum, especially with the detection of their effects on cancerous cells. Rize is a very rich province in terms of lady’s mantle species. Especially for endemic species, it is necessary to focus on the Eastern Black Sea Region and to carry out studies for its protection. Thanks to this review, these species that grow naturally in the region have been botanically classified, but there are rarely any studies in terms of economic and chemical content. The necessity of the extensive studies on the plant, which is so important and included in drug preparations, has been revealed.

REFERENCES

Baytop, T. (1997). Turkish Plant Names Dictionary. TDK press: 578, Ankara.

Condrat, D., Szabo, M.R., Crışan, F., & Lupea, A.X. (2009). Antioxidant activity of some phanerogam plant extracts. Food Science and Technology Research, 15(1): 95-98.

Davis, P.H. (1982). Flora of Turkey and The East Aegean Islands. Edinburgh University Press, Edinburgh, Vol 7: 308-309.

Eggensperger, H. (2006). Zur Anwendung pflanzlicher Gerbstoffe in der Dermatologie und Kosmetik. In: Multiaktive Wirkstoffe für Kosmetika (Eggensperger H., ed.). Verlag für chemische Industrie, Augsburg: 107-127.

Ekim, T., Koyuncu, M. & Vural, M. (2000). Red Book of Plants of Turkey (Fern and Seed Plants) Turkish Nature Conservation Association Publishers. ISBN 975-93611-0-8: 246.

Mills, M.S. & Hutchins, R. (2013). Alchemilla herba-Alchemilla Mantle, European Scientefic Cooperative on Phytotherapy (ESCOP) Monographs, Online series, ESCOP Notaries House, United Kingdom.

Falchero, L., Coppa, M., Esposti, S., & Tava, A. (2008). Essential oil composition of *Alchemilla alpina* L. em. Buser from Western Alpine Pastures. Journal of Essential Oil Research, 20: 542-544.

Falchero, L., Coppa, M., Fossi, A., Lombardi, G., Ramella, D., & Tava, A. (2009). Essential oil composition of mantle (*Alchemilla xanthochlora* Rothm.) growing wild in Alpine pastures. Natural Product Research, 23(15): 1367-1372.

Gruenwald, J., Brendler, T., & Jaenicke, C. (2004). Physician's Desk Reference (PDR) for Herbal Medicines. Thomson PDR, Montvale: 497.

Gül, V. (2014). An Overview of Medicinal and Aromatic Plants Belonging to the Rize Region. Iğdır University Natural Sciences Journal, 4(4): 97-107.

Güner, A.,Vural, M. & Sorkun, K. (1987). Flora and vegetation of Rize and analysis of lcoal honey. Hacettepe Üniversity, TÜBİTAK TBAG-650, s. 269, Ankara.

Hayirlioğlu, S., & Beyazoğlu, O. (1997). Chromosome numbers in species of *Alchemilla* L. belong to the series Sericeae Bus. and Pubescentes Bus.(section *Alchemilla* Rothm.) in Turkey. Caryologia, 50(1): 77-84.

Hayırlıoğlu-Ayaz, S., & Inceer, H. (2009). Three new *Alchemilla* L. (Rosaceae) records from Turkey. Pakistan Journal of Botany, 41(5): 2093-2096.

Izmailow, R., 1981, Karyological studies in species of *Alchemilla* L. from the Calycinae Bus. (section Brevicaulon Rothm.). Acta Biologica Cracoviensia Series Botanica, 23:117-130.

Kalheber, H. (1994). The genus Alchemilla L. (Rosaceae) in the Turkish Vilayet Rize (Northeastern Anatolia) with some remarks on the distribution of the genus in other parts of Northern Anatolia. Sendtnera, 2: 389-430.

Kaya, B., Menemen, Y., & Saltan, F. Z. (2012). Flavonoid compounds identified in *Alchemilla* L. species collected in the North-Eastern Black Sea Region of Turkey. African Journal of Traditional, Complementary and Alternative Medicines, 9: 418-425.

Komisyon, E., Kleın, S., Rister, R., Riggins, C. (1998). The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines. American Botanical Council, Germany.

Makau, J. N., Watanabe, K., & Kobayashi, N. (2013). Anti-influenza activity of *Alchemilla mollis* extract: Possible virucidal activity against influenza virus particles. Drug discoveries & Therapeutics, 7(5): 189-195.

Murathan, Z. T. (2018). Determination of the biochemical content and antioxidant properties of some medical plants grown in the North East Anatolia Region ecological conditions. Journal of Balikesir University Institute of Science and Technology, 20(2): 51-60.

Nikolova, M., Dincheva, I., Vitkova, A. & Badjakov, I. (2012). Phenolic acids and free radical scavenging activity of *Alchemilla jumrukczalica* Pawl. International Journal of Pharmaceutical Science and Research, 3(3): 802-804.

Olafsdottir, E.S., Omarsdottir, S. & Jaroszewski JW. (2001). Constituents of three Icelandic *Alchemilla* species. Biochemical Systematics and Ecology, 29: 959-962.

Pawlowski, B. & Walters, S.M. (1972). *Alchemilla* L. In Davis, P.H. (ed.), Flora of Turkey and the East Aegean Islands. Vol. 4. Edinburgh Univ. Press, Edinburgh.

Rothmaler, W. (1937). Systematische Vorarbeiten zu einer Monographie der Gattung *Alchemilla* (L.) Scop. VII. Aufteilung der Gattung und Nomenklatur. Repertorium Novarum Specierum Regni Vegetabilis, 42(11-15): 164-173.

Shrivastava, R., Cucuat, N., & John, G. W. (2009). Effects of *Alchemilla vulgaris* and glycerine on epithelial and myofibroblast cell growth and cutaneous lesion healing in rats. Phytotherapy Research, 23(9): 1336-1339.

Trendafilova, A., Todorova, M., Nikolova, M., Gavrilova, A., & Vitkova, A. (2011). Flavonoid constituents and free radical scavenging activity of *Alchemilla mollis*. Natıral Product Communications, 6(12): 1851-1854.

Türk, M., Kaya, B., Menemen, Y., & Oğuztüzün, S. (2011). Apoptotic and necrotic effects of plant extracts belonging to the genus *Alchemilla* L. Species on Hela Cells in Vitro. Journal of Medicinal Plant Research, 5(18): 4566-4571.

Yurteri, E. (2018). Cultivation Opportunities and Determination of Active Ingredients of Some Medicinal and Aromatic Plant Species of Lamiaceae Family Spreading in Rize Province. PhD.-Thesis. Ondokuz Mayıs Üniversity, Natural Science Institute, p.154.

CHAPTER 7

DETERMINATION OF THE ELEMENTAL LEVELS OF MEDICAL AND AROMATIC PLANT YARROW (*Achillea millefolium*) COLLECTED FROM SIVAS WILD FLORA

Dilara ÜLGER ÖZBEK[1]

[1]Advanced Technology Research and Application Center, Sivas Cumhuriyet University, Sivas, Turkey, e-mail: dilaraulger@cumhuriyet.edu.tr
ORCID ID:0000-0002-6834-020X

INTRODUCTION

Achillea millefolium L. an individual from the Asteraceae familyants, is utilized as an alternative cure product in many region (Vitalini et al., 2011). It is called 'Civanperçemi' in Turkish and there are forty species in Turkey (Davis, 1982). Many biological effects and chemical molecules of *Achillea millefolium* have been used to treat of many health problems from ancient times. To give examples of its biological effects, *Achillea millefolium* has vasoconstrictor, antiallergic, antioxidant, stimulant, diuretic, anti-atherosclerotic, anti-inflammatory, antispasmodic, antinociceptive, choleretic, anti-hypertensive, estrogenic and anti-microbial effects (Usmanghani et al., 1997). With these biological effects it cures, hepatit B and C, respiratory infection, gastrological disorders, abdominal pain, headache, bleeding, dermatological disorders, diabetes mellitus, fever, gynecological disorders, gout, rheumatism ailments (Yaeesh et al., 2006). Also, it includes phytochemicals and chemicals such as alkaloid, choline, apigenin, alpha-terpineol, borneol, azulene, salicylic acid, glucoside, luteolin-7-O-beta-D-glucuronide, volatile oil, camphor, dihydro-dehydrodiconiferyl alcohol 9-O-beta-D-glucopyranoside, eucalyptol, dicaffeoylquinic acids, sesquiterpenoids, chamazulene, beta-pinene, diphenylpicrylhydrazyl radical, artemetin (Falconieri et al., 2011; Akram, 2013).

Generally, aqueous and alcoholic extracts of *Achillea millefolium* are used. The products (essential oils, active ingredients) obtained of

Achillea millefolium are utilized in many sectors like textile, food, cosmetics and pharmaceutical industries.

These medicinal and aromatic plants, which are used in many sectors and most importantly for human health, can have harmful effects as well as benefitsThe justification for this is that might be contaminated with human-made impurities or harmful components formed during processing. In addition to these, water, air, and soil contamination in the region where the plant grows can cause the gathering of toxic components in plants.

Especially some heavy metals such as nickel (Ni), arsenic (As), mercury (Hg), lead (Pb), aluminum (Al), antimony (Sb), cadmium (Cd), tin (Sn) are dangerous for human health, and even their low concentrations may come together in the body and cause health issues (Tokalıoğlu, 2012). Microelements such as iron (Fe), copper (Cu), zinc (Zn), chrome (Cr), and manganese (Mn) are very important in the formation of considerable biomolecules and the smooth progress of many important biological reactions. These elements are essential nutrients, but their high concentrations are toxic (Asker et al., 2015). Macro elements such as calcium (Ca), sodium (Na), potassium (K) magnesium (Mg), and phosphorus (P) are present in higher concentrations than microelements. These macro elements act as structural elements in tissues, regulating metabolism and acid-base balance (Leśniewicz et al., 2006). The element levels of plants of the identical species differ according to the area where they are grown, characteristics, rainfall, and agricultural practices (Konieczyński et al., 2007). In light of all this knowledge, it means a lot to be aware the element levels that affect whether the plants are medicinal or harmful.

This study aims to measure the element levels of yarrow with a high-sensitivity ICP-MS instrument.

1. MATERIALS AND METHODS

Achillea millefolium was collected from the wild flora of Sivas Cumhuriyet University Campus. Collected samples were brought to Sivas Cumhuriyet University Advanced Technology Research and Application Center. The samples were washed firstly, after that dried in the sunlight. The dried plants were ground in a blender and turned into powder, 0.2 g of them were weighed. Then, 5 ml of HNO_3 and 1 ml of H_2O_2 were added. The organic phase was decomposed in the microwave digestion (Milestone ETHOS EASY, Italy). Element levels were determind by inductively coupled plasma mass spectrometry (ICP-MS) (Thermo Scientific iCAP Q, Germany). All elements are read 3 times. The obtained data were multiplied by the dilution factor and given in ppm (mg/L).

2. RESULTS AND DISCUSSION

In this current study, many element levels of yarrow (*Achillea millefolium)* were measured. Measured element levels of yarrow that were collected from the university campus are stated in Table 1, Table 2 are given macro element levels of yarrow. The limit levels of some elements determined by FAO/WHO in plants are stated in Table 3.

According to our analysis results, the yarrow macro element levels were found as follows, 0.188% Ca, 0.219% K, 0.015% Mg, and 0.001% Na. Microelement levels of yarrow were found as, 61.6mg/L Fe, 5.64mg/L Zn, 15.7mg/L Mn, and 1.41mg/L Cu. In a similar study, yarrow macro element levels were found to be 2.22% Ca, 2.43% K, and 0.70% Mg, while microelement levels were found to be 360mg/L Fe, 47.6mg/L Zn, 85.5mg/L Mn, 28.3mg/L Cu (Sarac, 2021). In another yarrow study, some element levels were found as 179mg/L Fe, 40.2mg/L Zn, 84.3mg/L Mn, 9.88mg/L Cu, 5.54mg/L Ni, 0.26 mg/L Cr, <0.10mg/L Co, Pb, Cd (Gogoasa et al., 2013). When the results are compared, the macro/microelement levels of the yarrow in our study are pretty low. This is because for this explainable by the related to the soil content in which the herbs grow.

Table 1: Element Concentrations of Yarrow

Elements	Concentrations (mg/L)	Elements	Concentrations (mg/L)
Li	0,07	**Zn**	5,64
Be	0,002	**As**	0,04
Al	43,6	**Mo**	0,10
V	0,23	**Cd**	0,02
Cr	0,63	**Sn**	0,14
Mn	15,7	**Sb**	0,005
Fe	61,6	**Tl**	0,001
Co	0,04	**Pb**	0,13
Cu	1,41	**Ni**	0,65
Hg	0,006	**-**	-

Table 2: Macro Element Levels of Yarrow

Elements	Concentrations (%)
Na	0,001
Mg	0,015
K	0,219
Ca	0,188

Table 3: WHO Permissible Limits for Heavy Metals in Plants (FAO/WHO, 1984.)

Elements	WHO Permissible Value of Plant (mg/L)
Cd	0,02
Zn	0,60
Cu	10
Cr	1,30
Pb	2
Ni	10
Mn	2
Fe	30
Li	Not specified
Be	Not specified
Al	Not specified
V	Not specified
Be	Not specified
As	Not specified
Sn	Not specified
Sb	Not specified
Tl	Not specified
Co	Not specified
Hg	Not specified

In a study examining the heavy metal levels of *Achillea millefolium*, the Al level was found to be 375.35mg/L while As level was found 0.281mg/L (Delavar et al., 2011). Again, if we compare it with the obtained data we determined Al was found at 43.6mg/L while As was found at 0.04mg/L. In our study yarrow, heavy metal levels were found to be quite low.

When the element levels of yarrow we used in our study are compared with the permissible limits for plants announced by WHO, Fe, Mn, and Zn levels exceed these values (FAO/WHO, 1984). WHO did not define a limit value for the levels of lithium (Li), beryllium (Be), aluminum (Al), vanadium, mercury (Hg), cobalt (Co), Arsenic (As), Molybdenum (Mo), tin (Sn), antimony (Sb), thallium (Tl) among the elements we examined in our study. These elements have never been measured before in the medicinal plant *Achillea millefolium*. Thusly, no remark can be made with respect to the low or elevated degrees of these components in the *Achillea millefolium*.

CONCLUSIONS

As a result, the general mineral levels of the *Achillea millefolium* plant, which we collected from the Sivas Cumhuriyet University Campus, are lower than the species in other regions. While there could be numerous different reasons past that, the strongest is thought to be low soil mineral levels and living in wild flora.

REFERENCES

Akram, M. (2013). Minireview on *Achillea millefolium* Linn. The Journal of membrane biology, 246(9): 661-663.

Asker, S., Asker, M., Yeltekin, A.C., Asla, M., & Demir, H. (2015). Serum levels of trace minerals and heavy metals in severe obstructive sleep apnea patients: correlates and clinical implications. Sleep and Breathing, 19(2): 547-552.

Davis, P.H. (1982). Flora of Turkey and the East Aegean Islands. University Press, Edinburgh, 5: 244.

Delavar, M., Asghari, G.R., Amiri, F., & Abdollahi, M. (2011). The study of toxic metals contamination (Pb, Cd, As, Al) on medicinal plants cultivated near arak industrial manufactures, 482-487.

Falconieri, D., Piras, A., Porcedda, S., Marongiu, B., Gonc¸alves, M.J., Cabral, C., Cavaleiro, C., & Salgueiro, L. (2011). Chemical composition and biological activity of the volatile extracts of *A. millefolium*. Nat Prod Commun, 6:1527–1530.

FAO/WHO, (1984). Contaminants. In Codex Alimentarius, FAO/WHO. Codex Alimentarius Commision, Rome 17(1).

Gogoasa, I., Jurca, V., Alda, L.M., Velciov, A., Rada, M., Alda, S., & Gergen, I. (2013). Mineral content of some medicinal herbs. Journal of Horticulture, Forestry and Biotechnology, 17(4): 65-67.

Konieczyński, P., & Wesołowski, M. (2007). Determination of zinc, iron, nitrogen and phosphorus in several botanical species of medicinal plants. Polish Journal of Environmental Studies, 16(5): 785-790.

Leśniewicz, A., Jaworska, K., & Żyrnicki, W. (2006). Macro- and micro-nutrients and their bioavailability in polish herbal medicaments. Food Chemistry, 99(4): 670–679.

Sarac, H. (2021). Nutrient Concentrations of Some Medicinal and Aromatic Plants Consumed as Functional Food. Research & Reviews in Science and Mathematics-II, 1938.

Tokalıoğlu, Ş. (2012). Determination of trace elements in commonly consumed medicinal herbs by ICP-MS and multivariate analysis. Food Chem, 134(4): 2504–2508.

Usmanghani, K, Saeed, A., & Tanweer, A. (1997). Traditional uses of *A. millefolium.* Indus Med., 1:93-95.

Vitalini, S., Berett, G., Iriti, M., Orsenigo, S., Basilico, N., Dall'Acqua, S., Iorizzi, M., & Fico, G. (2011). Phenolic compounds from Achillea millefolium L. and their bioactivity. Acta Biochim. Pol., 58: 203-209.

Yaeesh, S., Jamal, Q., Khan, A.U., Gilani, A.H. (2006). Studies on hepatoprotective, antispasmodic and calcium antagonist activities of the aqueous-methanol extract of A. millefolium. Phytother Res, 20: 546–551.

CHAPTER 8

DETERMINATION OF THE BIOLOGICAL ACTIVITY OF *Lavandula stoechas* L.

Hasan DURUKAN[1]
Ahmet DEMİRBAŞ[2]
Nuraniye ERUYGUR[3]

[1] Sivas Cumhuriyet University, Sivas Technical Sciences Vocational School, Department of Plant and Animal Production, Sivas, Türkiye,
e-mail: hasandurukan@cumhuriyet.edu.tr, ORCID ID: 0000-0002-2255-7016
[2] Sivas Cumhuriyet University, Sivas Technical Sciences Vocational School, Department of Plant and Animal Production, Sivas, Türkiye,
e-mail: ademirbas@cumhuriyet.edu.tr, ORCID ID: 0000-0003-2523- 7322
[3] Selçuk University, Faculty of Pharmacy, Department of Pharmacognosy, Konya, Türkiye, e-mail: nuraniye.eruygur@selcuk.edu.tr,
ORCID ID: 0000-0002-4674-7009

INTRODUCTION

Lavandula stoechas is an aromatic plant belonging to the *Lamiaceae* family (Dob et al., 2006; Kaplan et al., 2019; Bilenler and Gökbulut, 2019). It is known that *Lavandula stoechas* plant, which is in the form of a bush, does not shed its leaves (Carrasco et al., 2015). *Lavandula stoechas* plant prefers non-acidic soils, especially in open forests and dry hills (Mokhtarzadeh and Khawar, 2022). *Lavandula stoechas* is used in many areas such as cosmetics and food (Öztürk et al., 2005). *Lavandula stoechas* plant also has antimicrobial properties (Bilenler and Gökbulut, 2019). In traditional medicine, *Lavandula stoechas* is used as an analgesic, antiseptic (Celep et al., 2018), expectorant, antispasmodic, carminative (Giray et al., 2008; Zuzarte et al., 2013) in the treatment of ear, nose and throat diseases (Mokhtarzadeh and Khawar, 2022). *Lavandula stoechas* plant, whose dried flowers and leaves are used, is preferred in the treatment of insomnia and high blood pressure disorders (Leblebici et al., 2012).

Chemicals that prevent possible harmful effects by interacting with free radicals are called antioxidants (Tüzün et al., 2020). Many reactive oxygen species (ROS), such as superoxide anion ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2) and hydroxyl radical ($HO^{\cdot}$) are natural byproducts of body metabolism (Amarowicz et al., 2004). Herbal products have antioxidant properties thanks to their content such as flavonoids, cinnamic acid derivatives and phenolic compounds (Kolaç et al., 2017). Phenolic compounds, the second most abundant metabolite in plants, play an important role in the growth of plants (Noreen et al., 2017).

It is known that Alzheimer's disease is expressed as a type of disease that can be defined by the progressive degeneration of memory and cognitive function (Eruygur et al., 2019). Acetylcholinesterase (AChE), one of the cholinesterases, plays a role in the hydrolysis of acetylcholine to choline and acetic acid (Eruygur and Uçar, 2018). Diabetes mellitus is a disease that causes serious complications (Eruygur and Uçar, 2018). In the treatment of diabetes, inhibitors that reduce carbohydrate digestion such as α-amylase and α-glucosidase inhibitors are used (Aksoy et al., 2021). Tyrosinase; it is an enzyme that plays an important role in the synthesis of melanin in mammalian cells and in browning in plants and microorganisms. Since melanin, which is produced and accumulated in high amounts in human skin, causes hyperpigmentation, it is important to control excessive melanin production by using tyrosinase inhibitor agents (Eruygur and Uçar, 2018).

The study is important in terms of determining the chemical composition, antioxidant activity, TPC, TFC and inhibitory activities of some enzymes of 80% ethanol extract of *Lavandula stoechas* plant.

1. MATERIALS AND METHODS

Lavandula stoechas plant used in the study was collected from Sivas natural flora in 2021. The data obtained in the study were made in Sivas Cumhuriyet University Advanced Technology Research Center laboratories.

Preparation of the extract

After the plant sample was ground in the herb grinding mill, 10 g of the leaf sample was weighed and placed in 50 mL of 80% ethanol solvent and left to agitate in a shaker for one day. After shaking, the solution was filtered through coarse filter paper. To obtain the extract from the filtrate, the filtrate was dried at 40°C with an evaporator under low pressure, and this process was repeated three times.

Determination of chemical components

The chemical components of the extract were analyzed by GC-MS (Gas Chromatography/Mass Spectrometry) (Sacchetti et al., 2005).

Determination of antioxidant activity

Determination of antioxidant activity in *Lavandula stoechas* plant was made in 80% ethanol extract. In determining the free radical scavenging activity of the extract, using 2,2-diphenyl-1picrylhydrazyl (DPPH) with slight modification according to the method of Blois (1958), 2,2'-azinobi (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) was used with slight modification by Re et al. (1999) method.

Determination of total phenol content (TPC) and total flavonoid content (TFC)

While determining the total phenol content (TPC), the Folin-Ciocalteu spectrophotometric method was used (Gámez-Meza et al., 1999). A gallic acid was used as the standard when determining the total phenol content, and the phenol content was calculated as milligram gallic acid equivalents per gram of dry extract. Total flavonoid content (TFC) was determined according to the aluminum chloride colorimetric method of Molan and Mahdy (2014). Total flavonoid content is expressed as milligram of catechin equivalents per gram dry weight of the extract.

Determination of enzyme inhibitory activities

Determination of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibition was performed according to the method of Ellman (1961) (Ergül et al., 2019; Güçlü et al., 2022). In the study, inhibition of α-glucosidase Kumar et al. (2012), inhibition of α-amylase Kumar et al. (2013) according to the method reported In the study, acarbose was used as a positive control in both α-glucosidase and α-amylase inhibition methods. Tyrosinase inhibitory activity was determined by slightly modifying the 96-well plate spectrophotometric method described by Jeong et al. (2009).

2. RESULTS

2.1. Chemical Components

In the study, the chemical components determined by GC-MS (Gas Chromatography / Mass Spectrometry) analysis method in 80% ethanol extract of *Lavandula stoechas* are given in Table 1.

Table 1: Chemical components of 80% ethanol extract of *Lavandula stoechas*

No	R.T.	(%) Area	Chemical components
1	15.275	0.99	Butylethylacetaldehyde
2	18.691	1.21	1,4:3,6-Dianhydro-alpha-d-glucopyranose
3	19.017	4.19	4-Vinylphenol
4	22.604	3.23	2-Methoxy-4-vinylphenol
5	28.269	8.65	1-Dodecanol
6	28.876	1.19	Adamantane
7	29.385	2.50	2,4-Di-tert-butylphenol
8	32.629	3.17	N2-dimethylguanine
9	33.476	23.07	2-Propenoic acid, dodecyl ester
10	35.141	1.95	(-)-Loliolide
11	36.223	1.13	Neophytadiene
12	36.349	5.84	Hexahydrofarnesyl acetone
13	38.843	1.95	Ethyl palmitate
14	46.042	2.57	Steviol Methyl Ester

In the study, the highest amount of chemical components determined from 80% ethanol extract of *Lavandula stoechas* was "2- Propenoic acid, dodecyl ester" with 23.07%, followed by "1-Dodecanol" with 8.65% and "Hexahydrofarnesyl acetone" with 5.84% (Table 1).

2.2. Antioxidant Activity

DPPH and ABTS radical scavenging activity

DPPH and ABTS radical scavenging activity determined in 80% ethanol extract of *Lavandula stoechas* plant is given in Figure 1.

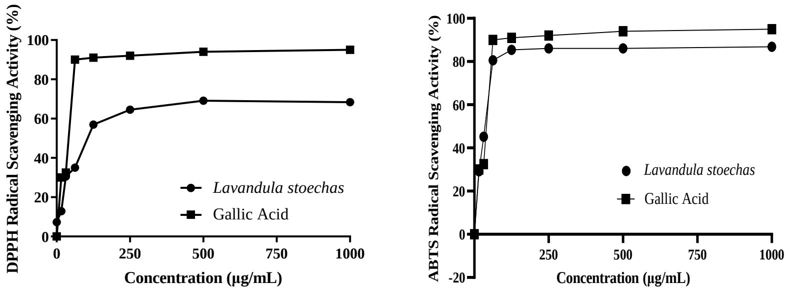


Figure 1: DPPH and ABTS radical scavenging activity of *Lavandula stoechas*

When the data obtained from the DPPH and ABTS radical scavenging activity test of *Lavandula stoechas* 80% ethanol extract were compared with the results of the gallic acid standard, it was determined that the antioxidant activity value was moderate compared to the DPPH test, but good in the ABTS test (Figure 1).

Total phenol (TPC) and total flavonoid contents (TFC)

TPC and TFC determined in 80% ethanol extract of *Lavandula stoechas* plant are given in Figure 2.

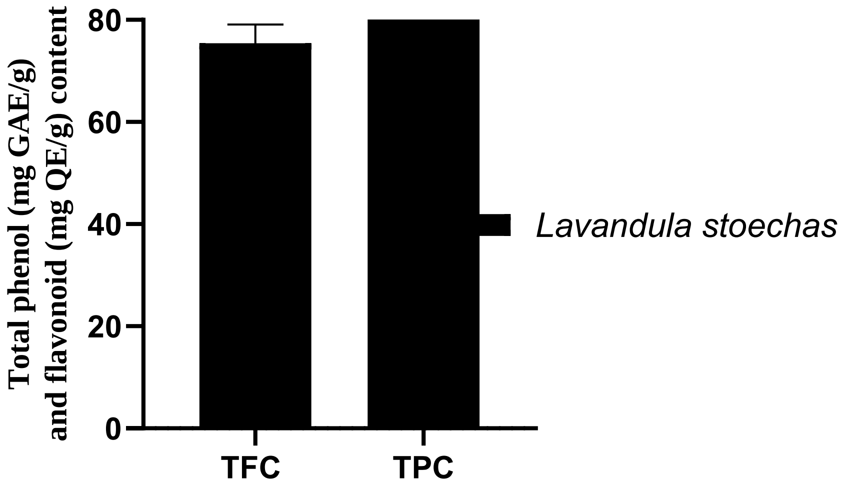


Figure 2: Total Phenol and Total Flavonoid Contents in 80% Ethanol Extract of *Lavandula stoechas* Plant

When the study was evaluated in terms of total phenol and total flavonoid contents, it was concluded that 80% ethanol extract of *Lavandula stoechas* plant had high levels of TFC and TPC (Figure 2.).

Enzyme inhibition activity

Comparison of the inhibition activities of some enzymes of 80% ethanol extract of *Lavandula stoechas* plant with reference drugs is given in Figure 3.

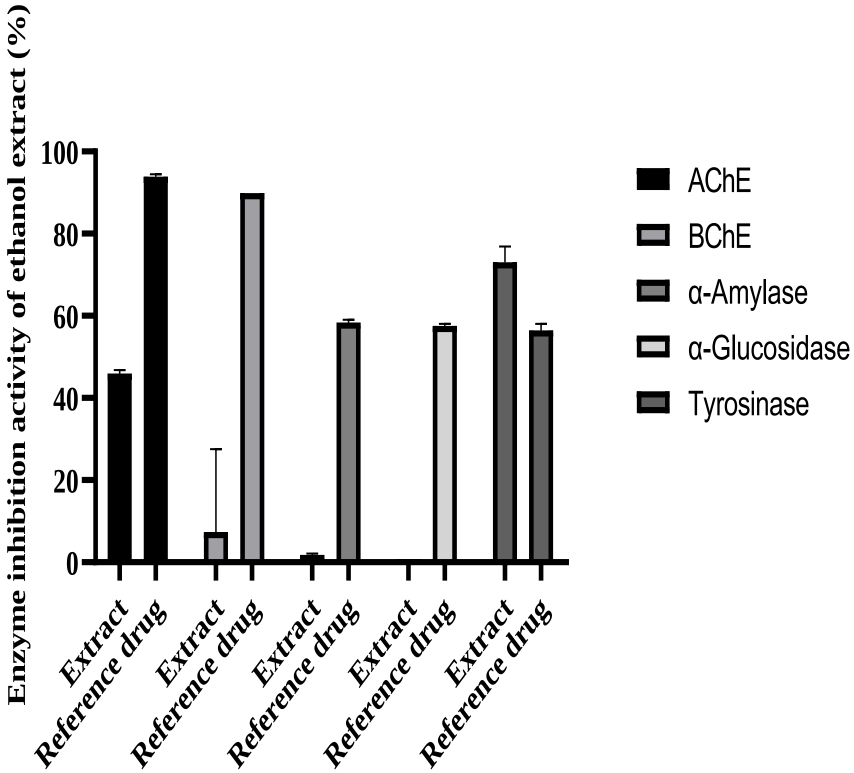


Figure 3: Comparison of the Inhibition Activities of AChE, BChE, α-Amylase, α-Glucosidase and Tyrosinase Enzymes of 80% Ethanol Extract of *Lavandula stoechas* Plant With Reference Drugs

AChE and BChE enzymes are effective on Alzheimer's, α-amylase and α-glucosidase enzymes are effective on diabetes and tyrosinase enzyme is effective on skin spots. Galanthamine, which was used as a reference drug in the study, was used to compare the inhibition activities of AChE and BChE enzymes. Acarbose, which was used as a reference drug in the study, was used to compare the inhibition activities of α-amylase and α-glucosidase enzymes. Kojic acid, which was used as a reference drug in the study, was used to compare the inhibition activity of tyrosinase enzyme. When the enzyme inhibition activity values of *Lavandula stoechas* plant on these diseases were examined, it was determined that the tyrosinase enzyme showed higher activity than the standard drug.

CONCLUSIONS

As a result of the study, 80% ethanol extract of *Lavandula stoechas* plant; chemical composition, antioxidant activity, TPC and TFC, and inhibitory activities of some enzymes were determined. The chemical components of *Lavandula stoechas* plant were determined as "2-propenoic acid, dodecyl ester", "1-dodecanol" and "hexahydrofarnesyl acetone" in the highest amount, respectively. It was determined that 80% ethanol extract of *Lavandula stoechas* plant showed moderate antioxidant activity in DPPH test and good level of antioxidant activity in ABTS test when compared with gallic acid. In the study, it was determined that the TPC and TFC of the plant were high. Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes associated with Alzheimer's disease, α-glucosidase and α-amylase enzymes associated with diabetes were found to be at low levels compared to the reference drugs, while tyrosinase enzyme, which is effective on skin spots, was found to be at a higher level than the reference drug.

REFERENCES

Aksoy, L., Suyundikov, M., & Düz, M. (2021). α-amylase, α-glucosidase, tyrosinase, acetylcholine esterase enzyme inhibition properties and essential oil composition of *Thermopsis turcica* Kit Tan, Vural&Küçüködük. Anadolu Journal of Agricultural Sciences, 36(3): 357-364.

Amarowicz, R., Pegg, R.B., Rahimi-Moghaddam, P., Barl, B., & Weil, J.A. (2004). Free-radical scavenging capacity and antioxidant activity of selected plant species from the Canadian prairies. Food Chemistry, 84: 551-562.

Bilenler, T., & Gökbulut, İ. (2019). Determination of sensitivity of hospital pathogens against commercial essential oil. Gümüşhane University Journal of Science and Technology, 9(3): 716-723. (In Turkish).

Blois, M.S. (1958). Antioxidant determinations by the use of stable free radical. Nature, 181: 1199-1200.

Carrasco, A., Ortiz-Ruiz, V., Martinez-Gutierrez, R., Tomas, V., & Tudela, J. (2015). *Lavandula stoechas* essential oil from Spain: Aromatic profile determined by gas chromatography–mass spectrometry, antioxidant and lipoxygenase inhibitory bioactivities. Industrial Crops and Products, 73: 16-27.

Celep, E., Akyüz, S., İnan, Y., & Yesilada, E. (2018). Assessment of potential bioavailability of major phenolic compounds in *Lavandula stoechas* L. ssp. *stoechas*. Industrial Crops & Products, 118: 111-117.

Dob, T., Dahmane, D., Agli, M., & Chelghoum, C. (2006). Essential oil composition of *Lavandula stoechas* from Algeria. Pharmaceutical Biology, 44(1): 60-64.

Ellman, G.L., Courtney, K.D., Andres, V., & Featherstone, R.M. (1961). A new and rapid colorimetric determination of acetylcholinesterase activity. Biochemical Pharmacology, 7(2): 88-95.

Ergül, M., Ergül, M., Eruygur, N., Ataş, M., & Uçar, E. (2019). *In vitro* evaluation of the chemical composition and various biological activities of *Ficus carica* leaf extracts. Turkish J. Pharm. Sci., 16(4), 401-409.

Eruygur, N., Ucar, E., Akpulat, H.A., Shahsavari, K., Safavi, S.M., & Kahrizi, D. (2019). In vitro antioxidant assessment, screening of enzyme inhibitory activities of methanol and water extracts and gene expression in *Hypericum lydium*. Molecular Biology Reports, 46: 2121-2129.

Eruygur, N., & Uçar, E. 2018. Cholinesterase, α-Glucosidase, α-Amylase, and Tyrosinase Inhibitory Effects and Antioxidant Activity of *Veronica officinalis* Extracts. Türkiye Tarımsal Araştırmalar Dergisi, 5(3): 253-259.

Gámez-Meza, N., Noriega-Rodríguez, J.A., Medina-Juárez, L.A., Ortega-García, J., Cázarez-Casanova, R., & Angulo-Guerrero, O. (1999). Antioxidant activity in soybean oil of extracts from thompson grape bagasse. JAOCS, 76: 1445-1447.

Giray, E.S., Kırıcı, S., Kaya, D.A., Türk, M., Sönmez, Ö., & İnan, M. (2008). Comparing the effect of sub-critical water extraction with conventional extraction methods on the chemical composition of *Lavandula stoechas*. Talanta, 74: 930-935.

Güçlü, G., Ergül, M., Uçar, E., Eruygur, N., Ataş, M., & Akpulat, H.A. (2022). Anticancer, antioxidant, antimicrobial and enzyme ınhibitory activities of *Inula aucheriana*. KSÜ Tarım ve Doğa Dergisi, 25(5): 946-954.

Jeong, S.H., Ryu, Y.B., Curtis-Long, M.J., Ryu, H.W., Baek, Y.S., Kang, J.E., Lee, W.S., & Park, K.H. (2009). Tyrosinase inhibitory polyphenols from roots of *Morus lhou*. J. Agric. Food Chem., 57: 1195-1203.

Kaplan, E.N., Çakı, M.N., & Paşa, S. (2019). *Lavandula stoechas* (karabaş otu) bitki özütünden kozmetik ürün eldesi. UMÜFED Uluslararası Batı Karadeniz Mühendislik ve Fen Bilimleri Dergisi, 1(1): 24-37.

Kolaç, T., Gürbüz, P., & Yetiş, G. (2017). Phenolic content and antioxidant characteristics of natural products. Journal of Inonu University Health Services Vocational School, 5(1): 26-42. (In Turkish).

Kumar, D., Gupta, N., Ghosh, R., Gaonkar, R.H., & Pal, B.C. (2013). α-Glucosidase and α-amylase inhibitory constituent of *Carex baccans*: Bio-assay guided isolation and quantification by validated RP-HPLC-DAD. Journal of Functional Foods, 5(1): 211-218.

Kumar, D., Kumar, H., Vedasiromoni, J.R., & Pal, B.C. (2012). Bio-assay guided isolation of α-glucosidase inhibitory constituents from *Hibiscus mutabilis* leaves. Phytochemical Analysis, 23(5): 421-425.

Leblebici, S., Bahtiyar, S.D., & Özyurt, M.S. (2012). Determination of the amount of heavy metal in some medicinal plants sold in herbalist in Kütahya. Journal of Science and Technology of Dumlupınar University, 29: 1-6.

Mokhtarzadeh, S., & Khawar, K.M. (2022). Optimization of tissue culture studies in *L. stoechas L. subsp. L. stoechas*. Turkish Journal of Agricultural and Natural Science, 9(2): 330-339. (In Turkish).

Molan, A.L., & Mahdy, A.S. (2014). Iraqi medicinal plants: Total flavonoid contents, free-radical scavenging and bacterial beta-glucuronidase inhibition activities. IOSR Journal of Dental and Medical Sciences, 13(5): 72-77.

Noreen, H., Semmar, N., Farman, M., & McCullagh, J.S.O. (2017). Measurement of total phenolic content and antioxidant activity of aerial parts of medicinal plant *Coronopus didymus*. Asian Pacific Journal of Tropical Medicine, 10(8): 792-801.

Öztürk, B., Konyalıoğlu, S., Kantarcı, G., & Çetinkol, D. (2005). Essentıal oil composition, antibacterial antifungal and antioxidant capacity of wıld Lavandula stoechas L. subsp. stoechas from İzmir. ANADOLU Journal of Aegean Agricultural Research Institute, 15(1): 61-72.

Re, R., Pellegrini, N., Proteggente, A., Pannala, A., Yang, M., & Rice-Evans, C. (1999). Antioxidant acivity applying an improved ABTS radical cation decolorization assay. Free Radical Biology & Medicine, 26(9/10): 1231-1237.

Sacchetti, G., Maietti, S., Muzzoli, M., Scaglianti, M., Manfredini, S., Radice, M., & Bruni, R. (2005). Comparative evaluation of 11 essential oils of different origin as functional antioxidants, antiradicals and antimicrobials in foods. Food Chemistry, 91(4): 621-632.

Tüzün, S., Baş, İ., Karakavuk, E., Sanyürek, N.K., & Benzer, F. (2020). Comparison of antioxidant activities detected by different methods in various molasses. Turkish Journal of Agricultural and Natural Science, 7(2): 323-330.

Zuzarte, M., Gonçalves, M.J., Cavaleiro, C., Cruz, M.T., Benzarti, A., Marongiu, B., Maxia, A., Piras, A., & Salgueiro, L. (2013). Antifungal and anti-inflammatory potential of *Lavandula stoechas* and *Thymus herba-barona* essential oils. Industrial Crops and Products, 44: 97-103.

CHAPTER 9

DETERMINATION OF CAFFEINE AND PHENOLIC SUBSTANCE CONTENTS OF BLACK TEA SMUGGLED ILLEGAL TO TÜRKİYE

Aysel ÖZCAN AYKUTLU[1]
Haydar KÜPLEMEZ[2]
Emine YURTERİ[3]
Fatih SEYİS[4]

[1] Recep Tayyip Erdoğan University, Faculty of Agriculture, Department of Field Crops, Rize, Türkiye, e-mail:aysel.ozcan@erdogan.edu.tr
ORCHID ID: 0000-0001-5210-7617
[2] Recep Tayyip Erdoğan University, Faculty of Agriculture, Department of Field Crops, Rize, Türkiye, e-mail: haydar.kuplemez@erdogan.edu.tr
ORCHID ID:0000-0003-4094-1318
[3] Recep Tayyip Erdoğan University, Faculty of Agriculture, Department of Field Crops, Rize, Türkiye, e-mail: emine.yurteri@ erdogan.edu.tr
ORCHID ID: 0000-0002-3770-2714
[4] Recep Tayyip Erdogan University, Faculty of Agriculture, Department of Field Crops, Rize, Türkiye, fatih.seyis@erdogan.edu.tr,
ORCHID ID: 000-0001-9714-370X

INTRODUCTION

Tea (*Camellia sinensis*) is obtained from the leaves of the plant from the tea family (Theaceae) that grows in tropical and subtropical climates. It was first cultivated in China and India in the world. Its homeland is Assam (Inner sides of India facing China) (Üstün and Demirci, 2013).

Tea, which is one of the most consumed beverages in the world after water, is prepared by processing the young leaves of the *Camellia sinensis* plant. Today, tea is grown commercially in more than 30 countries, led by China, India, Kenya, Sri Lanka, Türkiye, Vietnam, Iran and Japan (Seyis et al., 2018). Our country is the fifth largest producer of black tea in the world after Sri Lanka (FAO, 2013).

Teas consumed in our country can be divided in two groups; teas grown in the Eastern Black Sea Region and tea that comes to our country illegally and is frequently consumed especially in the Southeast Smuggled teas of Iranian origin, which have been brought to our country through various illegal methods from the border gates in the Eastern and Southeastern Anatolia Regions, have a negative impact on the tea industry in Türkiye (Rize Commodity Exchange, 2014).

High taxes on tea, up to 145%, cause an increase in illegal tea imports. Tea smuggling has become a trade in the Eastern and Southeastern Anatolia Region. Despite all the warnings and precautions, this trade could not be prevented and even continues to increase (Er, 2013).

Today, there are three different types of tea produced for commercial purposes. These are: Black, green and oolong tea (Katiyar and Mukhtar, 1997). Tea produced worldwide is about 76% is black tea, 22% is green tea, and 2% is oolong tea (Trevisanato and Young-In Kim, 2000).

The composition of tea leaves varies depending on climatological, cultural and genetic factors (Katiyar and Mukhtar, 1997). It is reported that there are around 4000 bioactively active compounds in tea leaf, 1/3 of which is polyphenols and the majority of them are flavanols (Sharangi, 2009; Seyis et al., 2018). The flavanol content in the tea leaf varies according to the processing technology and tea type, and the flavanol content in black tea decreases due to processing (Tosun and Karadeniz, 2005).

Fresh tea leaves contain a wide range of phenolic compounds. These are catechines, flavonols, proanthocyanidins and phenolic acids from flavonoids. Depending on the production of black tea, oolong tea and green tea, the fermentation of catechins is carried out by the endogenous enzyme's polyphenol oxidase and peroxidase. During fermentation, catechins are oxidized into dimeric and oligomeric compounds such as theaflavins, theacidrins, theacinensins, theanaptoquinones and thearubigins (Rains et al., 2011; Liu, 2013; Tan et al., 2017).

The main flavonols found in tea are quercetin, campherol, myricetin and rutin (Wang et al., 2000; Khokhar and Magnusdottir, 2002). According to the Turkish Food Codex, Tea Communiqué, (Communiqué No: 2015/30), decaffeinated black/green tea is defined as “tea whose caffeine content does not exceed 0.1% by weight in dry matter” (Turkish Food Codex, 2015). Caffeine is one of the main alkaloids found in tea and its amount can vary between 1.5 and 5% (Tan et al., 2017).

1. MATERIALS AND METHODS

1.1. Plant Material

In the research, 9 different tea classes brought from the Eastern Anatolia Region and abroad were used as material. Investigated Black tea grades are named as BOP, BOP1, BOPF, EL RUHA, OP, OPA, PD, PEK and PF1. The origins of black teas; PEK, OPA, PD and PF1 class are Kenya, El Ruha, OP, BOP and BOP1 class are Sri Lanka and BOPF class is India. A total of 27 samples were analyzed, with 3 replications from each of the 9 different tea classes supplied.

1.2. Preparation of Samples

For each class of black tea, 3 g samples were weighed in 3 replications. After adding 100 ml of boiled distilled water to the samples, shaking was performed for 5 minutes, and then it was left to infuse for another 10 minutes. After the brewing process was completed, the solution was passed through filter paper twice and the filtrate was taken into falcon tubes. Afterwards, the falcon tubes were centrifuged at 4000 rpm for 20 minutes and the precipitation process was performed, the remaining solution was removed and transferred to 2 ml chromatography vials.

Phtograph 1: Preparation of Black Tea Samples

Photograph 2: Brewing of Black Sea Samples and Extraction Phases

1.3. Determination of Cafein and Phenolic Components

The analysis of phenolic components were carried out in the plant analysis laboratory of the Department of Field Crops, Faculty of Agriculture, Recep Tayyip Erdogan University. The amounts of EGC, catechin, caffeine, EGCG, EC, caffeic acid, coumaric acid, rutin and quercetin in the extracts were determined using a high-pressure liquid chromatography (HPLC) device.

HPLC Conditions were:
Device: Shimadzu LC-2030 C 3D
Column: Purospher Star RP-18 5µm, 4.0x250mm (Merck)
Mobile Phase A: Methanol
Mobile Phase B: Bidest water
Dedector: Diode Array Dedector (DAD)

Photograph 3: View of HPLC device during analysis

2. RESULTS AND DISCUSSION

Within the scope of this study, the results of the analysis including the caffeine and phenolic substance amounts of the black tea classes called illegal tea are given in Table 1.

Table 1: Caffein content and phenolic components of smuggled black tea grades (ppm)

	EGC	Catechin	Caffeine	EGCG	EC	Caffeic acid	Coumaric acid	Rutin	Quercetin
BOP	1132.3	81.7	15859.5	1670.6	795.4	98.8	110.7	1704.4	201.6
BOP1	1522.8	54.9	20787.5	1644.8	706.9	173.0	153.7	2207.8	120.2
BOPF	1440.8	83.8	18680.6	1030.7	950.4	156.8	519.5	5978.2	183.6
EL RUHA	1996.6	53.8	22070.9	1252.2	1021.9	94.4	193.2	2658.6	81.7
OP	1119.9	137.3	21016.1	1826.7	881.4	567.2	393.0	1538.0	142.2
OPA	359.5	52.1	17015.8	168.9	120.9	73.5	85.1	1011.9	13.4
PD	4618.2	28.4	20825.4	363.9	169.3	85.3	121.7	3954.2	224.7
PEK	864.2	88.1	20417.4	3134.4	962.7	299.8	179.4	2196.8	36.1
PF1	3062.9	356.7	18986.8	1089.2	1534.1	306.2	267.9	7618.1	447.1

According to the results of the research; caffeine content varied from 15859.5 ppm to 22070.9 ppm. While the highest value in terms of caffeine content was obtained from the El Ruha (22070.9 ppm) class. It was followed by; OP (21016.1 ppm), PD (20825.4 ppm), BOP1 (20787.5 ppm), PEK (20417.4 ppm), PF1 (18986.8 ppm), BOPF (18680.6 ppm), OPA (17015.8 ppm) and BOP (15859.5 ppm) classes.

In a study investigating the caffeine content of teas processed with different methods in different exile periods (Türkmen, 2007). The caffeine content was found as 17.51-26.26 mg/g. Khokhar and Magnusdottir (2002) reported that amount of caffeine in 12 different black teas were determined as 25-28 mg/g. After the change of time and temperature in the fermentation application, the caffeine content in black teas were examined and the values were determined as 14.25-

16.95 mg/g KM (Obanda et al., 2001). As a result of the research on Iranian origin black teas, the amount of caffeine was determined in the range of 12.32-19.60 mg/g (Khanchi et al., 2007). In the light of this information the values specified in the literature and the caffeine contents reached in our research were generally compatible.

It is stated that the different levels of caffeine content of teas may be caused by factors such as the harvest period, regional differences, processing method and differences in leaf type and structure (Khokhar and Magnusdottir 2002; Zuo et al., 2002). In addition to these, the caffeine content of tea also varies according to the extraction method applied (Perva-Uzunalić et al., 2006).

When the EGCG compound which has an important place among the phenolic compounds is examined; the highest values were reached in the OP (1826.7 ppm) class and the lowest in the OPA (168.9 ppm) class. The amount of EGC, another important compound was found to be the highest in the PD (4618.2 ppm) class and the lowest in the OPA (359.5 ppm) class.

According to the study in which the EGCG content of 17 different types of teas were determined, the amount of EGCG varied between 0.72-3.53 mg/g ka (Liang et al., 2003). In a study on fermentation in black tea, EGCG content was reported as 2.95 mg/g ka (Obanda et al., 2001). Türkmen (2007) found EGCG content as 0.25-3.16 mg/g ka in his study in which he investigated the phenolic content of tea samples taken at different harvest periods using different processing methods. In a study conducted to determine the chemical properties of white, green and black teas; Atalay and Erge (2017) reported the EGC content of black teas as 2.48 mg/g and 3.33 mg/g. The amount of 168.9 ppm-1826.7 ppm EGCG we obtained in our study coincides with the EGCG amounts given in the literature. In addition, while the amount of EGC given in the literature and the EGC content of some tea classes that are the subject of our research are compatible with each other higher or lower EGC content has been determined in some tea classes than the aforementioned literature.

While the amount of EC compound among the other catechin derivatives examined in the study was in the range of 1534.1 ppm-168.9 ppm, the catechin content was found between 356.7 ppm-28.4 ppm. In addition, the amount of caffeic acid was determined as 567.2 ppm-73.5 ppm, the content of coumaric acid as 519.5 ppm-85.1 ppm, the amount of rutin as 7618.1 ppm-2196.8 ppm and quercetin as 447.1 ppm-13.4.

CONCLUSIONS

Tea smuggling or smuggled tea effects the quality in the local market due to different factors which are well known. Different tea trademarks are present in the Turkish tea market, but still nowadays smuggled tea is preferred specially in the South-Eastern part of Türkiye due to the local palatal delight of local people. The governmental institutions are producing and selling different tea trademarks and types for decreasing the consumption of illegal smuggled tea.

As a result of our study, it was concluded that both caffeine content and phenolic substance contents differ depending on investigated tea classes. The differences between analysis results can be explained by the origin of the tea classes, different harvesting periods, leaf sizes, fragmentation sizes and processing methods.

REFERENCES

Atalay, D. Erge, & H.S. (2017). Determination of some physical and chemical properties of white. green and black teas (*Camellia sinensis*). The Journal of Food, 42(5): 494-504.

Er, B. (2013). Alternative Product Likapa in Solving Problems in Tea Agriculture. II. Rize Development Symposium. 3-4 Mayıs. Rize.

FAO (2013). FAO web page. http://faostat.fao.org/site/ (Accessed date: 23.04.2013).

Katiyar, S.K. & Mukhtar, H. (1997). Tea antioxidants in cancer chemoprevention. Journal of Cellular Biochemistry, 27: 59-67.

Khanchi, A.R., Mahani, M.K. Hajihosseini, M., Maragheh, M.G., Chaloosi, M. & Bani, F. (2007). Simultaneous spectrophotometric determination of caffeine and theobromine in Iranian tea by artificial neural Networks and its comparison with PLS. Food Chemistry, 103: 1062-1068.

Khokhar, S., & Magnusdottir, S.G.M. (2002). Total phenol, catechin, and caffeine contents of teas commonly consumed in the United Kingdom. Journal of Agricultural and Food Chemistry, 50(3): 565-570.

Liang, Y., Lu, J., Zhang, L., Wu, S. & Wu, Y. (2003). Estimation of black tea quality by analysis of chemical composition and colour difference of tea infusions. Food Chemistry, 80: 283-290.

Liu, R.H. (2013). Health-promoting components of fruits and vegetables in the diet. Advances in Nutrition: An International Review Journal. 4(3): 384-392.

Obanda, M., Owuor, P.O. & Mangoka, R. (2001). Changes in the chemical and sensory quality parameters of black tea due to variations of fermentation time and temperature. Food Chemistry, 75: 395-404.

Perva-Uzunalić, A., Škerget, M.. Knez, Ž., Weinreich, B., Otto, F. & Grüner, S. (2006). Extraction of active ingredients from green tea (*Camellia sinensis*): Extraction efficiency of major catechins and caffeine. Food Chemistry, 96: 597-605.

Rains, T.M., Agarwal, S. & Maki, K.C. (2011). Antiobesity effects of green tea catechins: amechanistic review. The Journal of Nutritional Biochemistry, 22(1): 1-7.

Rize Commodity Exchange (2014). Tea Industry Problems and Solution Suggestions. Rize.

Seyis., F., Yurteri, E., Özcan, A., & Savsatli, Y. (2018). Organic tea production and tea breeding in Turkey: Challenges and possibilities. Ekin Journal, 4(1): 60-69.

Sharangi, A.B. (2009). Medicinal and therapeutic potentialities of tea (*Camellia sinensis* L.)- A review. Food Research International. 42: 529-535.

Tan, J., Engelhardt, U.H., Lin, Z., Kaiser, N., & Maiwald, B. (2017). Flavonoids. phenolic acids. alkaloids and theanine in different types of authentic Chinese white tea samples. Journal of Food Composition and Analysis, 57: 8-15.

Tosun, İ., & Karadeniz, B. (2005). Antioxidant activity of tea and tea phenolics. Ondokuz Mayıs University Journal of Agricultural Faculty, 20(1): 78-83.

Trevisanato, S.I. & Young-In Kim, M.D. 2000. Tea and Health. Nutrition Reviews. 58: 1-10.

Turkish Food Codex (2015). Çay Notice. (Notice No: 2015/30)

Türkmen, N. (2007). The Effect of Twisting Processes and Different Harvest Periods on the Phenolic Substance and Alkaloid Composition of Different Classes of Tea. PhD.-Thesis, Ankara University Natural Science Institue.

Üstün, Ç., & Demirci, N. (2013). Historical Development and Medical Evaluation of Tea Plant (*Camellia sinensis* L.). Lokman Hekim Journal, 3(3): 5-12.

Wang, H., Provan, G.J. & Helliwell, K. (2000). Trends in Food Science and Technology, 11: 152-160.

Zuo, Y., Chen, H. & Deng, Y. (2002). Simultaneous determination of catechins. caffeine and gallic acids in green. oolong. black and pu-erh teas using HPLC with a photodiode array detector. Talanta, 57: 307-316.

CHAPTER 10

CHARACTERIZATION TECHNIQUES OF HERBAL ESSENTIAL OILS

Ebru YABAŞ[1]
Fuat ERDEN[2]
Mehmet ŞİMŞİR[3]

[1]Sivas Cumhuriyet University, Advanced Technology Application and Research Center, Sivas, Türkiye, e-mail: eyabas@cumhuriyet.edu.tr,
ORCID ID: 0000-0001-7163-3057
[2]Sivas University of Science and Technology, Department of Aeronautical Engineering, Sivas, Türkiye, e-mail: fuaterden@sivas.edu.tr,
ORCID ID: 0000-0002-8261-4844
[3]Sivas Cumhuriyet University, Faculty of Engineering, Metallurgical and Materials Engineering, Sivas, Türkiye, e-mail: msimsir@cumhuriyet.edu.tr,
ORCID ID: 0000-0002-0552-9558

INTRODUCTION

Essential oils, which can be obtained from the leaves, fruit, bark or root parts of plants, are natural products that are liquid at room temperature, usually colorless or light yellow. Although essential oils are defined as oils because they do not mix with water, they are different from fixed oils and are largely composed of terpenes in their chemical structure. (Ceylan, 1983). It is also known that essential oils can be produced by many aromatic plants and consist of a mixture of various components such as terpenes, terpenoids, phenylpropenes (Mejri et. al, 2018). Essential oils are generally known for their fragrant, flavor-enhancing and therapeutic properties, as oxygenated derivatives exhibit odor, taste and therapeutic properties by oxidation of terpenes (Linskens and Jackson, 1997a). In recent years, the use of essential oil has increased, especially due to the interest in alternative medicine. In addition, herbal essential oils are widely used in production, cosmetics, food and cleaning industries, apart from alternative medicine. From this perspective, the production of essential oils from plants and their characterization become important. Distillation, extraction and pressing processes are generally used methods from past to present in the production of essential oils. Today, it is preferred in different modern methods, especially in order to increase the yield and quality of the product. These methods are microwave-assisted extraction, supercritical fluid extraction and solid-phase microextraction etc. can be classified as techniques.

Water distillation, steam distillation and vacuum distillation types are generally preferred among the distillation processes and carried out by utilizing the differences in boiling points of liquids. Water distillation is widely used and is carried out in small-scale and large-scale production in clevenger and distillation boilers, respectively. The basis of this method is based on the transportation of volatile oil molecules with the water vapor formed as a result of boiling the plant with water and then separating it from the water by condensation (Linskens and Jackson, 1997b). In the steam distillation method, the water vapor applied to the plants with the help of pressure ensures that the essential oils are entrained with steam and the essential oil is separated from the water as a result of condensation (Linskens and Jackson, 1997b). In vacuum distillation, it is generally applied to components with high boiling points. By reducing the pressure below the vapor pressure of the compound, boiling and distillation processes are applied.

In the extraction method, which is another separation technique, solvent extraction is generally used. In this method, plants can be kept directly in organic solvents at room temperature or boiled in soxhlet. After extraction, the organic solvent is removed by distillation and volatile compounds can be obtained in the remaining part.

Cold hydraulic pressing of the raw material can be applied in the production of essential oils that can deteriorate when distillation and extraction processes are applied.

Microwave-assisted extraction method, which is among the preferred modern methods today, is closed system extraction with temperature and pressure control. The basis of this method is based on heating the plant sample with the solvent by applying microwave. In this method, while product losses are reduced compared to other methods, the extraction time and the amount of solvent used are also significantly reduced (Kaufmann and Christen 2002; Kaufmann et al., 2007; Beejmohun et al., 2007).

Supercritical fluid extraction, which is among the modern separation techniques, attracts great attention with its feature of separating components dissolved at high temperature under normal conditions (Yamani et al., 2008). In this method, substances with supercritical fluid properties are used as solvents instead of organic solvents. Carbon dioxide is generally preferred as this solvent because of its low cost, high purity, ease of use and minimal environmental impact (Linskens and Jackson, 1997b).

Another method, solid-phase microextraction, combined sample preparation, extraction and concentration in a single solvent-free step. This method, which provides significant savings in processing time and costs, is especially used in the extraction of volatile and semi-volatile organic compounds in the samples (Vas and Vekey, 2004).

After the separation method is selected and applied depending on the properties of the essential oil components, their characterization is the second important step. In this study, we briefly summarized the separation techniques. The next section contains information about the characterization methods of the essential oils obtained.

In the characterization of essential oils, techniques such as Fourier-Transform Infrared Spectroscopy, Raman Spectroscopy, Gas Chromatography-Mass Spectrometry, Differential Scanning Calorimetry, Nuclear Magnetic Resonance Spectrometer are generally used. In this part of the chapter, information about these techniques is separately given.

Fourier-Transform Infrared Spectroscopy (FT-IR)

FT-IR is used to characterize organic and/or inorganic compounds. In FT-IR, measurements of the samples can be taken directly with the Attenuated Total Reflectance (ATR) technique or by preparing pellets with potassium bromide (KBr). The spectra obtained by this method contain vibrations (wave number) of molecular bonds in the infrared region (4000 to 400 cm-1), and absorption peaks at the frequencies formed by these vibrations give the characteristic peaks and fingerprint region of the samples. Samples with different molecular bonds can be detected with different vibration frequencies, as each component has characteristic peaks and fingerprint region depending on the chemical structure (Çağlar, Demirci and Çağlar, 2019; Büyüksırıt and Kuleasan, 2014).

The spectrum bands in the FT-IR correlate with the chemical bond structure of the functional groups in the molecules in the sample. The approximate values of the wave number range of bond types according to chemical groups are given in Table 1.

Table 1: Approximate wavenumber ranges of bond structures of functional groups (Settle, 1998)

Bonds	Wave Number Range
C–H, N–H, O–H or S–H	4000 - 2500 cm^{-1}
O–H and N–H	3700 - 2500 cm^{-1}
C–H	3300 - 2800 cm^{-1}
C–H aldehyde	2900 - 2700 cm^{-1}
C≡C, C≡N and C=C=C	2700 - 1850 cm^{-1}
C=C, C=N and C=O	1950 - 1450 cm^{-1}

Herbal essential oils can be characterized by determining the functional groups of the molecules in their chemical composition by FT-IR. Classification can also be made by taking into account the differences in the spectrum depending on the type of plant containing the essential oil, the production conditions, the geography where it is produced, etc. Depending on the composition of analyzed sample, FT-IR may be an adequate analysis technique for characterization. However, it is not an adequate characterization technique for the characterization of multicomponent samples. Because molecular bands in multicomponent samples may overlap and/or some bands may be masked (Filoda et al., 2018; Yadav, 2018; Yang et al., 2005). In this case, the spectral results obtained do not give accurate results about the chemical structure of the components.

In addition, the FT-IR technique is a very suitable alternative technique in terms of time and savings, without using solvents for purity evaluation with its high reproducibility.

FT-IR spectroscopy was also used for qualitative and quantitative analysis of different oil components mixed in certain portions in the literature. For example, FT-IR was used to detect blended soybean oil and sunflower oil to reduce the cost of avocado oil, which is mostly used in the cosmetics industry. For this purpose, it was analyzed by FT-IR by Jimenes-Sotelo et al and the results showed that it can be an accurate and reliable technique for the analysis of avocado oil (Jiménez-sotelo et al., 2016).

In another study, 36 samples prepared by mixing wheat oil obtained by cold pressing with pure sunflower and soybean oil in certain proportions were analyzed with FT-IR spectrometer. In the study conducted by Arslan et al., it was reported that oil mixtures below 1% could be determined by FT-IR (Arslan and Ça, 2018).

Many similar examples are given in the literature. Considering the advantages of the FT-IR method, such as its practicality, short analysis time, low cost, and no need for sample preparation, we can say that FT-IR is an effective characterization method that can be used to determine the chemical components and purity of oils.

Raman Spectroscopy

Raman spectroscopy is a branch of vibrational spectroscopy in which the spectrum of Raman-active vibrational modes generated by excited molecules as a result of exposure to an intense light beam is obtained (LiChan, 1996). As a result of the scattering of light by interaction with molecules, it has been observed that most of the wavelength is the same as the wavelength of the incoming light, and a very small part of it has been found to shift to different wavelengths. The shift of light to different wavelengths is Raman scattering, also known as inelastic scattering. During Raman scattering, the total energy is conserved, and the energy gained or lost by the photon must be equal to the energy between the vibrational energy levels of the molecule. Therefore, vibrational spectroscopy, in which information about the vibrational energy levels of molecules can be obtained thanks to the amount of energy gained or lost by the photon, is called Raman Spectroscopy (Ersöz, 2010).

Raman scattering is a spectroscopic analysis method that depends on the polarizability of functional groups as atoms vibrate, and functional groups such as C=O, N-H and O-H have strong infrared stretching vibrations and groups such as C=C, C-C and S-S form intense Raman lines. In this sense, FT-IR absorption and Raman scattering can also be seen as complementary to each other (LiChan, 1996).

For example, Raman spectroscopy analysis of 15 different essential oils preferred in the cosmetic industry was performed by Jentzsch et al. (Jentzsch et al., 2015) and principal component analysis of terpenoids in these essential oils with Raman spectra were successfully performed.

Gas Chromatography-Mass Spectrometry (GC-MS)

Chromatography is defined as the method used to separate substances with similar properties in complex mixtures. In the gas chromatography technique, the mobile phase is an inert gas and the sample is evaporated and injected into the column used as the stationary phase. Elution is carried out by the flow of the mobile phase, which is an inert gas. Elution is carried out by the flow of the mobile phase. The mobile phase in gas chromatography does not interact with the analyte molecules, but carries that analyte into the column. The GC-MS system is formed by connecting the gas chromatography device directly to various mass spectrometers. GC-MS is an analytical method that combines features of gas chromatography and mass spectrometry. The contents of the samples, which can be found in the gas phase or gasified by GC, can be mass separated and illuminated by advanced molecular determination. GC-MS system is used to recognize hundreds of substances in natural systems simultaneously (Skoog et al. 1998). GC-MS is a method mostly used for the determination of herbal essential oil components.

In a literature study, GC-MS was used for the characterization of essential oils and extracts obtained from the flowers, leaves and stems of Lippia origanoides plants growing wild in different regions of

Colombia. By principal component analysis of 139 substances detected in these essential oils and extracts, it was possible to classify L. origanoides into three chemotypes characterized by essential oil main components (Stashenko et al., 2010).

In another study in the literature, volatile compounds of cinnamon bark from three species and seven habitats were detected and identified for the first time by GC-MS and FTIR analysis. GC–MS analysis showed that the main compound in the essential oils of nine samples was trans-cinnamaldehyde (66.28–81.97%). In conclusion, this study has proven to be an effective strategy for species identification and geographic distribution, especially for assessing the quality of cinnamon for use in crude herbal medicines (Li et al., 2013).

Differential Scanning Calorimetry (DSC)

DSC provides important information about oils obtained from plants. DSC is generally known as a technique used to monitor the thermo-oxidative process against temperature. The transition between phases (liquid-solid, solid-liquid) is affected by the composition of the molecule. In this way, it can provide information about the purity of oil components. At the same time, melting and crystallization processes can provide information about oil quality, structure and origin. In the literature, the effect of heating and cooling rate on melting and crystallization thermograms is investigated, and in this way, researches are carried out on the use of calorimetric methods in quality control

(Anguili et al., 2006; Ferrari et al., 2007). Using DSC analysis, a relationship can be established between the quality and stability of oils.

In the literature, in a study examining the thermal properties of oils obtained from various plants, it was observed that the number of exothermic peaks occurring during the crystallization process and the number of endothermic peaks occurring during the melting process is different from oil to oil. The starting and ending temperatures of the peaks were calculated and it was examined whether there was a difference between them. As a result, it was determined that the difference between the crystallization initiation and melting end temperatures was statistically significant. It has been determined that DSC does not give direct information about the chemical composition of the herbal essential oils, but gives useful information about the thermodynamic changes that occur between phase transitions. Since these thermodynamic properties are sensitive to chemical composition, it has been concluded that they can be used in qualitative and quantitative evaluations. It has been suggested that the crystallization start temperature and the melting point temperature can be used to define the oil type (Tan and Man, 2000).

In another study in the literature, the relationship between the thermal properties and chemical composition of Biancolilla, Cerasuola and Nocellara type Sicilian olive oils were investigated. It was determined that in the Cerasulo type olive oil, which has a high unsaturation rate, the crystallization starts at a lower temperature and the melting starts at a higher temperature. Analysis results show that thermal properties are affected by olive oil composition, especially the unsaturation rate (Chiavaro et al., 2007; Chiavaro et al., 2008).

Nuclear Magnetic Resonance Spectrometer (NMR)

NMR is a spectroscopic technique that provides information about the structures, binding properties and chemical properties of organic molecules. Magnetic resonance occurs as a result of the interaction between an external magnetic field and the magnetic moment of atomic nuclei. NMR spectroscopy is a technique in which this magnetic resonance is monitored by radio waves. By measuring the magnetic moment of an atomic nucleus, which changes depending on its chemical environment, with NMR spectrometry, structure elucidation of organic molecules can be performed (Keeler, 2010; Günther, 2013).

The use of NMR, especially in the characterization of essential oils, has attracted attention in recent years. A major advantage of NMR is that essentially any organic compound can be easily detected with equal sensitivity without being subject to the detection limitations encountered in GC, such as volatility or lack of thermal stability (Schripsema et. al, 2022). In recent studies, it is seen that especially ^{1}H-NMR is used to determine the composition of herbal essential oils. If the results cannot be decided, the results can be supported with ^{13}C-NMR (Schripsema et. al, 2022).

In the literature, the components of the essential oils of Helichrysum species from South African medicinal plants by Adewinogo et al. were comparatively analyzed by GC-MS and NMR spectroscopy

(Adewinogo et. al, 2022). In recent years, it is observed that the number of similar studies has increased in the literature.

CONCLUCSIONS

When all the methods used in the production of essential oil are evaluated, the characteristics of the essential oil component and the purpose of producing the product are important when choosing the method. In particular, modern methods have attracted more attention in recent years due to their advantages such as giving results in a shorter time, creating less toxic waste, and high product purity. After the essential oils are obtained by appropriate separation techniques, the second important step is their characterization. As with the characterization of many components, many analysis techniques are used in the characterization of essential oil components. When the literature is investigated in detail, it is seen that methods such as FT-IR, GC-MS, Raman, DSC are widely used in the characterization of essential oils. In addition to these techniques, the use of NMR technique in the characterization of essential oils is also very important and its importance has been especially noticed in recent years. In summary, while a single analysis method may be sufficient to determine the content of some essential oils, comparisons need to be made using several techniques to determine the content of some components. This situation is closely related to the method used to obtain essential oils. If essential oils can be obtained pure, it will be easier to identify the components.

REFERENCES

Adewinogo, S. O., Sharma, R., Africa, C. W., Marnewick, J. L., & Hussein, A. A. (2022). Chemical Study and Comparison of the Biological Activities of the Essential Oils of *Helichrysum petiolare*, *H. cymosum*, and H. *odoratissimum*. Plants, 11(19): 2606.

Angiuli, M., Ferrari, C., Lepori, L., Matteoli, E., Salvetti, G., Tombari, E., Banti, A. & Minnaja, N. (2006). On testing quality and traceability of virgin olive oil by calorimetry. Journal of Thermal Analysis and Calorimetry, 84: 105-112.

Arslan, F.N., & Ça, F. (2018). Attenuated Total Reflectance–Fourier Transform Infrared (ATR-FTIR) Spectroscopy Combined with Chemometrics for Rapid Determination of Cold-Pressed Wheat Germ Oil Adulteration. Food Analytical Methods, 12: 355-370.

Beejmohun,V., Flınıaux, O., Grand, E., Lamblin, F., Bensaddek, L., Christen, P., Kovensky, J., Fliniaux, M. & Mesnard, F. (2007). Microwave-assisted extraction of the main phenolic compounds ın flaxseed. Phytochemical Analysis: An International Journal of Plant Chemical and Biochemical Techniques, 18(4): 275-282.

Ceylan, A. (1983). Tıbbi Bitkiler-II. Ege Üniversitesi Ziraat Fakültesi Yayını No:481, Bornova-İzmir.

Chiavaro, E., Vittadini, E., Rodriguez-Estrada, M.T., Cerratini, L., Bonoli, M., Bendini, A., & Lercker, G. (2007). Monovarietal extra virgin olive oils: correlation between thermal properties and chemical composition. Journal of Agricultural and Food Chemistry, 55: 10779-10786.

Chiavaro, E., Vittadini, E., Rodriguez-Estrada, M.T., Cerretani, L. & Bendini, A. (2008). Monovarietal virgin olive oils. Correlation between thermal properties and chemical composition: heating thermograms. Journal of Agricultural and Food Chemistry, 56: 496-501.

Çağlar, M.Y., Demirci, M., Şahiner, A., Çakır, B., & Çağlar, A.F. (2019). Spectroscopic Techniques Used in Food Analyses. Academic Food Journal, (March). 121-130. (In Turkish).

Ersöz, A. (2010). Aletli analiz. Anadolu Üniversitesi, Eskişehir.

Ferrari, C., Anguili, M., Tombari, E., Righetti, M.C., Matteoli, E. & Salvetti, G. (2007). Promoting calorimetry for olive oil authentication. Thermochimica Acta, 459(1-2): 58-63.

Filoda, P. F., Fetter, L. F., Fornasier, F., Cassia, R. De, & Schneider, D. S. (2018). Fast methodology for ıdentification of olive oil adulterated with a mix of different vegetable oils. Food Analytical Methods, 12: 293-304.

Günther, H. (2013). NMR spectroscopy: basic principles, concepts and applications in chemistry. John Wiley & Sons.

Jentzsch, P., Ramos, L., & Ciobotă, V. (2015). Handheld Raman spectroscopy for the distinction of essential oils used in the cosmetics industry, Cosmetics, 2(2): 162-176.

Jiménez-sotelo, P., Hernández-martínez, M., Osorio-revilla, G., Meza-márquez, O. G., García-ochoa, F., & Gallardo-, T. (2016). Food Additives & Contaminants: Part A Use of ATR-FTIR spectroscopy coupled with chemometrics for the authentication of avocado oil in ternary mixtures with sunflower and soybean oils. Food Add. & Contamin. Part A, 33(7): 1105-1115.

Kaufmann, B., & Christen, P. (2002). Recent Extraction Techniques For Natural Products: Microwave-Assisted Extraction And Pressurised Solvent Extraction. Phytochemical Analysis: An International Journal of Plant Chemical and Biochemical Techniques, 13(2): 105-113.

Kaufmann, B., Rudaz, S., Cherkaoui, S., Veuthey, J.L., & Chisten, P.. (2007). Influence of plant matrix on microwave-assisted extraction process. The case of diosgenin extracted from fenugreek (*Trigonella foenum-graecum* L.). Phytochemical Analysis: An International Journal of Plant Chemical and Biochemical Techniques, 18(1): 70-76.

Keeler, J. (2010). Understanding NMR spectroscopy. John Wiley & Sons.

Li, Y. Q., Kong, D. X., & Wu, H. (2013). Analysis and evaluation of essential oil components of cinnamon barks using GC-MS and FTIR spectroscopy. Industrial Crops and Products, 41: 269-278.

Li-Chan, E.C.Y. (1996). The applications of Raman spectroscopy in food science. Trends in Food Science & Technology, 11(7): 361-370.

Linskens, H.F., & Jackson, J.F. (1997a). Modern Methods of Plant Analysis. Vol. 19: Plant Volatile Analysis, Springer, Germany.

Linskens, H. F., & Jackson, J.F. (1997b). Modern Methods of Plant Analysis. Vol. 12: Essential Oils and waxes, Springer, Germany.

Mejri, J., Aydi, A., Abderrabba, M., & Mejri, M. (2018). Emerging extraction processes of essential oils: A review. Asian Journal of Green Chemistry, 2(3): 246-267.

Schripsema, J., da Silva, S. M., & Dagnino, D. (2022). Differential NMR and chromatography for the detection and analysis of adulteration of vetiver essential oils. Talanta, 237: 122928.

Settle, F. A. (1998). Handbook of instrumental techniqufoers for analytical chemistry. In IEEE Electrical Insulation Magazine, Vol. 14.

Skoog, D.A., Holler, F.J., & Nieman, T.A. (1998). Principles of Instrumental Analysis, Saunders College Publishing, USA, 849 s.

Stashenko, E. E., Martínez, J. R., Ruíz, C. A., Arias, G., Durán, C., Salgar, W., & Cala, M. (2010). Lippia origanoides chemotype differentiation based on essential oil GC-MS and principal component analysis. Journal of Separation Science, 33(1): 93-103.

Tan, C.P., & Che Man, Y.B. (2000). Differential scanning calorimetric analysis of edible oils: Comparision of thermal properties and chemical composition. Journal of the American Oil Chemists' Society, 77(2): 143-155.

Büyüksırıt, T. & Kuleasan H. (2014). Fourier transform ınfrared (ftır) spectroscopy and utilization in food. The Journal of Food, 39: 235-241.(In Turkish).

Vas, G., & Vekey, K. (2004). Solid-phase microextraction: apowerful sample preparation tool prior to mass spectrometric analysis. Journal of Mass Spectrometry, 39: 233-254.

Yamani, Y., Khajeh, M., Ghasemi, E., Mirza, M., & Javidnia, K. (2008). Comparison of essential oil compositions of salia mirzayanii obtained by supercritical carbondioxide extraction and hydrodistilaltion methods. Food Chemistry, 108(1): 341-346.

Yang, H., Irudayaraj, J., & Paradkar, M.M. (2005). Food Chemistry Discriminant analysis of edible oils and fats by FTIR, FT-NIR and FT-Raman spectroscopy. Food Chemistry, 93: 25-32.

CHAPTER 11

ALKALOIDS IN MEDICINAL AND AROMATIC PLANTS

Tuğba GÜRKÖK TAN[1]
Gülşen GÜÇLÜ[2]

[1] Çankırı Karatekin University, Food and Agriculture Vocational School, Department of Field Crops, Çankırı, Türkiye, e-mail: t.gurkok@karatekin.edu.tr ORCID ID: 0000-0003-0599-5628
[2] Sivas Cumhuriyet University, Health Services Vocational School, Department of Health Programs, Sivas, Türkiye, e-mail: gulsenguclu@cumhuriyet.edu.tr ORCID ID: 0000-0002-3599-213X

INTRODUCTION

The chemical components of plants can lead to many innovative results in terms of medicine, economy and agriculture. In recent years, there has been a remarkable acceleration thanks to important studies on plant chemistry. By searching plant metabolites, new ideas about nutrition, cosmetics, agricultural control and treatment of diseases can be developed.

Secondary metabolites are products that directly affect the plant's defence, reproduction and development mechanisms. Classification of secondary metabolites and revealing their effects on plants help to reveal both plant physiology and the effects of these metabolites on different living things.

1. PLANT SECONDARY METABOLITES

Plant secondary metabolites are agents that contain a large number of chemical compounds produced by plant cells through various metabolic pathways. This concept was first defined in 1910 by Nobel Prize winner in Physiology/Medicine Albrecht Kossel (Jones, 1953). With the development of chromatographic analysis methods towards the middle of the twentieth century, strong data could be obtained from phytochemical studies on secondary metabolites.

Secondary metabolites have a wide variety of functions in nature. They are important for defence and reproduction mechanisms as well as taking part in all interactions of plants with their environment. In particular, its antifungal, antiviral and antibiotic effects protect the plant from pathogens. They also minimize the harmful effects of the sun by absorbing the ultraviolet rays. In this way, the damage that may occur on the leaves is prevented.

Secondary metabolites' biosynthesis pathways have been determined in general terms but the plant-specific content and composition of secondary metabolites may vary depending on various effects.

2. PLANT ALKALOIDS

Alkaloids are a class of low molecular weight, amino acid-derived nitrogen-containing organic compounds produced in various organisms, such as plants, animals, fungi or bacteria (Moreira et al., 2018). These properties are an important feature in the production of medicines. They are less soluble in water and more soluble in organic solvents (Aniszewski, 2007).

Secondary metabolites are molecules with important biological activities are produced in plants in response to environmental stimuli, biotic and abiotic stress (Taha et al., 2009). Alkaloids provide protection from pests in plants, as well as regulate their growth and development (Chik et al., 2013). In addition to being a part of the organism's natural defense system in plants, it is also largely used in medicine and pharmacy. They are used therapeutically, in particular, as anesthetics, cardioprotective and anti-inflammatory agents. Among the most well-known alkaloids in the clinical field are morphine, strychnine, quinine, ephedrine, and nicotine (Kurek, 2019). Quinine alkaloids from *Cinchona ledgeriana* and morphine alkaloids from poppy (*Papaver somniferum*) were the first to be isolated, and the pharmacological properties of these compounds accelerated the study of alkaloids (Rosales et al., 2020).

Alkaloids are found in very small amounts in about 20% of plant species (Srivastava and Srivastava, 2013). Although it is more abundant in higher plants, at least 25% of these plants contain these molecules. Generally, plants containing more than 0.01% alkaloids are defined as alkaloid-containing plants (Hegnauer, 1988). In general, they are found in a certain organ of plants (such as root, bark, leaf, fruit, seed). Not every organ of an alkaloid-producing plant may contain alkaloids. Plants rarely contain only one type of alkaloid. Usually a group of alkaloids with the same structure with very minor differences coexist. One of them can be found more than the others or be more active. Most of the alkaloids are specific to a species or close species, while some are specific to a family (Aniszewski, 2007; Gürkök et al., 2010).

Based on their structure, alkaloids are divided into 3 main groups according to their shape and origin.

2.1. True alkaloids

True alkaloids are molecules that are derived from amino acids and they share a nitrogen-containing heterocyclic ring. Even at low doses, their biological activity is high. All true alkaloids have a bitter taste, and all of them are white and solid, except for nicotine, which is a brown liquid. These alkaloids are found in a limited number of species and families.

The primary precursors of the true alkaloids are the amino acids L-Histidine, L-Ornithine, L-Tryptophan, L-Phenylalanine/L-Tyrosine and L-Lysine (Dewick, 2002). Cocaine, quinine and morphine are the members of true alkaloids (Aniszewski, 2007).

2.2. Protoalkaloids

They contain a nitrogen atom, that is derived from an amino acid but is not part of the heterocyclic ring. These alkaloids include compounds derived from L-Tyrosine and L-Tryptophan. Examples of these alkaloids are hordenin, mescaline and yohimbine (Aniszewski, 2007).

2.3. Pseudoalkaloids

Basic carbon skeletons are are not directly derived from amino acids. These types of alkaloids are composed of precursors or postcursors of amino acids. Ephedrine, caffeine, capsaicin are very common examples of these alkaloids (Aniszewski, 2007).

3. CLASSIFICATION OF ALKALOIDS BASED ON THEIR HETEROCYCLIC RING SYSTEM AND BIOSYNTHETIC PRECURSOR

3.1. Indole alkaloids

The fact that indole alkaloids have anti-inflammatory, antinociceptive, antitumoral, antioxidant and antimicrobial properties has made this group of alkaloids remarkable. Indole alkaloids are derived from tryptophan amino acid. These compounds have a wide structural diversity and activity due to the species of plants that produce them. It is known that it covers more than 4000 compounds (Marinho 2016). Vincamine, vinblastine, strychnine, ajmalicin, vincristine and ajmalin are the most studied compounds (Wang et al., 2011). According to their chemical structures, indole alkaloids are examined in 3 groups: monoterpenoid indole alkaloids (MIA), ergolines and β-carbolic indole alkaloids (Rosales et al., 2020).

3.1.1. Monoterpenoid indole alkaloids (MIA)

They have more than 3000 identified varieties of alkaloids in the plant kingdom. The vast majority of these metabolites are physiologically active in mammals. They are synthesized in the families of Rubiaceae, Apocynaceae, Nyssaceae and Loganiaceae (De Luca et al., 2014). They are known as the group with the greatest number compounds among the indole alkaloids (Rosales et al., 2020). The main source of antitumor agents' vincristine and vinblastine alkaloids is the *Catharanthus roseus* and it is also used as a model organism (Pan et al., 2016).

3.1.2. Ergolines

Ergoline (ergot) alkaloids are a group of physiologically active indole alkaloids synthesized by the family Clavicipitaceae from the kingdom of fungi and plants such as *Turbina corymbosa* and *Ipomoea asarifolia* in the family Convolvulaceae from the plant kingdom. The pharmacological effects of various alkaloids or derivatives are due to their structural similarity to neurotransmitters such as noradrenaline, serotonin or dopamine (Tudzynski et al., 2001). They have features such as migraine or regulation of blood pressure regulation (Wadworth and Chrisp, 1992).

3.1.3. β-carboline indole alkaloids

β-carboline indole alkaloids are a large group of natural and synthetic indole alkaloids synthesized by various plants, sea creatures, insects and mammals. These compounds have a wide range of pharmacological properties including hypnotic, antiparasitic, sedative, antiviral, anticonvulsant, antimicrobial, anxiolytic as well as antitumor activities (Wadworth and Chrisp, 1992).

3.2. Isoquinoline alkaloids

Isoquinoline alkaloids are commonly found in higher plants which are one of the largest groups of substances. These alkaloids are the most abundant alkaloids in plants. They are derived from phenylalanine or tyrosine. These alkaloids contain a tetrahydroisoquinoline or an isoquinoline ring in their skeleton. Amaryllidaceae, Annonaceae, Berberidaceae, Fumariaceae, Papaveraceae, Ranunculaceae and Rutaceae families synthesize isoquinoline alkaloids (Kukula-Koch and Widelski, 2017). Alkaloids in this group have medicinal properties such as, anticancer, antiviral, analgesic, antifungal, antispasmodic,c antioxidant and enzyme inhibitor (Dey et al., 2020). According to their structure, they are divided into two groups: simple isoquinolines and benzylisoquinolines (Khan and Suresh Kumar, 2015). There are approximately 2,500 known members of the benzylisoquinoline alkaloids (BIA) and they have potential pharmacological properties.

Like other secondary or specialized metabolites, they are produced not for normal growth and development in the plant, but for defense against pathogens and herbivores. Morphine and codeine are powerful analgesics and have been known and produced for thousands of years. Other BIAs used pharmaceutically are antimicrobial agents sanguinarine and berberine, antitussive and strong antineoplastic (anticarcinogenic) noscapine, vasodilator papaverine, muscle relaxant (+)-tubocurarine (Alagoz et al., 2016). These alkaloids are mostly found in the Menispermaceae, Papaveraceae Ranunculaceae, Berberidaceae families; the most studied species are *Coptis japonica*, *Papaver somniferum*, *Eschscholzia californica* and *Thalictrum flavum* (Ziegler and Facchini, 2008).

3.3. Quinolizidine alkaloids

Quinolizidine alkaloids are derived from the L-lysine. In particular, they are found in genera such as *Lupinus*, *Cystus* and *Sophora* of the Leguminosae family (Bunsupa et al., 2012). The most widely known quinolizidine alkaloids are sparteine alkaloids (*Sarothamnus scoparius*), cytisine (*Laburnum* species) and lupanin (*Lupinus luteus*), (Kaur and Arora, 2015). These alkaloids show antimicrobial activity against a large number of microorganisms (Singh et al., 2011).

3.4. Quinoline alkaloids

Quinoline alkaloids are derived from L-tryptophan. It has been of interest to researchers for 200 years. Quinine, synthesized by the *Cinchona ledgeriana* which is used in the treatment of malaria, is the most important member of this group (Wiesner et al., 2003). Some other known members are pamakin, chloroquine, taphenoquine and bulakin (Kaur and Arora, 2015). Antibacterial, antiparasitic, antitumor, antimalarial, insecticidal, antifungal and, antiviral, antiplatelet, anti-inflammatory activities of alkaloids belonging to this group have been demonstrated by studies (Anjali et al., 2016; Shang et al., 2018).

3.5. Purine alkaloids

Purine alkaloids are the best known secondary metabolite synthesized from nucleotides. They are methylurates and methylxanthines, whose structure is based on xanthine and urate skeletons. The main purine alkaloid is caffeine, which is typically found in popular soft drinks such as tea, coffee and maté (a tea consumed in South America). Theobromine which is found in cocoa drinks and chocolate products is a purine alkaloid obtained from the seeds of *Theobroma cacao* (Zheng et al., 2004). However, "kucha tea", which is claimed to have analgesic and anti-inflammatory effects, is also obtained from the leaves of the *Camellia assamica* var. kucha plant and is often consumed for herbal medicine in China (Ashirira et al., 2017).

3.6. Piperidine alkaloids

They are derived from L-lysine. This group has about 700 members. Piperidine alkaloids lobelin, piperine and pelletierin are synthesized by *Lobelia inflata* (Lobeliaceae), *Piper nigrum* (Piperaceae) and *Punica granatum* (Lythraceae), respectively (Liu et al., 2010; Goel et al., 2018).

3.7. Pyridine alkaloids

These heterocyclic structures containing an unsaturated nitrogen radical in their nuclei are derived from the amino acid L-ornithine. Some common pyridine alkaloids are trigonelline, piperine, lobeline, coniine, arecaidine, arecoline, cysticine, guvacine, anabasin, nicotine, pellethyrine and sparteine (Kaur and Arora, 2015). In these alkaloids have a nitrogen atom, which have a distinctive structural skeleton in medicinal chemistry, plays a significant role in the compound of many drugs containing this structure (Vitaku et al., 2014).

3.8. Pyrolizidine alkaloids

More than 500 compounds have been identified, derived from the pyrrolizidine alkaloid amino acid ornithine. Pyrolizidine alkaloids are naturally occurs and are isolated from plants. They are known to cause severe hepatotoxicity, genotoxicity and neurological damage affecting farm animals, wildlife and humans (Neuman et al., 2015). Pyrolizidine alkaloids can be found mainly in the Boraginaceae and Asteraceae families (Schramm et al., 2019).

3.9. Tropane alkaloids

Tropane alkaloids are derived from ornithine and have a complex structure (Mao et al., 2014). They are among the first to be detected in nature. They have a wide application in various drug groups (Philipov and Doncheva, 2013). More than 200 alkaloids are found in this group and they are mostly found in different families such as Euphorbiaceae, Solanaceae and Brassicaceae (Jirschitzka et al., 2012). It is known that tropane alkaloids are abundant in the Solanaceae family, mostly in *Hyoscyamus* (scopolamine), *Atropa* (atropine) and *Datura* (hyoskyamine and scopolamine) genera (Ajungla et al., 2009; Wink, 2010; Guirimand et al., 2010). Cocaine is one of the tropane alkaloids derived from *Erythroxylum coca* (Erythroxylaceae). Only in this species 186 alkaloids were detected (Oliveira et al., 2010; Jirschitzka et al., 2012). Atropine is another common tropane alkaloid and is on the World Health Organization's list of essential drugs (Ranjitha and Sudha 2015).

4. ALKALOIDS IN MEDICINAL AND AROMATIC PLANTS

Alkaloids are secondary metabolites, many of which are synthesized by plants, with a unique mechanism of action. Medicinal plants, containing alkaloids with various biological activities, are pharmacologically valuable. In this section, medicinal and aromatic plants and their alkaloids showing important biological activities have been complied.

4.1. Alkaloids showing muscle relaxation properties

Alkaloids have muscle relaxant properties as well as many biological activities. Benzylisoquinoline derivative D-tubocurarine, obtained from *Chondrodendron tomentosum* (Menispermaceae) and *Strychnos toxifera* (Loganiaceae), shows antiparalytic activity by blocking acetylcholine receptor points at neuromuscular junctions of muscles (Gustafson, 1989; Das et al., 1997; Bowman, 2006). Aporphine alkaloids, such as corstuben, magnofluorine, isotebaine, and isochoridine isolated from *Mahonia aquifolium* (Berberidaceae), have been reported to relax noradrenaline-induced contractions in the rat aorta compared to those induced by KCl in in vivo studies (Sotnikova et al., 1997). Papaverine, a benzylisoquinoline alkaloid also produced by opium poppy (Papaveraceae), has smooth muscle relaxant properties. This alkaloid has a function on relaxing the smooth muscles of large blood vessels (Schmeller and Wink, 1998) Tubarine or jexin which are the tubocurarine derivatives have been applied as a muscle relaxant (Aniszewski, 2007).

4.2. Alkaloids showing antioxidant activities

Alkaloids are known to have antioxidant activities due to their free radical scavenging capacity, metal chelating or electron/hydrogen donating abilities. So far, thousands of studies have been conducted with a large number of plants in this area and studies are still ongoing. Many alkaloids were tested by DPPH assay but the isolation methods, the collection regions or environmental conditions makes it difficult to evaluate or compare results. Here, we give some examples of the alkaloids showing antioxidant properties.

It has been reported that four different alkaloids (vindoline, vindolidine, vindolicine, and vindoline) isolated from *Catharanthus roseus* L. show antioxidant activity in ORAC and DPPH tests, and among these, especially vindolicine has high antioxidant activity (Tiong et al., 2013). Correché et al. (2008) reported that alkaloids isolated from *Coptis japonica* and *Mahonia aquifolum*, such as berberine, canadine, anonain and antioquine, have antioxidant and cytotoxic effects similar to alpha-tocopherol and trolox (Račková et al., 2004).

A quinoline alkaloid obtained from of *Oryza sativa cv Heugjinmi*, has been reported to exhibit moderate antioxidant properties using DPPH radicals as a substrate (Chung and Woo, 2001). Five β-carboline alkaloids (harmaline, harmane, harmalol, harmine and 1,2,3,4-tetrahydroharmane-3-carboxylic acid) are examined for their antioxidant activity by using *in vitro* and molecular docking analysis. The results displayed that harmaline and harmalol have high antioxidant activity *in silico* and *in vitro* (Senhaji et al., 2022). In a study by Dalimunthe et al. in 2018, it was reported that alkaloids isolated from *Litsea cubeba* (Lour.) had high antioxidant capacity.

4.3. Alkaloids showing anticancer activities

Many studies have reported that alkaloids show chemotherapeutic, cytotoxic and antiproliferative properties (Mondal et al., 2019). Alkaloids are still of interest to researchers due to their effects on metabolic pathways such as proliferation, cell cycle and metastasis (Millimouno et al., 2014). Alkaloids such as, vinblastine, vincristine, camptothecin, sanguinarine, berberine, noscapine, vetetrandrin and matrine are well-known for their powerful chemotherapeutic properties. It has been reported that vindesine, vinblastine and vincristine obtained from *Catharanthus roseus* inhibit cell proliferation by affecting mitotic activity (Jordan et al., 1991). However, vinblastine and vincristine alkaloids are used in combination with chemotherapeutic agents in the treatment of many cancer diseases such as lung cancer, lymphoma, breast, leukaemia, advanced testicular cancer, and Kaposi's sarcoma (Cragg and Newman, 2005). Vinblastine is an autophagy maturation inhibitor and has been used in combination with nanoliposomal C6-ceramide (autophagy inducer) (Craig and Jensen, 2016). Thus, autophagy maturation of cells was reduced and increased apoptotic cell death in LS174T (human colon) and HepG2 (human hepatocarcinoma) cell lines (Adiseshaiah et al., 2013).

Prodigiosin, a pyrrole alkaloid synthesized by *Serratia marcescens*, suppressed cyclin D1 and showed cytotoxic effect against human oral squamous carcinoma cells. (Cheng et al., 2017). Fangquinoline isolated from *Stephania tetrandra* is a bisbenzylisoquinoline alkaloid and has been reported to induce apoptosis and autophagy in T24 and 5637 bladder cancer cells (Fan et al., 2017). The anthophin alkaloid, synthesized by *Cynanhum paniculatum*, has been found effective against A549 and HCT-8 cell lines (Mandhare et al., 2015).

Various studies have shown that berberine, an isoquinoline alkaloid, has an anticancer effect due to the fact that it interferes with the progression of the tumor to its formation, both in vitro and in vivo experiments (Sun et al., 2009). It has also been shown that piperine induced apoptosis and effect on G2/ M phase 4T1 cells (Lai et al.,2012).

4.4. Alkaloids showing antimicrobial activities

The excessive increase in the use of antibiotics in recent years has led to the emergence of a large number of drug-resistant microorganisms, which has accelerated the search for new antimicrobial compounds. Among the secondary metabolites investigated, polyphenols and alkaloids have revealed strong antimicrobial activity.

Diterpenoid alkaloids isolated from *Delphinium* have been reported to have moderate antifungal activity as well as anti-nutritive activity against insect species *Leptinotarsa decemlineata* and *Spodoptera littoralis* (Gonzalez-Coloma et al., 1998).

In their review on indole alkaloids, Gul and Hamann (2005) mentioned the antiviral activities of Eudistomin, which is isolated from *Eudistoma olivaceum*, against DNA viruses such as HSV-1, HSV-2, Vaccinia virus, RNA viruses such as horse rhinovirus, Coxsachie A-21.

De Luca (2006) found that imidazole derivatives have enormous therapeutic agent and also reported on their antimicrobial activity. It has been reported that the alkaloids in the ethanol extract of *Datura stramonium* have antimicrobial activity on some pathogenic microorganisms. Examined microorganisms were found to be more sensitive to ethanol leaf extract of the plant compared to standard antibiotics (Altameme et al., 2015). The antimicrobial activity of water and ethanol extracts of *Achillea millefolium* (Yarrow), which is known to contain essential oil rich in alkaloids and sesquiterpene lactones, on *Pseudomonas aeruginosa*, *Shigella flexneri*, *Staphylococcus aureus*, *Salmonella enterica subsp. enterica*, *Micrococcus luteus* ve *Enterococcus faecalis* was tested. Results indicated that yarrow extracts showed a broad spectrum of antibacterial activity at different rates against the tested bacteria (Hasson, 2011).

4.5. Various activities of alkaloids

The various pharmacological activities of some major alkaloids are summarized in the table below (Table 1).

Table 1: Plant Alkaloids and Their Use in Medicine

Alkaloids	Medicinal Effects	Plant	References
Atropine, hyoscyamine, scopolamine	Anticholinergic	*Duboisia myoporoides*	Palazon et al., 2003
Caffeine	Adenosine receptor and antagonist, stimulant	*Camellia sinensis*	Wang et al., 2011
Codeine	Analgesic, anti-cough	*Papaver somniferum*	Diamond and Desgagné-Penix, 2016
Colchicine	Gout, FMF diseases drug active ingredient	*Colchicum autumnale*	Kukula-Koch and Widelski, 2017
Emetine	Emesis, antiprotozoal agent	*Psychotria ipecacuanha*	Upcroft, 2001
Morphine	Analgesic	*Papaver somniferum*	Diamond and Desgagné-Penix, 2016
Nicotine	Nicotinic acetylcholine receptor agonist, stimulant	*Nicotiana tabacum*	Baranska et al., 2013
Physostigmine	Acetylcholinesterase inhibitor	*Physostigma venenosum*	Batiha et al., 2020
Quinidine	Antiarrhythmic	*Cinchona officinalis*	Raza et al., 2021
Quinine	Malaria treatment, antipyretic	*Cinchona officinalis*	Raza et al., 2021
Reserpine	Antihypertensive	*Rauwolfia serpentina*	Lobay, 2015
Tubocurarine	Muscle relaxant	*Plumeria alba*	Khan et al., 2021
Yohimbine	Aphrodisiac, stimulant	*Rauwolfia vomitoria*	Wibowo et al., 2021

CONCLUSIONS

Alkaloids are a group of compounds that have been widely used for medicinal purposes all over the world since ancient times. Both agricultural and biotechnological production, extraction and processing still continue to be the subject of current and widespread research. The diversity of alkaloids in their chemical structures, their distribution and functional properties are quite complex. In addition, it is known that alkaloids, which are very important from a pharmaceutical point of view, are used in the treatment of diseases that are difficult to treat, such as diabetes, neurological disorders and cancer. The search for new alkaloids to treat chemotherapy-resistant cancers is still ongoing.

However, due to the wide chemo-diversity of alkaloids, studies to define their structure and pharmacological properties are still needed, as well as preclinical and clinical studies to test their safe use in humans.

Medicinal plants are the major source to produce alkaloids. With future studies on known and to be discovered alkaloids, both the pharmaceutical botanical field and medical treatment methods are expected to develop significantly.

REFERENCES

Adiseshaiah, P.P., Clogston, J.D., McLeland, C.B., Rodriguez, J., Potter, T.M., Neun, B.W., ... & McNeil, S.E. (2013). Synergistic combination therapy with nanoliposomal C6-ceramide and vinblastine is associated with autophagy dysfunction in hepatocarcinoma and colorectal cancer models. Cancer Letters, 337(2): 254-265.

Ajungla, L., Patil, P.P., Barmukh, R.B., & Nikam, T.D. (2009). Influence of biotic and abiotic elicitors on accumulation of hyoscyamine and scopolamine in root cultures of *Datura metel* L. Indian Journal of Biotechnology, 8(3): 317-322.

Alagoz, Y., Gurkok, T., Zhang, B., & Unver, T. (2016). Manipulating the biosynthesis of bioactive compound alkaloids for next-generation metabolic engineering in opium poppy using CRISPR-Cas 9 genome editing technology. Scientific reports, 6(1): 1-9.

Altameme, H.J., Hameed, I.H., & Kareem, M.A. (2015). Analysis of alkaloid phytochemical compounds in the ethanolic extract of *Datura stramonium* and evaluation of antimicrobial activity. Afr. J. Biotechnol. 14: 1668-1674.

Aniszewski, T. (2007). Alkaloids-Secrets of Life: Aklaloid Chemistry, Biological Significance, Applications and Ecological Role. Elsevier. pp.334.

Anjali, Pathak, D., & Singh, D. (2016). Quinoline: A diverse therapeutic agent. Int J Pharm Sci Res, 7(1): 1-13.

Baranska, M., Roman, M., Schulz, H., & Baranski, R. (2013). Recent advances in Raman analysis of plants: alkaloids, carotenoids, and polyacetylenes. Current Analytical Chemistry, 9(1): 108-127.

Batiha, G.E.S., Alkazmi, L.M., Nadwa, E.H., Rashwan, E.K., Beshbishy, A.M., Shaheen, H., & Wasef, L. (2020). Physostigmine: A plant alkaloid isolated from *Physostigma venenosum*: A review on pharmacokinetics, pharmacological and toxicological activities. Journal of Drug Delivery and Therapeutics, 10(1-s):187-190.

Bowman, W.C. (2006). Neuromuscular block. British journal of pharmacology, 147(S1): S277-S286.

Bunsupa, S., Yamazaki, M., & Saito, K. (2012). Quinolizidine alkaloid biosynthesis: recent advances and future prospects. Frontiers in Plant Science, 3: 239.

Cheng, M.F., Lin, C.S., Chen, Y.H., Sung, P. J., Lin, S. R., Tong, Y. W., & Weng, C. F. (2017). Inhibitory growth of oral squamous cell carcinoma cancer via bacterial prodigiosin. Marine drugs, 15(7): 224.

Chik, S.C., Or, T.C., Luo, D., Yang, C.L., & Lau, A.S. (2013). Pharmacological effects of active compounds on neurodegenerative disease with gastrodia and uncaria decoction, a commonly used poststroke decoction. The Scientific World Journal, Article ID 896873.

Chung, H. S., & Woo, W. S. (2001). A quinolone alkaloid with antioxidant activity from the aleurone layer of anthocyanin-pigmented rice. Journal of Natural Products, 64(12): 1579-1580.

Correché, E.R., Andujar, S.A., Kurdelas, R.R., Lechón, M.J.G., Freile, M.L., & Enriz, R.D. (2008). Antioxidant and cytotoxic activities of canadine: Biological effects and structural aspects. Bioorganic & Medicinal Chemistry, 16(7): 3641-3651.

Cragg, G.M., & Newman, D.J. (2005). Plants as a source of anti-cancer agents. Journal of Ethnopharmacology, 100(1-2): 72-79.

Craig, S. L., & Jensen, V. B. (2017). Animal models in cancer nanotechnology. In Nanotechnology in Cancer (pp. 45-69). William Andrew Publishing.

Dalimunthe, A., Hasibuan, P. A. Z., Silalahi, J., Sinaga, S. F., & Satria, D. (2018). Antioxidant activity of alkaloid compounds from Litsea cubeba Lour. *Oriental* Journal of Chemistry, 34(2): 1149.

Das, M., Vedasiromoni, J. R., Chauhan, S. P. S., & Ganguly, D. K. (1997). Effect of green tea (*Camellia sinensis*) extract on the rat diaphragm. Journal of Ethnopharmacology, 57(3): 197-201.

De Luca, L. (2006). Naturally occurring and synthetic imidazoles: Their chemistry and their biological activities. Current Medicinal Chemistry, 13(1): 1-23.

De Luca, V., Salim, V., Thamm, A., Masada, S.A., & Yu, F. (2014). Making iridoids/secoiridoids and monoterpenoid indole alkaloids: progress on pathway elucidation. Current Opinion in Plant Biology, 19: 35-42.

Dewick, P.M. (2002). Medicinal Natural Products: A Biosynthetic Approach. John Wiley & Sons.

Dey, P., Kundu, A., Kumar, A., Gupta, M., Lee, B.M., Bhakta, T., ... & Kim, H.S. (2020). Analysis of alkaloids (indole alkaloids, isoquinoline alkaloids, tropane alkaloids). In: A. Sanches Silva, S. F. Nabavi, S. M. Nabavi. Recent Advances in Natural Products Analysis, Elsevier.

Diamond, A., & Desgagné-Penix, I. (2016). Metabolic engineering for the production of plant isoquinoline alkaloids. Plant Biotechnology Journal, 14(6): 1319-1328.

Goel, P., Alam, O., Naim, M. J., Nawaz, F., Iqbal, M., & Alam, M. I. (2018). Recent advancement of piperidine moiety in treatment of cancer-A review. European Journal of Medicinal Chemistry, 157: 480-502.

González-Coloma, A., Guadano, A., Gutiérrez, C., Cabrera, R., de la Pena, E., de la Fuente, G., & Reina, M. (1998). Antifeedant delphinium diterpenoid alkaloids. structure– activity relationships. Journal of Agricultural and Food Chemistry, 46(1): 286-290.

Guirimand, G., Courdavault, V., St-Pierre, B., & Burlat, V. (2010). Biosynthesis and regulation of alkaloids. In: E.C., Pua; M.R., Davey, Plant Developmental Biology-Biotechnological Perspectives, Springer, Berlin, Heidelberg.

Gul, W., & Hamann, M.T. (2005). Indole alkaloid marine natural products: An established source of cancer drug leads with considerable promise for the control of parasitic, neurological and other diseases. Life Sciences, 78(5): 442-453.

Gustafson, T. (1989). Pharmacological control of muscular activity in the sea urchin larva. I. Effects of nicotinic and muscarinic agents. Comparative Biochemistry and Physiology Part C: Comparative Pharmacology, 94(1): 1-14.

Gürkök, T., Boztepe, G., Kaymak, E., Parmaksız, İ. (2010) Alkaloid Biosynthesis Mechanism in Opium Poppy (*Papaver somniferum* L.). *Teknolojik Araştırmalar Dergis*i, 2: 31-45.

Hasson, R. (2011). Antibacterial activity of water and alcoholic crude extract of flower Achillea millefolium. Rafidain Journal of Science, *22*(5): 11-20.

Hegnauer, R. (1988). Biochemistry, distribution and taxonomic relevance of higher plant alkaloids. Phytochemistry, 27(8): 2423-2427.

Jirschitzka, J., Schmidt, G.W., Reichelt, M., Schneider, B., Gershenzon, J., & D'Auria, J.C. (2012). Plant tropane alkaloid biosynthesis evolved independently in the Solanaceae and Erythroxylaceae. Proceedings of the National Academy of Sciences, 109(26): 10304-10309.

Jones, M. E. (1953). Albrecht Kossel, a biographical sketch. The Yale Journal of Biology and Medicine, 26(1): 80.

Jordan, M.A., Thrower, D., & Wilson, L. (1991). Mechanism of inhibition of cell proliferation by Vinca alkaloids. Cancer Research, 51(8): 2212-2222.

Kaur, R. & Arora, S. (2015). Alkaloids-important therapeutic secondary metabolites of plant origin. J Crit Rev, 2(3): 1-8.

Khan, A. Y., & Suresh Kumar, G. (2015). Natural isoquinoline alkaloids: binding aspects to functional proteins, serum albumins, hemoglobin, and lysozyme. Biophysical Reviews, 7(4): 407-420.

Khan, I. A., Hussain, M., Syed, S.K., Saadullah, M., Alqahtani, A. M., Alqahtani, T., ... & Zeng, L. H. (2021). Pharmacological justification for the medicinal use of *Plumeria rubra* Linn. in cardiovascular disorders. Molecules, 27(1): 251.

Kukula-Koch, W.A., & Widelski, J. (2017). Chapter 9-Alkaloids A2-Badal, Simone. Pharmacognosy; Delgoda, R., Ed.; Academic Press*:* Boston, MA, USA, 163-198.

Kurek, J. (2019). Alkaloids: Their importance in Nature and Human life. BoD–Books on Demand.

Lai, L. H., Fu, Q. H., Liu, Y., Jiang, K., Guo, Q. M., Chen, Q. Y., ... & Shen, J. G. (2012). Piperine suppresses tumor growth and metastasis in vitro and in vivo in a 4T1 murine breast cancer model. Acta Pharmacologica Sinica, 33(4): 523-530.

Liu, H. L., Huang, X.Y., Dong, M.L., Xin, G.R., & Guo, Y.W. (2010). Piperidine alkaloids from Chinese mangrove Sonneratia hainanensis. Planta Medica, 76(09): 920-922.

Lobay, D. (2015). Rauwolfia in the treatment of hypertension. Integrative Medicine: A Clinician's Journal, 14(3): 40.

Mandhare, A., a Dhulap, S., & Biradar, S. C. (2015). Review on the anticancer and in-silico binding studies of phenanthroindolizidine alkaloids. Chemical Informatics.

Mao, Z., Huang, S., Gao, L., Wang, A., & Huang, P. (2014). A novel and versatile method for the enantioselective syntheses of tropane alkaloids. Science China Chemistry, 57(2): 252-264.

Millimouno, F. M., Dong, J., Yang, L., Li, J., & Li, X. (2014). Targeting apoptosis pathways in cancer and perspectives with natural compounds from mother nature. Cancer Prevention Research, 7(11): 1081-1107.

Mondal, A., Gandhi, A., Fimognari, C., Atanasov, A. G., & Bishayee, A. (2019). Alkaloids for cancer prevention and therapy: Current progress and future perspectives. European Journal of Pharmacology, 858: 172472.

Moreira, R., Pereira, D. M., Valentão, P., & Andrade, P. B. (2018). Pyrrolizidine alkaloids: Chemistry, pharmacology, toxicology and food safety. International journal of molecular sciences, 19(6): 1668.

Neuman, M.G., Cohen, L., Opris, M., Nanau, R.M., & Jeong, H. (2015). Hepatotoxicity of pyrrolizidine alkaloids. Journal of Pharmacy & Pharmaceutical Sciences, 18(4): 825-843.

Oliveira, S. L., da Silva, M. S., Tavares, J. F., Sena-Filho, J. G., Lucena, H. F., Romero, M. A., & Barbosa-Filho, J. M. (2010). Tropane alkaloids from Erythroxylum genus: distribution and compilation of 13C-NMR spectral data. Chemistry & Biodiversity, 7(2): 302-326.

Palazon, J., Moyano, E., Cusido, R. M., Bonfill, M., Oksman-Caldentey, K. M., & Piñol, M. T. (2003). Alkaloid production in Duboisia hybrid hairy roots and plants overexpressing the h6h gene. Plant Science, 165(6): 1289-1295.

Pan, Q., Mustafa, N. R., Tang, K., Choi, Y. H., & Verpoorte, R. (2016). Monoterpenoid indole alkaloids biosynthesis and its regulation in Catharanthus roseus: a literature review from genes to metabolites. Phytochemistry Reviews, 15(2): 221-250.

Philipov, S., & Doncheva, T. (2013). Alkaloids derived from ornithine: tropane alkaloids. In: Ramawat, K. G., Merillon, J.M., Natural Products. Springer.

Račková, L., Májeková, M., Košt'álová, D., & Štefek, M. (2004). Antiradical and antioxidant activities of alkaloids isolated from *Mahonia aquifolium* structural aspects. Bioorganic & Medicinal Chemistry, 12(17): 4709-4715.

Ranjitha, D., & Sudha, K. (2015). Alkaloids in foods. International Journal of Pharmaceutical, Chemical & Biological Sciences, 5(4): 896-906.

Raza, M.A., Rehman, F.U., Anwar, S., Zahra, A., Rehman, A., Rashıd, E., ... & Ilahı, H. (2021). The medicinal and aromatic activities of cinchona: a review. Asian Journal of Advances in Research, 42-45.

Rosales, P.F., Bordin, G.S., Gower, A.E., & Moura, S. (2020). Indole alkaloids: 2012 until now, highlighting the new chemical structures and biological activities. Fitoterapia, 143: 104558.

Schmeller, T., & Wink, M. (1998). Utilization of alkaloids in modern medicine. In: M. F., Roberts, M., Wink. Alkaloids. Springer, Boston, MA.

Schramm, S., Köhler, N., & Rozhon, W. (2019). Pyrrolizidine alkaloids: biosynthesis, biological activities and occurrence in crop plants. Molecules, 24(3): 498.

Senhaji, S., Lamchouri, F., Akabli, T., & Toufik, H. (2022). In vitro antioxidant activities of five β-carboline alkaloids, molecular docking, and dynamic simulations. Structural Chemistry, 33(3): 883-895.

Shang, X.F., Morris-Natschke, S.L., Liu, Y.Q., Guo, X., Xu, X.S., Goto, M., ... & Lee, K.H. (2018). Biologically active quinoline and quinazoline alkaloids part I. Medicinal research reviews, 38(3): 775-828.

Singh, K. S., Das, B., & Naik, C. G. (2011). Quinolizidines alkaloids: Petrosin and xestospongins from the sponge *Oceanapia* sp. Journal of Chemical Sciences, 123(5): 601-607.

Sotnikova, R., Kettmann, V., Kostálová, D., & Táborská, E. (1997). Relaxant properties of some aporphine alkaloids from *Mahonia aquifolium*. Methods and findings in experimental and clinical pharmacology, 19(9): 589-597.

Srivastava, S., & Srivastava, A. K. (2013). Biotechnology and genetic engineering for alkaloid production. In: G.K. Ramawat, J.M. Mérillon. Natural Products:

Phytochemistry, Botany and Metabolism of Alkaloids, Phenolics and Terpenes. 213-250.

Sun, Y., Xun, K., Wang, Y., & Chen, X. (2009). A systematic review of the anticancer properties of berberine, a natural product from Chinese herbs. Anti-cancer drugs, 20(9): 757-769.

Taha, H.S., El Bahr, M.K., & Seif, E.N.M. (2009). In vitro studies on Egyption *Catharanthus roseus* (L.). Ii. Effect of biotic and abiotic stress on indole alkaloids production. Journal of Applied Sciences Research, 5(10): 1826-1831.

Tiong, S.H., Looi, C.Y., Hazni, H., Arya, A., Paydar, M., Wong, W.F., ... & Awang, K. (2013). Antidiabetic and antioxidant properties of alkaloids from *Catharanthus roseus* (L.) G. Don. Molecules, 18(8): 9770-9784.

Tudzynski, P., Correia, T., & Keller, U. (2001). Biotechnology and genetics of ergot alkaloids. Applied microbiology and biotechnology, 57(5),: 593-605.

Upcroft, P., & Upcroft, J.A. (2001). Drug targets and mechanisms of resistance in the anaerobic protozoa. Clinical Microbiology Reviews, 14(1): 150-164.

Vitaku, E., Smith, D.T., & Njardarson, J.T. (2014). Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals: miniperspective. Journal of Medicinal Chemistry, 57(24),: 10257-10274.

Wadworth, A.N., & Chrisp, P. (1992). Co-dergocrine mesylate. Drugs & Aging, 2(3): 153-173.

Wang, L.Y., Wei, K., Jiang, Y.W., Cheng, H., Zhou, J., He, W., & Zhang, C.C. (2011). Seasonal climate effects on flavanols and purine alkaloids of tea (*Camellia sinensis* L.). European Food Research and Technology, 233(6): 1049-1055.

Wibowo, D.N.S.A., Soebadi, D.M., & Soebadi, M.A. (2021). Yohimbine as a treatment for erectile dysfunction: A systematic review and meta-analysis. Turkish Journal of Urology, 47(6): 482-488.

Wiesner, J., Ortmann, R., Jomaa, H., & Schlitzer, M. (2003). New antimalarial drugs. Angewandte Chemie International Edition, 42(43): 5274-5293.

Wink, M. (2010). Annual plant reviews, functions and biotechnology of plant secondary metabolites. John Wiley & Sons.

Zheng, X.Q., Koyama, Y., Nagai, C., & Ashihara, H. (2004). Biosynthesis, accumulation and degradation of theobromine in developing *Theobroma cacao* fruits. Journal of Plant Physiology, 161(4): 363-369.

Ziegler, J., & Facchini, P.J. (2008). Alkaloid biosynthesis: metabolism and trafficking. Annual review of plant biology, 59: 735.

CHAPTER 12

WIDELY PRODUCED ESSENTIAL OIL PLANTS IN THE WORLD

Doğan ARSLAN[1]
Hatice Kübra ÇELEBİ[2]

[1] Siirt University, Faculty of Agriculture, Department of Field Crops, Siirt, Türkiye e-mail: doganarslan@siirt.edu.tr, ORCID ID: 0000-0001-7156-5269
[2] Siirt University, Graduate School of Natural and Applied Sciences, Department of Field Crops, Siirt, Türkiye, e-mail: htckbrclbi.97@gmail.com
ORCID ID: 0000-0003-2046-6994,

INTRODUCTION

Since the beginning of mankind, medicinal and aromatic plants have been used as a preventive, therapeutic or supplementary food against diseases since its existence. Additionaly, these plants are also used as flavour, flavour flavouring, and sweetening (spice) to the dishes. There are over 425,000 species of flowering plants in the globe, and 70,000 of those have been classified as being medicinal and aromatic plants. Only 20,000 of them are known to be used for medicinal and aromatic purposes (Serencam et al., 2018; Baydar, 2013).

Since medicinal and aromatic plants are product groups rich in secondary metabolites, they are valuable as a natural source of secondary metabolites. The most fundamental items produced by the sector, both directly and indirectly, are secondary metabolites. Due to the essential oils, alkaloids, glycosides, saponins, balms, resins, waxes, natural rubber, natural dyes, and several other items they contain, medicinal and aromatic plants are extremely important to civilization (Baydar, 2013).

Essential oils, one of the valuable secondary metabolites contained in medicinal and aromatic plants have a wide range of uses from perfume to cosmetics, from medicine to food. Essential oils are usually colourless or light yellow, volatile, strong-smelling and oily mixtures that are obtained by various methods from parts of plants or plant sources such as roots, stems, leaves, fruits, bark, flowers, are liquid at room temperature, can sometimes freeze and easily crystallize. They are called "essential oil" because they can evaporate even at room temperature when left in the open, "etheric oil" because they evaporate like ether, and "essential oil" because they are fragrant and used in perfumery (Baydar, 2013, Yaylı, 2013).

Essential oils are complex mixtures of low-boiling secondary metabolites. When "essential oil plants" is mentioned, it is meant commercially important, essential oil yielding plant species. There are about 2000 essential oil plant species distributed across 60 plant families in the world. However, some families are more abundant and significant in terms of essential oil content, including Brassicaceae, Apiaceae, Lamiaceae, Myrtaceae, Rutaceae, Lauraceae, and Pinaceae. Currently, 150 essential oil plants are thought to be commercially significant (Arslan, 2021).

The economic importance of medicinal and aromatic plants, whose usage and consumption areas are increasing day by day, shows a serious increase in parallel with this situation. In this increase, especially the demand for essential oil plants draws attention. With their various contents, essential oil plants, which have their own distinct and lovely aromas, are also widely employed in a variety of industries (including the perfume and cosmetics industries). The use of essential oils, which have many properties such as cell renewal, pain reliever, muscle relaxant, wound healing in the pharmaceutical industry is another issue that increases their economic importance. In addition to some prescriptions and external uses spread among the public, its use as a raw material in pharmacology is increasing day by day (Serencam et al., 2018).

Global market value of essential oils whose usage areas (food, beverage and tobacco, perfume and cosmetics, home and personal care, aromatherapy, oral and dental care, pesticides, automobiles, paper and printing, rubber, plastic, textile, adhesives, drugs and veterinary etc.), amount of use and economic importance, which is increasing day by day, is expected to reach 27 billion dollars in 2022, which was 17 billion dollars in 2017. Orange, peppermint, and clove essential oils are three of the key essential oils that have seen increase in recent years. These three essential oils are primarily imported from countries like India, Indonesia, and Brazil, and the top producing nations for essential oils are Brazil, China, the United States, Egypt, India, Mexico, Guatemala, and Indonesia (Arslan, 2021). Additionally, the pharmaceutical industry uses 3% of the essential oils produced globally, the soft drink industry 34%, and the fragrance and flavor industry 63% (KUZKA, 2021).

According to global data, Brazil produces 58% of the world's orange essential oil, Indonesia produces 76% of the world's clove essential oil, and India produces 80% of the world's peppermint essential oil. The market for essential oils is dominated by Europe, the Asia-Pacific region, and North America. The three essential oils that account for the largest portion of the US market are eucalyptus, peppermint (mentha), and orange oil. In terms of volume, Europe led the market in 2019 with a 43.65% share (Arslan, 2021).

Important essential oil plants in the world (Arslan, 2021)

- *Citrus*
- Mint
- Eucalyptus
- Cedar tree
- *Lavandula* sp.
- Clove
- Camphor
- Coriander
- *Litsea cubeba*

Approximately 80% of the world essential oils market is met by these 10 abovementioned essential oils, and the remaining 20% by approximately 150 essential oils. Three essential oils (orange, mint and clove) account for more than two-thirds of the total essential oil production. Therefore, when calculating production, it may be appropriate to consider products with a demand of 20 tons per year or more for a new industry (FAO 2021, OEC WORLD 2021).

The aim of this study is to briefly and comprehensively introduce the most widely used essential oils in the world together with the plants from which they are derived. Important details about these plants are provided below.

1. CITRUS

Citrus fruits are members of the "Rutaceae" family. *Citrus* is a young plant community cultivated all around the world and includes species belonging to the genus "" such as orange, lemon, mandarin and goldenball (grapefruit). The modern cultivation of *Citrus* fruits, which originated in Southeast Asia, started in the USA in the 19th century and spread rapidly. *Citrus* fruits, which are the most grown and consumed fruit group in the world, are grown between 40°N latitude and 40°S latitude in the world. While these plants' fruits are used as food, their peels, leaves, or blossoms can be utilized to extract essential oils that are used in perfumery to add scent. Essential oils obtained from *Citrus* fruits, which are mostly consumed for table use, are among the leading products of the essential oil market in the world due to their pleasant and refreshing scent Because they are so rich in beneficial elements including vitamins, fiber, minerals, organic acids, and other phytochemicals, *Citrus* fruits like oranges, tangerines, limes, grapefruits, bitter oranges, and lemons are consumed daily, either raw or processed. The members of the genus *Citrus* encompass rare fruits that are the subject of production, consumption, industry and commerce in the world and in Türkiye, due to their species and variety richness, a very long harvest period, a very long storage period, being suitable for transportation and being an industrial raw material. group. Due to these characteristics, the primary commercial varieties of orange, mandarin, lemon, and goldentop (grapefruit) fruits; It offers employment opportunities to a significant number of people in the fundamental stages such as production, preparation for the market, industry-processing, transportation, domestic, and international sales. Therefore, they have very important contributions to both the agricultural sector and the country's economy. *Citrus* fruits are products that are ready for consumption as soon as they are harvested. It is necessary to keep these perishable products ready in the freshness, form and time desired by the consumer, wherever they want. Marketing the product by performing services such as packaging, transportation and storage in delivering such products to the consumer is another very sensitive issue (Zan Sancak and Aygören, 2010; Seçer, 2012).

The names of some important *Citrus* species are given below.

- Bitter orange (*C. aurantium)*
- Bergamot (*C. bergamia)*
- Lemon (*C. limon)*
- Mandarin (*C. reticulata)*
- Orange (*C. sinensis)*
- Lime (*C. aurantifolia)*
- Grapefruit (*C. paradisi)*

Essential oils and flavonoids are concentrated in the peel of *Citrus* fruits such as orange (*Citrus sinensis*), lemon (*Citrus limon*) and bergamot (*Citrus bergamia*). The use of oils found in *Citrus* peels has gained importance recently due to their antimicrobial and antioxidant properties. These parts contain high amounts of essential oils such as limonene and linalool. The most important characteristic of *Citrus* essential oils is their high *limonene* content. It has been reported that the antioxidant activity of *limonene*, the most important component of orange peel oil, is quite high. It has been stated that the *limonene* content of *Citrus* oils (bergamot, *Citrus*, mandarin, orange and tangerine) varies between 36.54% and 96.10%, and the content of *limonene* in *Citrus* oils reaches up to 97.30%. *Limonene* is used in many industrial areas (Gölükcü et al., 2015; Erhan and Aktaş, 2017).

2. MINT (*Mentha*)

Peppermint is a perennial and herbaceous medicinal and aromatic plant. peppermint essential oil is obtained from mint, a member of Labiate family which has many medicinal benefits. The evaluated part of the mint is the leaves with a high amount of essential oil. This herb is used in cosmetics, hygiene products, foods, and pharmaceuticals for both its flavoring and fragrance properties. It also has various therapeutic properties and is used in products such as aromatherapy, bath preparations, mouthwashes, toothpastes (ORAN, 2015).

Peppermint plant has medicinally antispasmodic and carminative, antiseptic, anesthetic, stomachic, cooling, stimulating and diuretic effects and is widely used in the form of spice and herbal teas. Peppermint oil is the richest natural source of *menthol*, which has a wide range of applications in the pharmaceutical, food and cosmetic industries (Özgüven and Kırıcı, 1999).

3. CLOVE (*Syzygium aromaticum*)

Carnation, member of family Mirtaceae, which is a perennial and woody plant, is a naturally evergreen, long-lived tree up to 15 m in height in the tropical regions of Asia, Africa and Australia, and grows up to an altitude of 600 m from sea level. If the precipitation is evenly spread throughout the year, it can be profitably cultivated in regions that need an average daily temperature of 24-33°C and 2000-3000 mm of rainfall. It is cultivated in many tropical countries such as Seychelles, Madagascar, India, Indonesia, Zanzibar and Sri Lanka. It is usually propagated by seedlings produced from seeds obtained from mature fruits. Each clove tree can be used economically for at least 100 years as both a spice and a source of essential oil. The buds are hand-picked one by one just before blooming and dried under the sun. Clove essential oil is obtained from clove buds and stem leaves by water/steam distillation. The main ingredients in clove essential oil are *eugenol* (80-90%), *eugenyl acetate* (1-5%) and *beta caryophyllene* (5-15%). *Eugenol* is used as a raw material in the production of vanillin. It is an important herbal source as an antimicrobial agent and resistance enhancer. Due to its beneficial effect on dental health and its pleasant smell, clove is used against bad breath. In addition to its wide range of uses such as food, cosmetics, and medicine, it is also used for its smell and aroma (Koptaget, 2019, Baydar, 2013).

4. LAVANDULA

Lavandula is one of the important members of the Labiate (Lamiaceae) family. Although this plant's fresh and dried blossoms can be sold, it is mostly cultivated for its essential oil. The name lavender is derived from the medieval Latin name "Livendula", which is a combination of the words livere (blueizing) and lavare (wash). Lavender is an important part of the perfumery and cosmetic industry due to its unique and pleasant smell. It is mainly used in the production of perfumes, cosmetics and herbal teas. The most important essential oil components are "*linalyl acetate, linalool, 1,8-sineol, camphor, alpha-pinene*". Three different types of oils are obtained from lavender and these oils are named according to the plants from which they are obtained. The oil obtained from the species *Lavandula officinalis* is defined as "Lavender oil", the oil obtained from the species *Lavandula hybrida* is defined as "Lavandin oil" and the oil obtained from the species *Lavandula latifolia* Vill. syn. *L. spica* D. C. is defined as "Spike Lavender oil". The essential oil of lavender, which is cultivated in many countries in the world (Argentina, Brazil, Bulgaria, Cyprus, Greece, Croatia, Hungary, Iran, Italy, Russia, Spain, Türkiye, Japan and Great Britain), is widely used in areas such as aromatherapy, cosmetics, personal care products, high-quality perfume making and food industry because of its pleasant smell and antiseptic properties. The essential oil obtained mainly from the fresh flowers of lavender is evaluated economically and furthermore dry buds that are dried after harvest and separated from the stems are used. Although there are about 39 lavender species (*Lavandula* spp.), most of which are of Mediterranean origin, there are three important lavender species with high commercial value in the world. These are lavander (*Lavandula angustifolia* Mill. = *L. officinalis* L. = *L. vera* DC), lavandin (*Lavandula intermedia* Emeric ex Loisel. = *L. hybrida* L.) and spike lavander (*Lavandula spica* = *L. latifolia* Medik.). The essential oil quality of lavander varieties called English lavenderas relatively has higher, while lavandin varieties called hybrid lavender have higher essential oil yield. Lavender is a perennial, semi-bushy-looking Mediterranean plant. The most important ingredient of lavender flower is essential oil of colorless or slightly yellow color. The quality of the essential oil is especially evaluated according to the ratio of *linalyl acetate* and *linalool* in the oil. In addition, *luteolin*-type flavonoids in the content of essential oil have bacteriostatic and spasmotic effects. It also contains compounds such as *β-pinene*, *linalool*, *camphor*, *terpineol*, *borneol* and *cineol*. Up to 200 tons of lavander oil, 1000 tons of lavandin oil and 150 tons of spike lavander oil are produced each year in the world. The most cultivated varieties in the world belong to *L. angustifolia* Mill and *L.* x *intermedia* Emeric ex Loisel. lavender, a perennial, semi-bushy-looking Mediterranean plant, is a dicotyl plant with a strong pile root. Although the roots depend on the soil and climatic conditions, they can go deep to 80-100 cm. The stem, which has 4 corners, is bare or pubescent. The color is gray-green. The plant gives a large number of side branches. Aging branches become woody over time. The leaf is attached to the stem with or without very short stems in knuckles on upright standing stems. The leaves are located opposite each other in the knuckles and are 2-6 cm long. So the leaves are pointed at the edges, and the edges are straight, inwardly curved, and stripe-shaped. At the tip of the flower, stalk is the flower spike-inflorescence axis 15-20 cm long. On the axis of the spike, there are 4-6 clusters of flowers. Inside each flower cluster, there are a varying number of floret (6-14 pieces) depending on some factors. The flowers are protected by 4 pot sheets of gray-blue color and longitudinal stripes up to 5 mm long, with a flat inside and pubescent outside. The color of the fruit varies from dark brown to black. The weight of 1000 grains is less than 1 g. The most important ingredient of lavender flower is its essential oil, colorless or slightly yellow color. According to the codexes, genuine lavender flowers should contain at least 1% essential oil. Baths to be prepared with lavender flowers should be applied regularly for the healthy rearing of children. In addition to these benefits, the plant is acclaimed for its ability to treat skin conditions like eczema, acne, burns, ulcers, and superficial inflammatory wounds. With gargle, it cleans small wounds in the mouth, overcomes paralysis of the tongue and stuttering, and relaxes nerves and contracted muscles. It strengthens the lung with massages on the chest. Lavender flower is a stomach friend, and diuretic and provides sweating. It is good for dizziness, headaches, nausea, loss of appetite, stomach and intestinal swelling, nerves, heart palpitations, tremors, flu, liver and gallbladder disorders, jaundice, general weakness, blood collection and general visual weakness. Lavender flower in all its forms, especially in the form of rubbing, lotion, and bathing; It is used against wounds, bruises and cuts, bulges, sprains, dents and athletes' "falling out of shape". It is an outstanding plant for gout and rheumatism. With the method of incense, it accelerates the treatment of colds, flu, angina and bronchitis. With compresses on the liver, it helps with the hard work undertaken by the "chemical factory" of the body. It contributes to the rapid healing of pneumonia, pleurisy, and blood accumulation in the lungs. When the lavender flower is rubbed into the body, it revitalizes the body, strengthens it, and relieves pain. Also, rheumatism isolates intestinal gases. It calms the nerves and relieves the pains. Lavender essential oil is calming, sedative, antidepressant, emotional stabilizer. It is effective against insomnia, headaches, stress and high blood pressure. It is antiseptic, effective in insect bites, cuts, wounds, burns, bruises, spots, allergies, throat infections and rheumatism. In the pharmaceutical industry, it is involved in the composition of drugs that regulate the central nervous system, giving odor to some preparations. (Arslan et al., 2012).

5. CORIANDER (*Coriandrium sativum*)

The medically used part of coriander is its fruits, which contain essential oils and fatty acids, which are its most important components. It is one of the important medicinal and aromatic plants with a single-year and herbaceous structure. It is used in the composition of food flavors, perfumes, cosmetics, and pharmaceutical products. The coriander plant has many positive effects on human health. It is used in folk medicine and the pharmaceutical industry due to the antioxidant, hypoglycemic, anti-inflammatory, hypolipidemic, painkilling, sedative antimutagenic, diuretic, antimicrobial, gassing, antispasmodic and muscle relaxant properties of essential oils and some of its extracts obtained from plant fruits (Beyzi and Güneş, 2017).

6. EUCALYPTUS (*Eucalyptus*)

The homeland of eucalyptus, a genus of the Myrtaceae family, is Australia. Members of this genus, which has about 700 species, can easily grow and reach 60-70 meters in length. Very fast-growing eucalyptus are evergreen, have straight edges, and are arranged in the form of willow leaves or scythes. The flowers are individually umbrella according to their species and are yellow, white or red in color. Research shows that the eucalyptus tree grows in climatic conditions with a wide range from warm to heat, from half moist to half dry in natural spreading areas, and that the average high temperature of the hottest month in the spreading areas is 27-40 degrees and the average low temperature of the coldest month is 3-15 degrees. Given these environmental characteristics, it is clearer why it can be produced well in regions with a Mediterranean climate. A typical eucalyptus tree absorbs and releases 250 tons of water each year into the atmosphere (Özgün, 2013). Eucalyptus oil is an essential oil obtained by distillation of water vapor from the leaves of different eucalyptus species. The oil contains a large percentage (at least 70%) of *1,8-cineol* (*eucalyptol*), *α-pinene*, very little *fellandren* and other terpenes. It is very slightly soluble in water and 70% soluble in alcohol. It can be stored in well-filled containers, protected from light at a temperature not exceeding 250°C. Eucalyptus essential oils are generally classified under three groups as defined below;

Syneolic Essential Oils: They are the most important and common essential oils in the *eucalyptus* genus and are produced in large quantities. They are suitable oils for medical use and usually derived from *E. polybractea, E. smithii* and *E. globulus*.

Perfumery Essential Oils: Oils in this class are derived from *E. citriodora, E. staigeriana* and *E. macathuri*. *Citronellal*, which contains 65-85% of *E.citriodora* oil, is an important product in perfumery.

Industrial Essential Oils: Three types are the main source of these oils. *E. radiata* var. "B" essential oil is rich in α-fellandrene. *E. dives* "type" and *E. radiata* var. "C" oils contain piperitone, which is used in the synthesis of *thymol* and *menthol* (Başer et al., 2018).

7. CEDAR TREE (*Cedrus*)

Cedar tree is a species that finds natural habitat in Lebanon, Syria and Türkiye and has the largest spread in the world with an area of 324.453 hectares in Türkiye. There are many cultural forms of the *cedar* genus, also known as "tar" in Türkiye. Cedar forests are beautiful in smell and color; In addition, due to its non-decay, it was tried to be seized by many states in Antiquity and was often destroyed. The first written information about this tree appears in Egyptian sources. The tree used in a variety of contexts is referred to as "GIERN" in Hittite cuneiform inscriptions (Akrep, 2013).

There are four distinct types of cedar:

- Atlas Cedar spreading in North Africa (*C. atlantica* Manetti)
- Taurus Cedar (*C. libani* A. Rich), which is spread in a small area in Southern Anatolia and in the Niksar-Erbaa region, as well as in Lebanon.
- Cyprus Cedar (*C. brevifolia* Hen.) seen on the island of Cyprus. This species is considered by some botanists to be a varietal of the Taurus Cedar (*C. libani* var. *brevifolia* Hook.).
- Himalayan cedar (*C. deodara* Loud.) spread over the northwestern Himalayas, in Afghanistan, India and Pakistan (Anonim, 2015).

8. LITSEA *(Litsea cubeba)*

Litsea cubeba Pers. is a genus belonging to the family Lauraceae and contains more than 400 species. It grows intensively in tropical and subtropical regions of India, Southeast Asia, southern China, Taiwan and Japan. Litsea is an evergreen, fast-growing tree that reaches a height of about 8 m, spreading naturally in the eastern Himalayas, Assam, Manipur and Arunachal Pradesh up to an altitude of 2700 m above sea level. The plant has white to yellowish flowers in the spring, turning into small pepper-like spherical fruits with a diameter of 4-5 mm, during ripening it turns from green to black until September. In the Indian state of Assam, the tree is known as "mejankari", while in China it is commonly referred to as "May Chang" or "Chinese pepper". *Litsea* species are used as medicines in traditional medicine. In addition, muga is considered as a food source for silkworms (Antheraea assama). Muga silk ("mejankari pat") produced from the *Litsea* plant is very attractive and more expensive than silk produced from other plants. Different extracts from plant parts such as bark, leaves, roots, and fruits have been used in traditional Chinese medicines to treat various diseases. Fresh green fruits are used for culinary purposes, such as salad preparation, Indian pickles, pickles. *L. cubeba* essential oil (LEO), extracted from fresh fruits, contains about 60-90% citral content and is an essential oil with volatile compounds. It is a fresh, sweet-flavored, water-insoluble oil with an intense lemon-like taste (Asija et al., 2022; Thielmann and Muranyib, 2019).

9. CAMPHOR (*Camphorae*)

The genus *Cinnamomumum*, belonging to the Lauraceae family, consists of evergreen aromatic trees and shrubs. Its leaves and bark are a rich source of aromatic oil. More than 250 species of the breed are distributed in South Asia, China and Australia. Twenty-six species of *Cinnamomum* are found in India, 12 of which are in northeastern and southern India. It is also found naturally in Japan, Mongolia, Taiwan and Bhutan. About 60% of the world's cinnamon trade is from Sri Lanka, which produces the best quality cinnamon peel. The leaves are thick, leathery, dark green, narrow, pointed, oval-shaped and are characterized by a layer of wax, which makes them shiny. Camphor tree is large, with pale brown bark, dark green to yellowish leaves and small white flowers, followed by small purple fruits. Camphor tree is very attractive with its camphor scent and grows at different altitudes in tropical rainforests. The bark of the species *Cinnamomum* is one of the most important and popular spices. It is also used for medical purposes. Cinnamon is mainly used in the aroma and essence industry due to its smell. It is said to be among the oldest spices. There are only two species known to have a camphor scent: *Cinnamomum camphora* is cultivated in China, Taiwan, Japan, and Korea, and *C. capparucoronde* is a tree very commonly found in the forests of Sri Lanka. *Cinnamomum* has a fragrant, sweet and warm taste. Cinnamon is distinguished from all spices by its "warmth" and takes second place after pepper. As a seasoning, cinnamon is considered one of the best sweet spices. 27,000-35,000 tons of cinnamon are produced annually worldwide. Cinnamon essential oil consists of cinnamaldehyde and trans-cinnamaldehyde, which are responsible for the odor and various biological activities observed in cinnamon. It has also been used to treat diarrhea and other problems of the digestive system. It shows high antioxidant activity. Cinnamon exerts pharmacological effects in the treatment of type II diabetes and colon cancer. It is also added to flavored gummies as it contains mouth refreshing effects. As a coagulant, cinnamon prevents bleeding, accelerates blood circulation in the uterus and accelerates tissue regeneration. This plant plays a vital role as a spice. It also has important biological activities, including antimicrobial, antifungal, antioxidant, antidiabetic. *Cinnamomum camphora* is used as a plasticizer in the preparation of explosives and disinfectants (Rani et al., 2017; Malabadi et al., 2021; Kumar and Kumari, 2019).

10. TOP THREE PLANTS MOST TRADED IN ESSENTIAL OIL IN THE WORLD

10.1. Orange (*Citrus sinensis*)

50 thousand tons of orange essential oil is produced in the world. Brazil ranks first in the world with an average annual production of 15 thousand tons of orange oil. It is the country that exports the most orange oil by exporting an average of 200 million dollars annually. With an import data of $ 103 million, the country that imports the most orange oil is the USA. Orange essential oil has an annual market of $500 million (FAO, 2021; OEC WORLD, 2021).

Table 1: World Production of Orange Plants

World	Produce Amount (ton)	Production Area (da)	Yield (kg/da)
2018	73.458,495	38.202,830	1.922
2019	75.992,530	39.240,130	1.936
2020	75.458,588	38.845,860	1.942

Source: OEC WORLD, 2021

Table 2: Three Important Countries in Orange Production in 2020

Countries	Produce Amount (ton)	Production Area (da)	Yield (kg/da)
Brazil	16.707,897	5.726,980	2.917
India	9.854,000	6.700,000	1.470
Chinese	7.641,167	3.935,980	1.334

Source: OEC WORLD, 2021

10.2. Mint

The globe produces 45.000 tons of peppermint essential oil each year. More than 80% of the plants from which the oil produced is obtained are collected from nature. According to OEC data, the world peppermint oil market is 210 million dollars. The United States has an export market share of $83 million (FAO 2021; OEC WORLD 2021).

Table 3: World Production Amount of Mint Plant

World	Produce Amount (ton)	Production Area (da)	Yield (kg/da)
2018	106.669	34.220	3.117
2019	74.223	27.790	2.670
2020	48.437	26.510	1.827

Source: OEC WORLD, 2021

Table 4: Three Important Countries in Mint Production in 2020

Countries	Produce Amount (ton)	Production Area (da)	Yield (kg/da)
Morocco	40.403	25.510	1.583
Argentina	6.991	4.660	1.510
Mexican	1.010	980	1.030

Source: OEC WORLD, 2021

10.3. Clove (*Syzygium aromaticum*)

Clove essential oil is most often produced in Indonesia in the world. 200 million dollars of the 400 million dollars clove essential oil market is obtained through exports from Indonesia. The largest buyer is India, with 150 million dollars (OEC WORLD, 2021).

Table 5: Clove Plant World Production Amount

World	Produce Amount (ton)	Production Area (da)	Yield (kg/da)
2018	179.936	6.715,520	26
2019	181.322	6.676,310	27
2020	183.258	6.519,180	28

Source: OEC WORLD, 2021

Table 6: Three Countries Important in Clove Production in 2020

Countries	Produce Amount (ton)	Production Area (da)	Yield (kg/da)
Indonesia	133.604	5.528,570	24
Madagascar	23.931	741.360	32
Tanzania	8.602	68.170	120

Source: OEC WORLD, 2021

11. TÜRKIYE'S PLACE IN ESSENTIAL OILS

Türkiye, which has an important place in the production of rose oil in the world, has a long history in this regard. However, Türkiye is unfortunately far from its rightful place in the essential oils market.

Türkiye's share in the world's total essential oil exports in 2019 remained below 1%. Türkiye ranks 19th in world essential oil exports (Arslan, 2021).

Table 7: Türkiye's Essential Oil Exports by Years

Years	Essential Oil Export		Rose Oil Export	
	Amount (ton)	Value (kg)	Amount (kg)	Value (1000$)
2017	176	44.469	-	18.534
2018	202	37.591	10.546	14.597
2019	181	30.651	8.624	13.245
2020	270	-	-	-

Source: Arslan, 2021

CONCLUSIONS

Essential oil plants are the products obtained from medicinal aromatic plants that are most exchanged in the world. Recently, the awareness of the side effects of chemical and artificial products on living things has led researchers to develop alternative strategies based on essential oils. In this study, ten plant species that are used in many areas in the world and traded with the most production are mentioned. Among these ten species, the production area of three plants (*Citrus*, mint, cloves), the amount of production, and the amount of essential oils obtained together with the trade market are discussed. The worldwide market capitalization of essential oils is expected to reach $27 billion in 2022, up from $17 billion in 2017. This growth is mainly due to the growth of three main essential oils, such as orange essential oil, peppermint essential oil and clove essential oil.

REFERENCES

Akrep, M.Y. (2013). Eskiçağ Anadolusu'nda Sedir Ağacinin Önemi. Mavi Atlas Gümüşhane Üniversitesi Edebiyat Fakültesi Dergisi, S. 1 (In Turkish).

Anonim, (2015). Sedir Ormanlarının Rehabilitasyonu Eylem Planı-II. T.C. Orman ve Su İşleri Bakanlığı Orman Genel Müdürlüğü, (2015-2019) (In Turkish).

Arslan, D., Arslan, H. & Bayraktar, Ö.V. (2021). Bazı Önemli Tıbbi ve Aromatik Bitkilerin Siirt İlinde Tarımının Yaygınlaştırılması Projesi. T.C. Sanayi ve Teknoloji Bakanlığı Güneydoğu Anadolu Projesi (GAP), Bölge Kalkınma İdaresi Başkanlığı Tarımsal Araştırma Destekleri Proje Sonuç Raporu, Siirt (In Turkish).

Arslan, N., (2021). Dünyadaki Uçucu Yağ Pazarı ve Türkiye'nin Bu Alandaki Potansiyeli. Ülkemizdeki Tıbbi ve Aromatik Bitkilerin Potansiyeli, Sorunları ve Geleceği Çalıştayı, Muş Alparslan Üniversitesi, Kasım-2021, Muş Türkiye. S.30-41 (In Turkish).

Asija, R., Kumari, P., Khanijau R. & Verma, T. (2022). A Review on Litsea Cubeba. Chemistry Research Journal, 7(3): 60-72.

Başer, K.H.C., Gülbaba, A.G., Azcan, N., Kara, M., Kırımer, N., Kürkçüoğlu, M., Özek, T. & Özkurt, N. (1988). Türkiye'de Yetiştirilen Bazı Okaliptüs (Eucalyptus) Türlerinin Uçucu Yağ Verim ve Bileşimlerinin ve Üretim Teknolojilerinin Belirlenmesi. Odc: 892.62, Teknik Bülten No: 7, Orman Bakanlığı Doğu Akdeniz Ormancılık Araştırma Enstitüsü. Orman Bakanlığı Yayın No: 084 ISSN: 1300 – 7912 DOA Yayın No: 11 Tarsus (In Turkish).

Baydar, H. (2013). Tıbbi, Aromatik ve Keyf Bitkileri Bilimi ve Teknolojisi. Süleyman Demirel Üniversitesi Yayınları, Yayın No:51, Isparta (In Turkish).

Beyzi, E. & Güneş, A., (2017). The effects of boron application on essential oil components of coriander plant (*Coriandrum sativum* L.). Journal of AgriculturalFaculty of GaziosmanpasaUniversity, 34 (1): 146-152. (In Turkish)

Du, Y., Zhou, H., Yang, L., Jiang, L., Chen, D., Qiu, D. & Yang, Y. (2022). Advances in biosynthesis and pharmacological effects of *Cinnamomum camphora* (L.) presl essential oil, Forests, 13, 1020.

Erhan, M.K. & Aktaş, Ş.C.B. (2017). The effects of citrus peel oils on fatty acid composition and shelf life of muscle in broilers. Atatürk University Journal of Veterinary Sciences, 12(2): 157-166 (In Turkish).

FAO, (2021). Food and Agriculture Organization of the United Nations, (http://www.fao.org) (Access date: 02.12.2022)

Gölükcü, M., Toker, R., Tokgöz, H. & Turgut, D.Y. (2015). Bitter orange (*Citrus aurantium* L.) peel essential oil compositions obtained with different methods. Derim, 32(2): 161-170. (In Turkish).

Koptaget, E., (2019). Tarçın Yağının ve Karanfil Yağının Antimikrobiyal Etkinliğinin Mikrobiyolojik Miktar Tayini Yöntemi ile Araştırılması, Yüksek Lisans Tezi, Sağlık Bilimleri Enstitüsü, Sakarya (In Turkish).

Kumar, S. & Kumari, R. (2019). Cinnamomum: review article of essential oil compounds, ethnobotany, antifungal and antibacterial effects. Open Access Journal of Science, 3(1): 13-16.

KUZKA, (2021). Kastamonu İli Tıbbi Aromatik Bitkilerden Distilasyon Yöntemiyle Uçucu Yağ Üretimi, Ön Fizibilite Raporu, Kuzey Anadolu Kalkınma Ajansı, Sanayi ve Teknoloji Bakanlığı (In Turkish).

Malabadi, R.B., Kolkar, K.P., Meti, N.T. & Chalannavar, R.K. (2021). Camphor tree, *Cinnamomum camphora* (L.); ethnobotany and pharmacological updates, biomedicine. 41(2): 181-184.

OEC WORLD (2021). Essential oil dataset. (https://oec.world/en) (Access date: 01.06.2022).

ORAN Kalkınma Ajansı, (2015). Tıbbi ve Aromatik Bitkiler Sektör Raporu. Gıda Tarım ve Hayvancılık Bakanlığı, Kayseri (In Turkish).

Özgün, C. (2013). A new and exotic species in the Ottoman tree culture: Eucalyptus. Journal of Modern Turkish History Studies, XIII/26 ss. 5-29 (In Turkish).

Özgüven, M. & Kırıcı, S. (1999). Research on yield, essential oil, contents and components of mint (*Mentha*) species in different ecologies. Turkish Journal of Agriculture and Forestry, 23(5): 465-472 (In Turkish).

Rani, A., Pande, C., Tewari, G. & Patni, K. (2017). A review on aroma profile of cinnamomum species in North and North East India. World Journal of Pharmaceutical Research, 6(11): 200-221.

Sancak, A. Z., & Aygören, E. (2010). Turunçgiller: Durum ve Tahmin: 2010/2011. Tarım ve Köyişleri Bakanlığı, Tarımsal Ekonomi Araştırma Enstitüsü. Yayın No: 183. Ankara. (https://arastirma.tarimorman.gov.tr/tepge/Belgeler/Yay%C4%B1n%20Ar%C5%9Fivi/2006-2011%20Yay%C4%B1n%20Ar%C5%9Fivi/Yay%C4%B1nNo183.pdf) (Accessed: 01.10.2022) (In Turkish).

Seçer, A. (2012). Doğu Akdeniz Kalkınma Ajansı Doğrudan Faaliyet Destek Programı Narenciye Sektör Raporu Projesi TR63-11-DFD-127. Doğu Akdeniz Kalkınma Ajansı Hatay. (https://www.dogaka.gov.tr/assets/upload/dosyalar/www.dogaka.gov.tr_890_WY5S27CP_Narenciye-Sektor-Raporu-Projesi-TR63-11-DFD-127.pdf) (Accessed: 27.11.2022) (In Turkish).

Serencam, H., Gül, V., Gıdık, B. & Sefalı, A., (2018). Tıbbi ve Aromatik Bitkiler: Uçucu Yağlı Bitkiler, İksad Yayınevi (In Turkish).

Thielmann, J. & Muranyib, P. (2019). Review on the chemical composition of *Litsea cubeba* essential oils and the bioactivity of its major constituents citral and limonene. Journal of Essential Oil Research, 31(5): 361-378.

Yaylı, N., (2013). Uçucu Yağlar ve Tıbbi Kullanımları, 1. İlaç Kimyası, Üretimi, Teknolojisi, Standardizasyonu Kongresi, Kimyagerler Derneği, 29-31 Mart, Antalya (In Turkish).

CHAPTER 13

THE IMPORTANCE OF MEDICINAL AND AROMATIC PLANTS (MAP) IN THE WORLD AND IN TÜRKİYE

Doğan ARSLAN [1]
Yakup SÜRÜCÜ[2]

[1] Siirt University, Faculty of Agriculture, Department of Agronomy, Siirt, Türkiye
e-mail: doganarslan@siirt.edu.tr, ORCID ID: 0000-0001-7156-5269
[2] Siirt University, Graduate School of Natural and Applied Sciences, Department of Field Crops, Siirt, Türkiye, e-mail: ykpsrc65@gmail.com
ORCID ID: 0000-0002-3412-5050

INTRODUCTION

Aromatic plants are plants that give smell and taste. On the other hand, medicinal plants are used for the prevention and treatment of diseases. If any plant is consumed directly in the pharmaceutical industry, it is considered a medicinal plant. A plant is considered an aromatic plant if it is used in the fragrance and flavour industry. On the other hand, if it is used in the medical industry and other related industries, it is considered both, a medicinal and aromatic plant (Anonymous, 2017).

From an agricultural point of view, the following description will be more appropriate and comprehensive: Containing bioactive substances (secondary metabolites) such as alkaloids, terpenoids, and phenolic substances that have pharmacological activity in one, several or all plant parts such as leaves, stems, bark, flowers, fruits, seeds, roots, rhizomes, onions, and tubers. These plants are used as a perfume, spice, dyestuff, etc. (Baydar, 2019), have a valuable market and economic value, and are cultivated and used only for medicinal and aromatic purposes.

1. USAGE AREAS OF MEDICINAL AND AROMATIC PLANTS

Medicinal and aromatic plants have been used in fields such as food, cosmetics, paint, textile, medicine, agriculture, and landscaping from the past till the present. The first thing that comes to mind is their use for therapeutic purposes. About 80% of people in developing and undeveloped countries are treated with herbal products. While this rate increases to 95% in some countries in the Middle East, Asia, and Africa. This rate decreases in developed countries with 40-50% in Germany, 42% in the USA, 48% in Australia, and 49% in France (Acıbuca and Budak, 2018; Göktaş and Gıdık, 2019).

Uses of MAP in Treatment

Treatment methods with medicinal plants are generally called 'alternative medicine' or phytotherapy. The first person mentioned to be using the concept of phytotherapy was the French Doctor Henri Leclerc (1870-1955). The fact that pharmacognosy, by examining secondary metabolites, supports that herbal treatment will be more beneficial to people with fewer side effects and are more affordable compared to synthetic drugs, has contributed to the development of phytotherapy. In phytotherapy, herbal drugs are used in both fresh and dried forms. It has been known - by observation -whether the plants would be beneficial or not. The saying "Every problem has a herbal remedy, the point is to find it", which was said approximately 2000 years ago, is still weighty today.

Use of MAP Plants in Food and Beverage

One of the most popular uses of medicinal and aromatic plants is spice production. People have been using spices in food for many reasons since ancient times. Spices are defined as products obtained by drying and grinding various plant parts such as seeds, buds, fruits, flowers, shells, roots, stems, rhizomes, tubers, and leaves. Spices are used to add colour, taste, and flavour to food. Spices can also be used in the preservation of food as well as an additive flavour and aroma. Spices used in food products such as sausage and pastrami add flavour and provide a protective medium, granting the long-term storage of food. In addition, some spices have appetizing and digestive effects.

Uses of TAB in Perfumery and Cosmetics Industry

There is an increasing consumer preference for natural products. Synthetic products cause a significant level of negative effects on people and the environment, which makes natural products even more appealing. This trend increases the demand for medicinal and aromatic plants in the cosmetic sector. Likewise, the preference for natural and relatively harmless products instead of perfumes containing petroleum derivatives causes an increase in natural perfume consumption. As a result of this, there is an increased demand for perfumes produced with oils from medicinal and aromatic plants. This increase in demand causes an increase in the value of such perfumes. In line with this increasing demand for natural-based products, the cosmetics industry is increasing the production of products containing medicinal and aromatic plants. Various plant parts are used to extract and manufacture plant-based perfumes.

Use of MAP as Biofuel

Today, the increasing population, unplanned urbanization, and industrialization have led to excessive consumption of non-renewable fossil fuels. The gradual decrease in non-renewable fuels has led human beings to search for alternatives. In addition, the negative effects of fossil fuels on the environment led humans to search for alternative energy sources that can be used instead of fossil fuels. For these reasons, the search for energy and fuel sources that cause less harm to the environment increased. Likewise, it is known to everyone that there is a huge effort to be done to find and produce more sustainable energy sources than fossil fuels. Studies conducted during this process show that biofuels are a candidate to be an ideal fuel and energy source in the future, both economically and environmentally. Various studies on this subject have been carried out nationally and internationally (Göktaş and Gıdık, 2019).

Uses of Medicinal and Aromatic Plants as Ornamental Plants

The ornamental plant sector is another area of use for medicinal and aromatic plants. Medicinal and aromatic plants, which are traditionally planted in home gardens as ornamental plants for medicinal and cosmetic uses, are now being used in the landscaping of parks and gardens (Dönmez et al., 2016; Kösa and Güral, 2019). Medicinal and aromatic plants, which are being used more in the landscape, find the opportunity to be used in landscape designs at different scales. The use of medicinal and aromatic plants, which are commonly found in the flora of Türkiye, in landscape areas is increasing day by day. In Türkiye, many studies have been made and continue to be done to reveal the importance of medicinal and aromatic plants in the fields of medicine and pharmacy. However, the place and importance of these plants in landscape architecture have not been fully revealed (Pouya and Demir, 2017; Kösa and Güral, 2019). Essential oil plants, which have beautiful and characteristic odors, are cultivated as medicinal plants in many gardens around the world due to their healing properties. Most aromatic plants, which have a beautiful appearance as ornamental plants, offer a strong potential alternative in landscape design. Medicinal and aromatic plants in landscaping are used in collection gardens, healing-therapy gardens, botanical gardens, rock gardens, roof and terrace gardens, dry stone walls, parterres, flower pots, sloped areas, and paths (Arslan et al., 2015; Kösa and Güral, 2019).

Health/Healing Gardens: "Healing gardens" are gardens designed for hospital staff, patients, and visitors to encourage their separation from the stressful environment (Ulrich, 1999; Pouya et al., 2015; Kösa and Güral, 2019). In fact, "healing" is a beneficial process when people accept new environments and feel good about themselves (Akın, 2006; Pouya et al., 2015; Kösa and Güral, 2019). Healing garden designs differ according to the age groups and disease states of patients and staff. For example; In a therapy garden designed for elderly people, it is necessary to provide silence and calmness. Whereas, freedom of play and the discovery of new things is many important elements in a therapy garden designed for children. Although the features affecting the design criteria differ, one of the most important steps in designing healing gardens is the herbal design phase to be carried out with medicinal and aromatic plants in the garden. Medicinal and aromatic plants have essential functions in these gardens in terms of aesthetics and functionality. Various activities with medicinal and aromatic plants help to activate the senses of those who visit the garden. For example; the sense of smell with fragrant plants that bloom in different seasons, the sense of touch with plants with different textures, and the sense of sight with aesthetically valuable leaves, flowers, and fruits are stimulated. In addition, the taste of produce also stimulates the sense of taste (Arslan et al., 2015; Kösa and Güral, 2019).

Botanical Gardens: Botanical gardens include collections of plants grown indoors to use them in scientific research, recreation, conservation, botanical and horticultural education, as well as for public landscape aesthetics. Botanical gardens can play an important role in agricultural studies and plant sciences due to their rich plant diversity. They are organizations that grow in wild and cultivated plants in accordance with their purposes, in a certain order, introduce and educate students and the public, provide information about botany, albeit limited, and respond to recreational needs. In addition to that, botanical gardens are crucial in terms of creating green spaces in urban areas, ecotourism, economic objects, and people's welfare (Faraji and Karimi 2020, Heywood 1987; Önder and Konaklı 2011; Kösa and Güral 2019). In botanical gardens, there are sections specialized under the name of medicinal and aromatic plants. These sections provide an important opportunity to learn detailed information about medicinal and aromatic plants. At the same time, they provide diversity in design as they form a separate section within the botanical gardens.

Rock Gardens: Medicinal and aromatic plants are used in different ways in landscaping according to their colour, form, texture, and size characteristics. Therewithal they have very different textures and colour properties in similar sizes, and their potential for use in rock gardens is also quite high.

Roof and Terrace Gardens: Considering the emergence and historical process of roof gardens, it can be said that aromatic plants grown in tin cans are the first examples to be grown on the roof (Brandmaillive, 2009; Köse and Güral, 2019).

2. ECONOMIC IMPORTANCE WORLDWIDE OF MAP

According to a study conducted by the World Health Organization in 2005, there are 21,000 plant species used for medicinal purposes in the world. It has been emphasized that the number of herbal drugs that are widely used varies between 4,000 and 6,000. The number of MAP plants traded is approximately 3,000 (FAO, 2005; Boztaş et al., 2021). According to the latest research, there are 28,187 medicinal plants whose medicinal use has been recorded in the world till today, and only 4,478 of them are mentioned in medical sources as herbal medicine (Allkin, 2017; Kırıcı et al., 2020; Boztaş et al., 2021). Today, 25% of pharmaceutical drugs used are produced from medicinal plants. Again, according to the Food and Agriculture Organization of the United Nations (FAO), 30% of the medicines sold worldwide contain compounds derived from plant materials (FAO, 2005; Boztaş et al., 2021).

Trade in Medicinal Aromatic Plants

The countries with the highest import and export of medicinal and aromatic plants are the USA, China, United Kingdom, Germany, France, India, and the Netherlands (Binici, 2002; Boztaş et al., 2021). The species of medicinal and aromatic plants that Türkiye trades is 347 in total, including subspecies. 139 of the 347 species are exported (Özgüven et al., 2005; Boztaş et al., 2021). Türkiye is one of the important countries in medicinal and aromatic plant trading due to its geographical location, climate, plant diversity, agricultural potential, and large areas (Bayram et al., 2010; Boztaş et al., 2021). It is estimated that the number of medicinal and aromatic plants economically important for trade in Türkiye is more than 500 while about 200 of them have export potential (Baytop, 1999; Ekim et al., 2000; Aydın, 2004; Faydaoğlu and Sürücüoğlu, 2011). In terms of the medicinal and aromatic plants used in Türkiye, 90% of them are collected from nature while the remaining species are cultivated. Half of the medicinal and aromatic plants produced in Türkiye are collected from nature and the remaining 50% are obtained

While the total exports of coffee, tea, Paraguayan tea, and spices were 12.5 billion dollars in 2001, they quadrupled to reach 48.5 billion dollars in 2015. However, in 2016, exports did not increase much compared to the previous year (2015), which amounted to 48.7 billion dollars. In 2017, exports increased reaching approximately 3 billion dollars compared to the previous year in which 51.5 billion dollars were recorded. In 2018, a drop of approximately one and a half billion dollars in export values was recorded compared to 2017, reaching 50.1 billion dollars. This decline in exports continued in 2019 reaching 48.7 billion dollars. Brazil, China, Vietnam, India, and Germany are the leading countries in exporting coffee, tea, Paraguayan tea, and spices. While the export value of lacquers, gums, resins, herbal essence water, and extracts was 2.1 billion dollars in 2001, it increased more than 3 fold reaching 7.1 billion dollars in 2015. In the following years (2016 and 2017), export values remained at the same level and had been appraised at 7.1 billion dollars. In 2018 and 2019, exports reached 8.1 billion dollars. In the group of lacquer, gum, resin, herbal juices, and extracts, the highest exports are recorded by China, India, the USA, France, Germany, and Spain. The export values of essential oils, resinoids, perfumery, and cosmetic products obtained from medicinal and aromatic plants are higher than the product groups mentioned above. While the world's total export value of essential oils, resinoids, perfumery, and cosmetic products obtained from medicinal and aromatic plants was 34.1 billion dollars in 2001, it hits 150.7 billion dollars in 2019. In the group of essential oils, resinoids, perfumery, and cosmetic products, the leading exporting countries are France, the USA, Germany, and Ireland. In the same period (2001-2019), there was a remarkable increase in imports. While the world imports of medicinal and aromatic plants were 48.9 billion dollars in 2001, this amount hits 205.9 billion dollars in 2019. While the import value of coffee, tea, Paraguayan tea, and spices group was 13.4 billion dollars in 2001, it reached 48.6 billion dollars in 2019. In the coffee, tea, Paraguayan tea, and spice group, countries recording the highest imports are the USA, Germany, France, and Italy. The import value of product groups of lacquer, gum, resin, etc. herbal water, and extracts showed an increase from 2.4 billion dollars to 8 billion dollars. While the USA had the largest share in the imports of lacquer gum, resin, etc. herbal water, and extracts product group, followed by Germany, France, and China. There have been great changes over the years in the import of medicinal and aromatic plants worldwide. The biggest change in the trade of medicinal and aromatic plants has been the product group containing essential oils and resinoids, perfumery, cosmetics, etc. Import values increased from 33 billion dollars to 149.2 billion dollars (between 2001 and 2019). In this product group, the highest imports were made by China, the USA, Germany, England, Hong Kong, and France (Boztaş et al., 2021).

The increasing trend in the world has also been observed in Türkiye's foreign trade. While the export value of coffee, tea, and spices in Türkiye's trade of medicinal and aromatic plants was 57.9 million dollars in 2001, it increased 3 folds in 2019 compared to 2001 reaching 168.4 million dollars. While lacquer, gum, resin, herbal juices, and extracts had an export volume of about 2 million dollars in 2001, this volume increased to 9.1 million dollars in 2015, 10.3 million dollars in 2016, 12 million dollars in 2017, 16.4 million dollars in 2018, and reaching 18.5 million dollars in 2019. Türkiye has the highest income from medicinal and aromatic plants, in parallel with world data, from essential oils, resinoids, perfumery, and cosmetic products. While Türkiye exported 83.6 million dollars' worth of medicinal and aromatic plant products in 2001 it realized an initial increase in export worth 695.5 million dollars in 2015. Its exports in this field increased to 696.5 million dollars in 2016, 762.5 million dollars in 2017, 782.9 million dollars in 2018, and 829.5 million dollars in 2019. Exports of medicinal and aromatic plants increased by 707% between 2001 and 2019, reaching $1.02 billion from $143.6 million. Essential oils and resinoids, perfumery, cosmetics, etc. product group had the largest share in exports worth 829.4 million dollars. In the product group (tea, coffee, Paraguayan tea, and spices) in which thyme, laurel, and poppy plants are among the products that Türkiye is leading in world trade, the USA, Germany, Vietnam, and Holland are the countries Türkiye exports to the most. Although Türkiye is the homeland of many endemic plants and has a climate and soil structure suitable for the cultivation of many medicinal and aromatic plants, it has a very low export income (Boztaş et al., 2021).

Having an important place among the countries exporting herbal drugs, Türkiye also imports many medicinal and aromatic plants. While Türkiye's imports of coffee, tea, Paraguayan tea, and spices were 26.5 million dollars in 2001, they reached 199.8 million dollars in 2015 with an 8-fold increase. This increase reached 216 million dollars in 2016, 319.6 million dollars in 2017, 266.3 million dollars in 2018 reaching 282.1 million dollars in 2019. While Türkiye's imports of lacquers, gums, resins, and herbal extracts were 18.5 million dollars in 2001, they increased to 39.6 million dollars in 2015. This increase was 43.8 million dollars in 2016, 51.7 million dollars in 2017, and 51 million dollars in 2019. Turkiye's essential oils and resinoids, perfumery, cosmetics, etc while the import figure of medicinal and aromatic plants was 237.6 million dollars in 2001, it exceeded one billion dollars today. There are two main reasons why Türkiye imports medicinal and aromatic plants. The first reason is that many imported products (such as coffee, black pepper, ginger, turmeric, ginseng, nutmeg, and cinnamon) cannot be cultivated in Türkiye due to its ecological conditions. The second reason is that some of the imported products are processed domestically and converted into products with higher added value (reexport) and sold (Boztaş et al., 2021).

Türkiye is one of the leading countries in the trade of medicinal and aromatic plants, thanks to its geographical location, rich plant diversity, climate, and ecological structure, and large natural and agricultural areas. Today, medicinal and aromatic plants, which are used as raw materials for advanced industries such as herbal medicine, food, and additives, cosmetics, and perfumery, whose current use is increasing in many developed countries, are widely found in the flora of Türkiye (Bayram et al., 2010; Boztaş et al., 2021).

Türkiye exports medicinal plants to nearly 100 countries around the world. For example, among the exported species, while plants such as laurel, linden, mahaleb, fenugreek, juniper, and licorice are collected from nature, many plants such as poppy, cumin, thyme, tea, anise, black cumin, and coriander are cultivated. Among the cultivated species, poppy, thyme, bay, and black tea are the most exported plants. The data on export amount and value of Türkiye's main spices, tea, and other products between 2015 and 2019 are as follows: While 12 thousand tons of poppy seeds were exported in 2015 for 37.7 million dollars, 25.2 thousand tons were exported for 90.5 million dollars in 2019. While 15.2 thousand tons of thyme was exported for 55.7 million dollars in 2015, 16.7 thousand tons were exported for 53.2 million dollars in 2019. While 12.7 thousand tons of bay leaves were exported for 35.8 million dollars in 2015, 13.5 thousand tons of them were exported for 38.2 million dollars in 2019. While 5.5 thousand tons of black tea was exported for 22.7 million dollars in 2015, 3.9 thousand tons were exported for 14 million dollars in 2019. While 3.7 thousand tons of cumin was exported as a spice in 2015 for 11.1 million dollars, 3.9 thousand tons were exported for 13.3 million dollars in 2019. Finally, another most exported medicinal and aromatic plant, anise, was exported 3.2 thousand tons for 11.6 million dollars in 2015, while 2.1 thousand tons were exported for 8.7 million dollars in 2019 (Boztaş et al., 2021). Türkiye is in the leading position in the world of thyme trade with its production potential and meets 80% of the world's thyme trade. Approximately 80% of the thyme exported in the last 10 years has been produced under cultural conditions, and the rest has been collected from nature (Bayram et al., 2010; Boztaş et al., 2021). Today, this ratio has changed in parallel with the increase in both, production area and amount, approximately 90% of the exported thyme is produced under field conditions, while 10% is collected from nature (Boztaş et al., 2021). Being an important exporter of medicinal and aromatic plants, Türkiye also imports some plant species. The import amount and monetary values of Türkiye's main spices, tea, and other products between 2015 and 2019 are as follows. The most imported product is coffee. While 46.1 thousand tons of coffee was imported for 146.8 million dollars in 2015, 73.5 thousand tons of coffee was imported for 194.8 million dollars in 2019. The reason for this is that coffee is not grown in Türkiye. While 5.4 thousand tons of black tea was imported for 16.2 million dollars in 2015, 18.9 thousand tons were imported for

38.8 million dollars in 2019. While 5.3 thousand tons of peppers (Capsicum and Pimenta species) were imported for 10.7 million dollars in 2015, 10.8 thousand tons were imported in 2019 for 16.2 million dollars. While 3.1 thousand tons of black pepper spice was imported for 5.6 million dollars in 2015, 6.2 thousand tons were imported for 11.3 million dollars in 2019. Although the carob plant is grown in Türkiye, it is among the imported plants. While 4.9 thousand tons were imported for 5 million dollars in 2015, 3.5 thousand tons were imported for 9.5 million dollars in 2019. Finally, while 2.5 thousand tons of garlic was imported for 8.1 million dollars in 2015, 6 thousand tons were imported for 6.7 million dollars in 2019 (Boztaş et al., 2021).

CONCLUSIONS

In this study, the agricultural importance of medicinal and aromatic plants, their usage areas, their position in Türkiye, and world trade are discussed. Medicinal and aromatic plants from past to present; As a result of their use in many fields such as food, cosmetics, paint, textile, medicine, agriculture, and landscaping and the increasing demand for these plants, the trading volume of medicinal and aromatic plants in Türkiye and world trade is increasing day by day. Although Türkiye has high production potential for numerous medicinal and aromatic plants, it is still far from the desired ranking in the continuously growing market. However, if the right collection and marketing strategies are followed for medicinal and aromatic plants, most of which grow naturally in the country's flora, Türkiye will certainly contribute much more to this market. Similarly, many medicinal and aromatic plants that do not naturally grow in the flora of Türkiye have the opportunity to be successfully cultivated. According to the data of the world medicinal and aromatic plant market, although Türkiye is among the top ten countries with the highest number of names in this market, Türkiye's level of share in this market is very low. It is a major exporter of raw drugs. Developing countries such as Türkiye are known as raw material producers in this market. This causes Türkiye to earn a low income compared to the world trade volume. However, the countries having the highest share in this market are countries that have completed their development and are advanced in plant processing. To have a say in the world medicinal and aromatic plants market and to gain a higher market share, it is necessary to produce products with high added value derived from medicinal and aromatic plants, in addition to cultivation and collecting. In addition, Türkiye needs to develop itself in terms of finding or creating a market for the export of medicinal and aromatic plants. If these points are achieved, Türkiye's contribution to the world medicinal and aromatic plants sector will be elevated more.

REFERENCES

Acıbuca, V. & Bostan Budak, D. (2018). Dünya'da ve Türkiye'de Tıbbi ve Aromatik Bitkilerin Yeri ve Önemi. Çukurova Journal of Agriculture and Food Science, 33(1): 37-44. (In Turkish).

Akın, Z. Ş. (2006). Çocuklar İçin İyileştirme Bahçeleri. Yüksek Lisans Tezi, Fen Bilimleri Enstitüsü, Ankara.

Allkin, B. (2017). Useful Plants–Medicines. At Least 28,187 Plant Species are Currently Recorded as Being of Medicinal Use. In: Willis KJ, Editor. Royal Botanic Gardens, London.

Anonymous, (2017). Doğu Karadeniz Bölgesi tıbbi ve aromatik bitkilerin envanterinin çıkarılması, ticari kullanımının araştırılması ve üreticilerin eğitimi projesi eğitim kitabı. https://www.kalkinmakutuphanesi.gov.tr/assets /upload/dosyalar/15-tibbi-ve-aomatik-bitkiler-projesi-egitim-kitabi-2017-pdf-242110-rd_35.pdf (Accessed date: 13.09.2022).

Arslan, N. Baydar, H. Kızıl, S. Karik, Ü. Şekeroğlu, N. & Gümüşçü, A. (2015). Tıbbi ve Aromatik Bitkiler Üretiminde Değişimler ve Yeni Arayışlar. TMMOB Ziraat Mühendisliği VIII. Teknik Kongresi, 12-16 Ocak, Ankara.

Aydın, S. (2004). Anadolu Diyagonali: Ekolojik Kesinti Tarihsel-Kültürel bir Farklılığa İşaret Edebilir mi? Kebikeç İnsan Bilimleri İçin Kaynak Araştırmaları Dergisi, 17, ss.117-137.

Baydar, H. (2019). Tıbbi ve Aromatik Bitkiler Bilimi ve Teknolojisi (6. Basım). Nobel Akademik Yayıncılık, Yayın, 2328. p.21

Bayram, E. Kırıcı, S. Tansı, S. Yılmaz, G. Arabacı, O. Kızıl, S. & Telci, İ. (2010). Tıbbi ve Aromatik Bitkiler Üretiminin Arttırılması Olanakları. TMMOB Ziraat Mühendisleri Odası, Ziraat Mühendisliği VII. Teknik Kongresi, 11-15 Ocak, Ankara.

Baytop, T. (1999). Türkiye'de Bitkiler ile Tedavi, Geçmişte ve Bugün. Nobel Tıp Kitabevleri, II. Baskı ISBN: 975-420-021- 1. 480s. İstanbul.

Binici, A. (2002). Baharat Değerlendirme Raporu. Orta Anadolu İhracatçı Birlikleri Genel Sekreterliği, 1-37.

Boztaş, G. Avcı, A. B. Arabacı, O. & Bayram, E. (2021). Economic status of medicinal and aromatic plants in Turkey and in the World. Theoretical and Applied Forestry, 1: 27-33. (In Turkish).

Brandmaillive. (2009). http://www.brandmaillive.com/2009/05/ sayi_16/ng.html (Accessed date: 21.05.2019).

Ekim, T. Koyuncu, M. Vural, M. Duman, H. Aytaç, Z. & Adıgüzel, N. (2000). Red Data Book of Turkish Plants (Pteridophyta and Spermatophyta). pp.246, Ankara. (InTurkish).

Dönmez, Ş., Çakır, M. & Kef, Ş. (2016). Utilization of some medicinal aromatic plants in landscape architecture growing in Bartın province. Journal of Architectural Sciences and Applications, 1(2):1-8. (In Turkish).

FAO. (2005). Trade in medicinal plants. http://www.fao.org/3/af285e/af285e00.pdf (Accessed date: 18.04.21).

Faraji, L. & Karimi, M. (2020). "Botanical Gardens as Valuable Resources in Plant Sciences." Biodiversity and Conservation, 1-22.

Faydaoğlu, E. & Sürücüoğlu, M. S. (2011). History of the Use of Medical and Aromatic Plants and their Economic Importance. Kastamonu University Journal of Forestry Faculty, 11(1): 52-67. (In Turkish).

Göktaş, Ö. & Gıdık, B. (2019). Uses of Medicinal and Aromatic Plants. Bayburt Üniversitesi Fen Bilimleri Dergisi, 2(1): 145-151. (In Turkish).

Heywood, V. H. (1987). The Changing Role of the Botanic Garden, IUCN (International Union for Conservation of Nature) Monitoring Centre, Kew, England, UK.

Kırıcı, S. Bayram, E. Tansı, S. Arabacı, O. Baydar, H. Telci, İ. İnan, M. Kaya, D.A. & Özel, A. (2020). Tıbbi ve Aromatik Bitkilerin Üretiminde Mevcut Durum ve Gelecek. Türkiye Ziraat Mühendisliği IX. Teknik Kongresi, 13-17 Ocak, Ankara.

Kösa, S. & Güral, S. M. (2019). Tıbbi ve Aromatik Bitkiler ve Peyzajda Kullanımları. PEYZAJ-Eğitim, Bilim, Kültür ve Sanat Dergisi, 1(1): 41-54.

Önder, S. & Konaklı, N. (2011). The determination of planning principles of botanic garden for Konya. Journal of Tekirdag Agricultural Faculty, 8(2): 1-12. (In Turkish)

Özgüven, M. Sekin, S. Gürbüz, B. Şekeroğlu, N. Ayanoğlu, F. & Ekren, S. (2005). Tütün, Tıbbi ve Aromatik Bitkiler Üretimi ve Ticareti. Türkiye Ziraat Mühendisliği VI. Teknik Kongresi, 3-7 Ocak, Ankara.

Pouya, S. Bayramoğlu, E. & Demirel, Ö. (2015). Investigation of Healing Garden Design Methods. Kastamonu University Journal of Forestry Faculty, 15(1): 15-25. (In Turkish).

Ulrich, R. S. (1999). Effects of gardens on health outcomes: Theory and research. In C. CooperMarcus & M. Barnes (Eds.), Healing Gardens: Therapeutic Benefits and Design Recommendations. New York: John Wiley, pp. 27- 86.

CHAPTER 14

DRUG DELIVERY SYSTEMS FOR LOADING OF MEDICINAL AND AROMATIC PLANTS (MAPS) AND THEIR BIOMEDICAL APPLICATIONS

Neşe KEKLİKCİOĞLU ÇAKMAK[1]

[1] Sivas Cumhuriyet University, Faculty of Engineering, Department of Chemical Engineering, Sivas, Türkiye, e-mail: nkeklikcioglu@cumhuriyet.edu.tr
ORCHID ID: 0000-0002-8634-9232

INTRODUCTION

Medicinal aromatic plants are natural raw materials. For many years, these natural compounds have been widely used globally in herbal medicines, food products and cosmetics (Paramanya et al., 2022). Phytomolecules extracted from medicinal and aromatic plants (MAPs) are in high demand due to their major significance, notably in the pharmaceutical sectors. This has led to a growth in the use of medicinal plants. Phytopharmaceuticals are of great interest due to their superior therapeutic activities and fewer side effects compared to modern drugs (Chakraborty et al., 2016). Scientific and methodical approaches are needed for the application areas of herbal pharmaceuticals, which is a current research topic. The improved formulae are thought to provide exceptional advantages over traditional and previously employed methods in terms of solubility, bioavailability. In addition to its advantages, MAPs have several disadvantages such as low solubility of pharmaceutically active components in some media, low biological applicability, less stability and unpredictable toxicity (Gunesakaran et al., 2014). In recent years, it has been aimed to overcome these disadvantages by using nanotechnology-based drug carriers. Nanomedicine is defined as the use of nanoscale devices and structures for molecular monitoring, treatment, and remodelling of human biological systems. In additon, nanomedicine offers numerous opportunities in the health sector for early diagnosis, appropriate treatment and follow-up of diseases (Tüylek, 2021). By interfering with the systems at the molecular level with nanotechnology, early diagnosis, appropriate treatment and follow-up of diseases are possible. With the development of creative methods that enable not only the identification of diseases but also the delivery of drugs directly to cells, the use of nanotechnology in treating diseases has recently shown promise. The aim of this section is to reveal the types of medicinal and aromatic plants loaded on nanocarriers and to focus on the promising use of nanomedicine and their role in various disease treatments.

1. NANOCARRIER IN DRUG DELIVERY SYSTEM

The development of drug delivery systems (DDS) for herbal medicines has received a lot of attention over the past 20 years. Humans have employed herbal medicines for a variety of diseases since the ancient period. However, these herbal medicines are subject to limitations due to their disadvantages related to their stability and lipid solubility. To overcome these problems, DDSs of herbal medicines are designed for herbal ingredients. Studies to create such carrier systems and to ensure the release of active ingredients in the body have attracted great interest in recent years (Dzobo, 2022, Chopra et al., 2021,Balunas et al., 2005) By applying nanotechnology to drugs, nanoparticles have been used to mimic or modify biological processes (Singh et al., 2009). Solid colloidal particles called nanoparticles range in size from 10 nm to 1000 nm, although for nanomedical applications, fewer than 200 nm is recommended (Biswas et al., 2014). By utilizing various drug carrier systems, nanodrugs such as liposomes, dendrimers, polymeric micelles, nanoparticles, polymer-drug/protein conjugates, and carbon nanotubes play a significant role in the treatment of diseases such chronic diseases like asthma, diabetes, psoriasis from skin diseases, some rheumatic diseases and cancer.

A major portion of herbal medicine does not reach the intended area because of the stomach's ability to break down different herbal medicine components before they enter the bloodstream and the liver's ability to digest the remaining components. The therapeutic action of the medicine is ineffective if the recommended dosage cannot reach the desired location. To overcome this problem, nanocarriers are crucial in delivering significant amounts of drugs to targeted sites, overcoming all barriers such as the highly acidic pH of stomach and liver metabolites. (ud Din et al., 2017). Due to the large dimensions of traditionally applied drug delivery systems, nano drug delivery systems are emerging as a new approach. Since nano drug delivery systems have high surface area, their drug loading capacity is quite high. It also has advantages such as improving solubility, show enhanced penetration and retention effect, have very lesser side effects, reducing medicinal doses and side effects. The accumulation of the medication at the target site, which is independent of the route or mechanism of delivery, is known as drug delivery to the target (Patra et al., 2018). A pharmacological target is a molecule, typically a protein, that is intimately linked to a specific disease process in the body and can be targeted by a medication to have the intended therapeutic efficacy. The following targeted drug delivery system objectives are given as a few examples (Mohammadi et al., 2022).

- Eliminating or minimizing the disadvantages seen in conventional treatment,
- Increasing delivery to cellular levels,
- Improving medication concentration and release kinetics in the circulation or other biological samples,
- Changing the pharmacokinetic and pharmacodynamic properties of drugs,
- To provide effective and safe treatment at low or high doses,
- To remove toxic and immunogenic properties,
- To increase the stability of drugs,
- It aims to accomplish the required amount of pharmacological reaction in the target area without producing any unfavorable interactions in other different parts of the body.

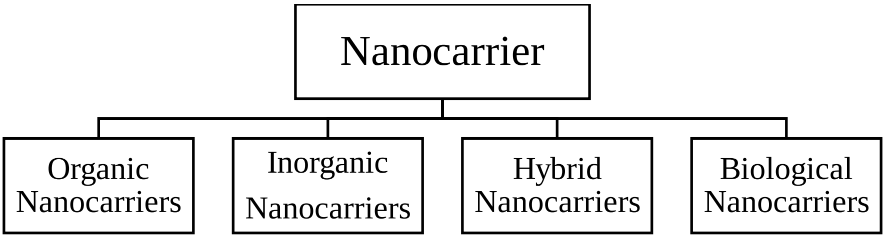
In order to achieve the above-mentioned goals, drug targeting studies are characterized into three classes: passive drug targeting, active drug targeting and physical targeting (Khan et al., 2022, Pereira et al., 2015).

Nanoparticles can be effectively localized into the tumor microenvironment thanks to passive targeting. Especially inorganic nanoparticles attract a lot of attention due to their extraordinary properties. When inorganic nanoparticles are applied to living cells, they are designed to increase drug delivery only and largely to the tumor site. Thanks to the unique dimensions of these nanoparticles, drug delivery with the effect of EPR (enhanced permeability retention) can be selectively accumulated in the tumor area through "passive targeting". Although passive targeting has found clinical application, some tumors may not be transported by the effect of EPR because their vascular permeability is different. Therefore, the approach of active targeting of the nanocarrier has emerged (Peer et al., 2007).

In active targeting, ligand-receptor mediated targeting is performed by changing the surface charge and surface hydrophobicity. Changing the surface charge is known to remove negatively charged ones from the blood faster than positively charged and neutral ones. It has been understood that opsonization is prevented or delayed and the residence time in circulation is extended by coating the surface of the carrier system with hydrophilic polymer. In active targeting, antibodies and peptides are combined with the drug delivery system to bind to receptor structures expressed at the target site. Since the nutrient requirement of the tumor increases more than the healthy tissue, it increases the number of different receptors in diseased tissues and cells. Since the tumor site is usually a mixture of healthy and cancerous cells, the design of nanocarriers that can distinguish them is of paramount importance. In active targeting, the nanocarrier is coated with specific targeting ligands that will recognize receptors that are more abundant on tumor cell surfaces or vascular regions than in healthy cells (Martínez-Carmona et al., 2015). In this way, the cytotoxic effect of the anticancer agent is increased and the side effects on healthy tissue are minimized. This modification of the nanocarrier provides active targeting, increases the therapeutic effect of cytotoxic drugs and reduces multidrug resistance (Steichen et al., 2013). In order to increase selectivity, the antigen or receptor on the surface must be more numerous than normal cells. As a result of the binding of the ligand bound to the nanocarrier with its receptor, uptake by receptor-mediated endocytosis can occur, which is very important for the release of the drug into the cell.

Physical targeting makes use of physical differences between the target site and the surrounding area, such as (Pereira et al., 2015) magnetic sensitive systems, ultrasonic sensitive systems, temperature sensitive systems, targeting hypoxia, and targeting acidity.

It is possible to classify nanocarriers in four main groups according to their types: organic nanocarriers, inorganic nanocarriers, hybrid nanocarriers and biological nanocarriers.



Organic Nanocarriers

- Lipid and Polymer-Based Nanocarrier
- Solid Lipid Nanoparticle (SLN)
- Nanostructured Lipid Carrier (NLC)
- Nanoemulsion (NE)
- Nanocapsule (NC)
- Liposome

- Lipid Drug Conjugate (LDC) or Polymer Drug Conjugate (PDC)
- Transferosome
- Niosome
- Ethosome
- Dendrimer
- Micelle
- Nanosphere (NS)
- Nanocrystals
- Phytosome or Herbosome
- Self Nanoemulsifying Drug Delivery System (SNEDDS)
- Nanofiber
- Polymersome (PS)
- Cubosome
- Biopolymer-Based Nanocarrier (BBN)
- Pure Biopolymer Nanoparticles (PBN)
- Biopolymer-based Hydrogels (BBH)
- Biopolymer Drug Conjugate (BDC)

Inorganic Nanocarrier

- Metal Nanoparticle (MN)
- Mesoporous Silica Nanoparticle (MSN)
- Magnetic Nanoparticle (MNP)
- Calcium Carbonate ($CaCO_3$) Nanoparticle
- Nanotube

Hybrid Nanocarrier (HNC)

Biological Nanocarriers (BNC)

1.1. Organic Nanocarriers

Organic nanocarriers made of lipid or polymeric materials are widely used in a variety of fields, particularly in the delivery of anticancer medicines to specific tumor tissues. Lipids function as an appropriate penetration enhancer of drugs in the digestive systems by promoting the dissolution of drugs around the stomach, reducing first pass metabolism by diffusion of the drug into the circulatory system via the lymphatics.

Solid lipid nanoparticles (SLN), also known as colloidal drug carriers, are particles with a size range of 50 to 1000 nanometers that are made from solid lipids at body and room temperatures and stabilized with emulsifiers. SLNs are generally composed of solid lipids, emulsifiers and water. Lipids include triglycerides, partial glycerides, fatty acids (stearic acid, etc.), steroids (cholesterol, etc.), and waxes (cetyl palmitate, etc.). Lipids are generally physiological compounds. All types of emulsifiers can be used to stabilize the lipid dispersion, depending on their charge and molecular weight. Stabilization is provided with 1-5% emulsifier or emulsifier/co-emulsifier complex. The choice of emulsifier depends on the route of administration. Emulsifiers that can be used for parenteral applications are quite limited. Examples of substances used as emulsifiers are lecithins, poloxamers, ethoxylated monoglycerides and polysorbates. (Lim et al., 2022).

For oral administration of phytomolecules, surface-modified SLNs made with heparin, albumin, PEG, and polysaccharides ensured their prolonged release in the stomach environment. As a model method for the oral distribution of phytomolecules, SLNs have been introduced. Despite other emerging drug delivery methods, its affordability, stability and bulk production still make SLN a better option (Ganesan et al., 2018) . Quercetin remains the most studied flavonoid for NP strains since other natural flavonoids show low absorption. Li et al. (Li et al., 2009) created SLN using glyceryl monostearate and soy lecithin for low-temperature emulsification-solidification method to enhance its absorption and bioavailability. As a result of the study, it was determined that SLNs have five times more bioavailability and absorption. In the result of the working on enhancing oral and intravenous bioavailability in rats, it was determined that encapsulation of aposine in a chitosan-based solid lipid nanoparticle showed this potential (Aman et al., 2018). Ding et al. (Ding et al., 2015) prepared the Quercetin SLN to detect whether there is improvement in motor nerve activity recovery after spinal injury. It was revealed that SLN achieved a recovery of 39.75% and therefore could be used as a potential. Chen-yu et al. (Chen-yu et al., 2012) performed a study to examine the response of quercetin NLCs in topical application treatment. According to the results, it was determined that quercetin is retained in the epidermis and dermis in greater amounts with higher antioxidant effects by facilitating its absorption. Resveratrol is a commonly used compound in cardiovascular disease (CVD). Its poor pharmacokinetic features, such as limited water solubility, low photostability, and severe first pass metabolism, cause poor bioavailability, however, which makes it difficult to utilize clinically. Lipid nanoparticle nanotechnology offers the chance to create novel therapies as a solution to this issue. Furthermore, regulated and site-specific drug administration is possible with solid lipid nanoparticles (Hesari et al., 2021). In a different study SLN is puerarin-loaded SLN was studied for biocompatibility and as a targeted carrier in rats (Luo et al., 2011, Luo et al., 2013).

Nanoemulsions (NE) are a two-phase mixture of oil and aqueous phase stabilized by surfactant molecules. They are normally created by mixing an aqueous phase with a hydrophilic emulsifier and an oil phase with a hydrophobic drug. The structure formed as a result of the orientation of the surfactant molecules gives NEs unique properties. NEs are one of the main nanocarriers in pharmaceuticals and essential oils due to their unique properties (Patel et al., 2018). Due to their quick digestion in the gastrointestinal tract, nanoemulsions are very effective at increasing the bioaccessibility and bioavailability of hydrophobic compounds. By giving the lipase molecules more opportunity to bond, nanoemulsions' high specific surface area lipid droplets can be rapidly digested. For a variety of uses, herbal drugs such camptothecin, emodin, genistein, resveratrol, and quercetin, as well as berberine, ferulic acid, and zedoary, have been loaded into NE (Patel et al., 2012). Celecoxib (Moghimipour et al., 2017) acetazolamide (Morsi et al., 2017), and curcumin (Esperón-Rojas et al., 2020) have all been demonstrated to have higher bioaccessibility or bioavailability when combined with plant-based nanoemulsions.

Polymeric NPs in drug delivery systems have been developed for delivery of the targeted formulation. These nanoparticles provide controlled and targeted drug release by reducing the administered dose. Depending on the structural organization, polymeric NPs are divided into nanocapsules and nanospheres two parts. Nanocapsules have a polymeric coating with a central core containing active constituents. On the other hand, the nanosphere is just a polymeric structure with an adsorbed active drug. Most frequently employed as matrices are poly(methyl methacrylate) (PMMA), glycol acid polymers (PGA), or combinations of them poly lactic-*co*-glycolic acid (PLGA). The drug is contained by a reservoir or in a cavity encircled by a polymer membrane or coating in this nanovesicular colloidal dispersion system, which has a conventional core-shell configuration. The active component may be present in the cavity as a liquid (oily or aqueous core), a solid, or a molecule form, with the NC's core-shell structure and composition serving as its primary distinguishing characteristics and particularly regulating drug release. Similarly, depending on the technique of synthesis and the raw materials utilized, this structure can be either hydrophobic or lipophilic. Enhancing the oral bioavailability of the hydrophilic active components was the primary goal in the development of this composition (Bonifacio et al., 2014, Censi et al., 2012, Ibili et al., 2022, Mora-Huertas et al., 2010). Many plant extract-based drugs and antioxidants have been produced using these polymeric nanoparticles (NPs). Researchers continue to place the most emphasis on and study the anticancer properties of plant extracts and their phytoconstituents. The constituent has been continuously developed in a focused and dose-dependent manner. Polymeric NPs have enabled both in vitro and in vivo testing of the effectiveness of such formulations and have provided novel, effective drug delivery platforms.

Chitosan, gelatin, and alginate were used to encapsulate the crystals of the drug artemisinin (ART) from the plant Artemisia annua in order to control the release of the medication by the self-assembly of the polyelectrolytes on the drug crystals and increase the crystal's hydrophilicity (Chen et al., 2009). El-Gogary et al created polymeric nanocapsules with quercetin and folic acid integrated for both passive and active targeted administration of the medication on folate-expressing cancer cells (El-Gogary et al., 2014). It has been noted that thyme essential oil loaded chitosan nanoparticles have more inhibitory effect against Staphylococcus aureus and exhibit inhibitory action against Bacillus cereus (Sotelo-Boyás et al., 2017).

A colloidal aqueous solution called a nanosphere can be amorphous or crystalline and range in size from 10 to 200 nm. It is made up of a polymeric core that contains active chemicals or adsorbes them onto nanoparticles (Baldissera et al., 2017, da Silva et al., 2014). Improved solubility, tissue targeting, therapeutic efficacy, and permitted the transport of active principle via the blood-brain barrier were seen in a research with nerolidol-loaded nanospheres (Baldissera et al., 2017).

(BBB). After oral gavage, produced a successful removal of Trypanosoma evansi from the central nervous system (CNS) in female mice. Silymarin-loaded PLGA has increased encapsulation effectiveness, sustained release, high cellular internalization, and selective toxicity (da Silva et al., 2014).

Liposomes are closed vesicles of spherical shape, consisting of one or more lipid bilayers, with an aqueous phase inside and between the layers. Its main components are phospholipids. Phospholipids are amphiphilic structures that contain both hydrophilic and lipophilic groups. The hydrophilic heads of the phospholipids are the innermost and outermost, with the hydrophobic tails between them. When liposomes enter the bloodstream, they interact with plasma proteins and are removed by the RES (reticulo-endothelial system). Targeting to RES organs is advantageous as the active substance is localized there, but it is a significant disadvantage that it cannot reach other systems since it is excreted from the body. Therefore, it was desired to be integrated into drug delivery systems (Jafari et al., 2017). These systems can be created using plant-based phospholipids, such as those from soybeans or sunflowers. Schmitt et al. found that curcumin in liposomal carriers (LipoCur) was more effective than free curcumin at suppressing the proliferation and reactivity of human microglia and astrocytes (human fetal astrocyte cell line, SVGA) in a glioma study. LipoCur was equally efficient in reducing glial scarring, according to immunostaining of mouse organotypic brain segments that had been exposed to lipopolysaccharide (LPS) after eight days (Schmitt et al., 2020).

Niosomes (non-ionic surfactant vesicles) are microscopic lamellar structures synthesized when mixing non-ionic surfactants of the alkyl or dialkyl polyglycerol ether class with cholesterol. They can be monolayer or multilayer depending on the method of preparation. In the double layer model, the hydrophilic heads are located on the outermost and innermost parts. Hydrophilic active substance can be retained between the two layers, hydrophobic active substance can be retained within the vesicle (Ambwani et al., 2018). Resveratrol and Zingiber cassumunar Roxb (Zingiberaceae) were loaded and studied with niosomes. It has been stated that these carrier-loaded drugs are promising candidates for the topical treatment of skin malignancies (Rameshk et al., 2018, Pando et al., 2015, Priprem et al., 2016).

Dendrimers are cellular macromolecules synthesized by growing repeating monomers in steps from the center to the surface. It consists of 3 parts: core, branches and reactive functional groups. By changing these parts, properties such as solubility, thermal stability, conjugation of substances with different properties can be gained. Dendrimers are macromolecules with high drug loading capacity, easily synthesized, stable, functionalized, controlled in size, and effective in active targeting (Madaan et al., 2014). Polyamidoamine (PAMAM) dendrimers are obtained with functionalized nanoscale formulas. For this purpose, since they can be developed in various shapes, sizes and surfaces, their use as carriers has recently been studied in studies.

Puerarin loaded PAMAM dendrimer structure was investigated and found to improve oral bioavailability, solubility, and sustained release in rats. Fresh rat erythrocytes exposed to this dendrimer in an in vitro hemolytic toxicity assay showed no signs of hemolysis (Gu et al., 2013).

The macromolecular structure known as a micelle has a spherical core and an outer shell. Amphiphilic, they consist of a single polymer chain and these chains are called "unimers". Amphiphilic diblock (hydrophilic polymer-hydrophobic polymer) and triblock (hydrophilic polymer-hydrophobic polymer-hydrophilic polymer) co-polymers and graft polymers are used. The center of micelles made of diblock polymers is hydrophobic, whereas the shell is hydrophilic. Hydrophilic active substances can be loaded on the shell and hydrophobic active substances on the core, but it is stated in the literature that it is more appropriate to load the active substance on the hydrophobic core. The hydrophilic shell also acts as a physical barrier (Ghezzi et al., 2021). Eases ischemia-reperfusion induced cardiomyocyte injury study was carried out with Tilianin and Tilianin nano-micelles structure was created to increase water solubility in the study, the compound of polyethylene glycol that is covalently linked to amphiphilic diblock polymers produced by propylene sulfide. Tilianin is encapsulated in a hydrophobic shell to produce nano-micelles in the aqueous solution. Nanoscale micelles of about 70 nm in size, called thylianin-loaded micelles (TLMs), have been created (Wang et al., 2018). In a study on berberine and diosmin-loaded casein mycelium, improved solubility, delivery, and premature drug release were observed (Abdelmoneem et al., 2018).

Nanocrystals are defined as crystalline pharmaceutical active substances whose particle size is reduced to nano level by various methods. The most distinctive feature that distinguishes nanocrystals from drug delivery systems is that drug nanocrystals consist almost entirely of drug substance. Its advantages are that they increase oral bioavailability and act quickly, the dose can be reduced due to high bioavailability, organic solvents are not used, the production method and application are easy, and drugs with water solubility problems can be prepared (Junghanns et al., 2008). In a study with apigenin nanocrystals, in vitro solubility, stability, bioavailability, biodistribution and drug loading properties were improved. Available for dermal application due to its doubled antioxidant capacity (Al Shaal et al., 2011, Srivalli et al., 2016). In a study using curcumin nanocrystals, improved solubility, stability, bioavailability, and biodistribution were examined. Using porcine skin in vitro, improved skin penetration and absorption as well as targeting hair follicles are also observed (Vidlářová et al., 2016).

Cross-linked polymeric networks with hydrophilic properties known as biopolymer-based hydrogels (BBH) provide places for homing aqueous biological fluids. Hydrogels are polymeric and reticulated systems with swelling feature, formed by the bonding of cationic polymers with specific polyanions or cross-linking of polymers. They consist of hydrophilic polymer hydrogel structures that are insoluble in water and biological fluids and can absorb 10-20% of their weight in water. The most important feature is the swelling feature. Factors such as ionic strength, pH, temperature change the swelling property of nanogels. Another important feature is their high drug loading capacity and very good stability. The advantages of nanogel drug delivery systems are that they protect active substances against environmental effects, increase their oral bioavailability by preventing enzymatic degradation of active substances, facilitate the crossing of the blood-brain barrier, bind ligands with covalent bonds for targeting, be taken up by the cell and provide intracellular drug transport (Vashist et al., 2014, Dreiss et al., 2020). In a study with yerba mate loaded on calcium alginate hydrogel containing corn starch, it was revealed that yerba mate polyphenols increased the in vitro capture capacity, modulated the release rate of antioxidants, and reduced the contribution of matrix erosion to the overall release mechanism. The traditional calcium alginate process was invented and showed promise for supplying yerba mate antioxidants to food products (Córdoba et al., 2013).

1.2. Inorganic Nanocarrier

Different kinds of inorganic nanocarriers have recently been developed and studies on the interactions of plant active ingredients with these nanocarriers have been emphasized. These nano carriers, which act as the systems' skeletons, can exhibit good biocompatibility and pharmacological qualities while also holding the ability to load and release medications and maintain the blood circulation system's structural integrity. The most commonly researched inorganic nano carriers are silver, copper, calcium carbonate, gold, zinc oxide, iron oxide, quantum dots, mesoporous silica nanoparticles (MSN), graphene oxide (GO) and black phosphorus (Canbaz et al., 2019, Sekar et al., 2022, Canbaz et al., 2022, Keklikcioglu Cakmak et al., 2022, Valizadeh et al., 2012, Tas et al., 2021). Even some of inorganic nano carriers based nanomedicines are evaluated in clinic (Liang et al., 2014). In a study with MSN, one of the inorganic nanocarriers, silybin-meglumine was encapsulated with MSN and it was revealed that it has high drug loading capacity, in vitro, sustained release and in vivo absorption ability (Cao et al., 2012). In a study with Licochalcone A (from *Glycyrrhiza inflata*)-loaded Au- nanoparticle, it has been shown to improve stability, solubility, biocompatibility, biodegradability and release. It has been suggested that this synthesized carrier is a suitable formula for anticancer drug release (Sun et al., 2017).

1.3. Hybrid Nanocarrier (HNC)

Hybrid nanocarriers are either a combination of two different organic materials or a combination of organic and inorganic materials for drug delivery systems (Rahman et al., 2020). Hybrid nanocarrier was synthesized using superparamagnetic iron oxide nanoparticles and polymeric nanocarriers to induce a controlled release system by application of external magnetic field (Grillo et al., 2016). One of the most promising technologies for nanomedicine is hybrid nanocarriers because they integrate the characteristics of various systems into a single system, improving the performance of materials for both therapeutic and diagnostic applications.

Little is understood about the real mechanisms of action and toxicity of drug delivery systems in spite of numerous studies in recent years, which opens up possibilities for new study. Furthermore, there has been a surge in research on the manufacturing of nanocarriers based on chemical processes that are safe for the environment and employ plant extracts and microbes (Jahangirian, et al., 2017).

1.4. Biological Nanocarriers (BNC)

Biological nanocarriers are extremely varied naturally occurring nanoparticles that have a capsid protein shell around their viral DNA or RNA genomes (Rawal et al., 2021). Viruses are devoted to attacking the most specialized organisms and tissues in this regard. Hundreds to thousands of protein molecules make up a virus particle, which self-assembles into a hollow scaffold that contains the viral nucleic acid. Viruses and virus-like particles offer considerable benefits such morphological homogeneity, biocompatibility, and simple functionalization as an essential and growing nanocarrier platform. They can also have several recognizable shapes and range in size from 10 nm to over a micron (mostly icosahedrons, spheres, also in tubes). In recent years, it has been demonstrated that viruses are genetically adaptable for use as catalysts, reagents, and scaffolds in chemical reactions. Virus nanoparticles (VNP) are used in the majority of applications, whereas virus-like particles (VLP) are naturally occurring viral capsid proteins that lack nucleic acid to prevent infection (Ojha et al., 2022). It is clear that research on the in vivo application of modified VNP and VLP for vaccination to generate immunity against the primary virus or to alter other diseases is ongoing and has picked up steam in recent years.

CONCLUSIONS

Worldwide, the use of herbal medicines as a traditional form of therapy has gained popularity. However, the conventional methods for delivering herbal medications are outdated. The focus of study has shifted to phytomolecules extracted from aromatic and therapeutic plants in order to take advantage of their many health benefits using nanotechnology. The use of phytomolecules isolated from medicinal and aromatic plants is limited due to their poor solubility in water and bioavailability. In order to overcome these problems, studies on the use of nanocarrier systems have been carried out in recent years. Research suggests that nanomedicine is a viable approach for diagnosis, imaging, and therapeutics for the treatment and management of a variety of diseases, including cancer, arthritis, diabetes, hyperglycemia, heart disease, and anemia.

Several formulations of natural plant extracts encapsulated in nanocarriers are now being tested in clinical or preclinical settings. Some of these include modifications that have been given FDA approval and can be used to treat diseases in a way that is both safe and effective. Despite significant recent progress, the field is still in the discovery phase. Thanks to the advantages of these carrier systems today and in the future, it is estimated that the studies to be carried out will accelerate and there will be drugs that can be used traditionally. It is hoped that the information in this area will clarify new findings and aid in understanding MAPs, nanotechnology, and nanocarrier systems.

REFERENCES

Abdelmoneem, M.A., Mahmoud, M., Zaky, A., Helmy, M.W., Sallam, M., Fang, J.Y., ... & Elzoghby, A.O. (2018). Dual-targeted casein micelles as green nanomedicine for synergistic phytotherapy of hepatocellular carcinoma. Journal of Controlled Release, 287: 78-93.

Al Shaal, L., Shegokar, R., & Müller, R. . (2011). Production and characterization of antioxidant apigenin nanocrystals as a novel UV skin protective formulation. International Journal of Pharmaceutics, 420(1): 133-140.

Aman, R.M., Hashim, I.I.A., & Meshali, M.M. (2018). Novel chitosan-based solid-lipid nanoparticles to enhance the bio-residence of the miraculous phytochemical "Apocynin". European Journal of Pharmaceutical Sciences, 124: 304-318.

Ambwani, S., Tandon, R., Ambwani, T.K., & Malik, Y.S. (2018). Current knowledge on nanodelivery systems and their beneficial applications in enhancing the efficacy of herbal drugs. J Exp Biol Agric Sci, 6(1): 87-107.

Baldissera, M. D., Souza, C. F., Boligon, A. A., Grando, T. H., De Sa, M. F., Da Silva, A. S., ... & Monteiro, S. G. (2017). Solving the challenge of the blood–brain barrier to treat infections caused by Trypanosoma evansi: evaluation of nerolidol-loaded nanospheres in mice. Parasitology, 144(11): 1543-1550.

Balunas, M.J., & Kinghorn, A.D. (2005). Drug discovery from medicinal plants. Life sciences, 78(5): 431-441.

Biswas, A.K., Islam, M.R., Choudhury, Z.S., Mostafa, A., & Kadir, M.F. (2014). Nanotechnology based approaches in cancer therapeutics. Advances in Natural Sciences: Nanoscience and Nanotechnology, 5(4): 043001.

Bonifacio, B.V., da Silva, P.B., dos Santos Ramos, M.A., Negri, K.M.S., Bauab, T. M., & Chorilli, M. (2014). Nanotechnology-based drug delivery systems and herbal medicines: A review. International Journal of Nanomedicine, 9: 1-15.

Canbaz, G.T., Açıkel, U., & Açıkel, Y.S. (2022). Heavy Metal Removal with ZnO-Chitosan Composite. European Journal of Science and Technology, (35): 603-609.

Canbaz, G.T., Çakmak, N.K., Eroğlu, A., & Açıkel, Ü. (2019). Removal of Acid Orange 74 from wastewater with TiO2 nanoparticle. International Advanced Researches and Engineering Journal, 3(1): 75-80.

Cao, X., Deng, W.W., Fu, M., Wang, L., Tong, S.S., Wei, Y.W., ... & Yu, J.N. (2012). In vitro release and in vitro–in vivo correlation for silybin meglumine incorporated into hollow-type mesoporous silica nanoparticles. International Journal of Nanomedicine, 7: 753.

Censi, R., Martena, V., Hoti, E., Malaj, L., & Di Martino, P. (2012). Permeation and skin retention of quercetin from microemulsions containing Transcutol® P. Drug Development and Industrial Pharmacy, 38(9): 1128-1133.

Chakraborty, K., Shivakumar, A., & Ramachandran, S. (2016). Nano-technology in herbal medicines: a review. Int J Herb Med, 4(3): 21-27.

Chen, Y., Lin, X., Park, H., & Greever, R. (2009). Study of artemisinin nanocapsules as anticancer drug delivery systems. Nanomedicine: Nanotechnology, Biology and Medicine, 5(3): 316-322.

Chen-yu, G., Chun-fen, Y., Qi-lu, L., Qi, T., Yan-wei, X., Wei-na, L., & Guang-Xi, Z. (2012). Development of a quercetin-loaded nanostructured lipid carrier formulation for topical delivery. International Journal of Pharmaceutics, 430(1-2): 292-298.

Chopra, B., & Dhingra, A. K. (2021). Natural products: A lead for drug discovery and development. Phytotherapy Research, 35(9): 4660-4702.

Córdoba, A. L., Deladino, L., & Martino, M. (2013). Effect of starch filler on calcium-alginate hydrogels loaded with yerba mate antioxidants. Carbohydrate Polymers, 95(1): 315-323.

da Silva, P.B., dos Santos Ramos, M.A., Bonifacio, B.V., Negri, K.M.S., Sato, M.R., Bauab, T.M., & Chorilli, M. (2014). Nanotechnological strategies for vaginal administration of drugs—A review. Journal of Biomedical Nanotechnology, 10(9): 2218-2243.

Ding, H., Zhu, L., Wei, X. K., & Shen, Q. (2015). Solid lipid nanoparticles of quercetin (a flavonoid) in recovery of motor function after spinal injuries. Journal of Biomaterials and Tissue Engineering, 5(6): 509-513.

Dreiss, C. A. (2020). Hydrogel design strategies for drug delivery. Current Opinion in Colloid & Interface Science, 48: 1-17.

Dzobo, K. (2022). The role of natural products as sources of therapeutic agents for innovative drug discovery. Comprehensive Pharmacology, 408.

El-Gogary, R.I., Rubio, N., Wang, J.T.W., Al-Jamal, W.T., Bourgognon, M., Kafa, H., ... & Al-Jamal, K.T. (2014). Polyethylene glycol conjugated polymeric nanocapsules for targeted delivery of quercetin to folate-expressing cancer cells in vitro and in vivo. ACS nano, 8(2): 1384-1401.

Esperón-Rojas, A.A., Baeza-Jiménez, R., Santos-Luna, D., Velasco-Rodríguez, L.D. C., Ochoa-Rodríguez, L.R., & García, H.S. (2020). Bioavailability of curcumin in nanoemulsions stabilized with mono-and diacylglycerols structured with conjugated linoleic acid and n-3 fatty acids. Biocatalysis and Agricultural Biotechnology, 26: 101638.

Ganesan, P., Ramalingam, P., Karthivashan, G., Ko, Y.T., & Choi, D.K. (2018). Recent developments in solid lipid nanoparticle and surface-modified solid lipid nanoparticle delivery systems for oral delivery of phyto-bioactive compounds in various chronic diseases. International Journal of Nanomedicine, 13: 1569.

Ghezzi, M., Pescina, S., Padula, C., Santi, P., Del Favero, E., Cantù, L., & Nicoli, S. (2021). Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. Journal of Controlled Release, 332: 312-336.

Grillo, R., Gallo, J., Stroppa, D.G., Carbó-Argibay, E., Lima, R., Fraceto, L.F., & Bañobre-López, M. (2016). Sub-micrometer magnetic nanocomposites: insights into the effect of magnetic nanoparticles interactions on the optimization of SAR and MRI performance. ACS Applied Materials & Interfaces, 8(39): 25777-25787.

Gu, L., Wu, Z.H., Qi, X., He, H., Ma, X., Chou, X., ... & Jiao, F. (2013). Polyamidomine dendrimers: an excellent drug carrier for improving the solubility and bioavailability of puerarin. Pharmaceutical Development and Technology, 18(5): 1051-1057.

Gunasekaran, T., Haile, T., Nigusse, T., & Dhanaraju, M.D. (2014). Nanotechnology: an effective tool for enhancing bioavailability and bioactivity of phytomedicine. Asian Pacific Journal of Tropical Biomedicine, 4: S1-S7.

Hesari, M., Mohammadi, P., Khademi, F., Shackebaei, D., Momtaz, S., Moasefi, N., ... & Abdollahi, M. (2021). Current advances in the use of nanophytomedicine therapies for human cardiovascular diseases. International journal of nanomedicine, 16: 3293.

Ibili, H., Dasdemir, M., Çankaya, İ. İ. T., Orhan, M., Güneşoğlu, C., & Arabacı Anul, S. (2022). Investigation of poly (lactic acid) nanocapsules containing the plant extract via coaxial electrospraying method for functional nonwoven applications. Journal of Industrial Textiles, 51(3_suppl): 5304S-5327S.

Jafari, S. M., & McClements, D. J. (2017). Nanotechnology approaches for increasing nutrient bioavailability. Advances in Food and Nutrition Research, 81: 1-30.

Jahangirian, H., Lemraski, E.G., Webster, T.J., Rafiee-Moghaddam, R., & Abdollahi, Y. (2017). A review of drug delivery systems based on nanotechnology and green chemistry: green nanomedicine. International Journal of Nanomedicine, 12: 2957.

Junghanns, J.U.A., & Müller, R.H. (2008). Nanocrystal technology, drug delivery and clinical applications. International Journal of Nanomedicine, 3(3): 295.

Keklikcioglu Cakmak, N., & Eroglu, A. (2022). Doxorubicin and tamoxifen loaded graphene oxide nanoparticle functionalized with chitosan and folic acid for anticancer drug delivery. Polymer Bulletin, 1-15.

Khan, M.I., Hossain, M.I., Hossain, M.K., Rubel, M.H.K., Hossain, K.M., Mahfuz, A.M.U.B., & Anik, M.I. (2022). Recent progress in nanostructured smart drug delivery systems for cancer therapy: A review. ACS Applied Bio Materials, 5(3): 971-1012.

Li, H., Zhao, X., Ma, Y., Zhai, G., Li, L., & Lou, H. (2009). Enhancement of gastrointestinal absorption of quercetin by solid lipid nanoparticles. Journal of Controlled Release, 133(3): 238-244.

Liang, R., Wei, M., Evans, D.G., & Duan, X. (2014). Inorganic nanomaterials for bioimaging, targeted drug delivery and therapeutics. Chemical communications, 50(91): 14071-14081.

Lim, C.L., Raju, C.S., Mahboob, T., Kayesth, S., Gupta, K.K., Jain, G.K., ... & Nissapatorn, V. (2022). Precision and advanced nano-phytopharmaceuticals for therapeutic applications. Nanomaterials, 12(2): 238.

Luo, C.F., Hou, N., Tian, J., Yuan, M., Liu, S.M., Xiong, L.G., ... & Chen, M.S. (2013). Metabolic profile of puerarin in rats after intragastric administration of puerarin solid lipid nanoparticles. International Journal of Nanomedicine, 8: 933.

Luo, C.F., Yuan, M., Chen, M.S., Liu, S.M., Zhu, L., Huang, B.Y., ... & Xiong, W. (2011). Pharmacokinetics, tissue distribution and relative bioavailability of puerarin solid lipid nanoparticles following oral administration. International Journal of Pharmaceutics, 410(1-2): 138-144.

Madaan, K., Kumar, S., Poonia, N., Lather, V., & Pandita, D. (2014). Dendrimers in drug delivery and targeting: Drug-dendrimer interactions and toxicity issues. Journal of Pharmacy & Bioallied Sciences, 6(3): 139.

Martínez-Carmona, M., Colilla, M., & Vallet-Regí, M. (2015). Smart mesoporous nanomaterials for antitumor therapy. Nanomaterials, 5(4): 1906-1937.

Moghimipour, E., Salimi, A., Yousefvand, T. (2017). Preparation and evaluation of celecoxib nanoemulsion for ocular drug delivery. Asian Journal of Pharmaceutics (AJP), 11(03): 543-550.

Mohammadi, K., Sani, M.A., Azizi-Lalabadi, M., & McClements, D.J. (2022). Recent progress in the application of plant-based colloidal drug delivery systems in the pharmaceutical sciences. Advances in Colloid and Interface Science, 102734.

Mora-Huertas, C.E., Fessi, H., & Elaissari, A. (2010). Polymer-based nanocapsules for drug delivery. International journal of pharmaceutics, 385(1-2): 113-142.

Morsi, N., Ibrahim, M., Refai, H., & El Sorogy, H. (2017). Nanoemulsion-based electrolyte triggered in situ gel for ocular delivery of acetazolamide. European Journal of Pharmaceutical Sciences, 104: 302-314.

Ojha, S.K., Pattnaik, R., Singh, P.K., Dixit, S., Mishra, S., Pal, S., & Kumar, S. (2022). Virus as a nanocarrier for drug delivery redefining medical therapeutics-A status report. Combinatorial Chemistry & High Throughput Screening, 25(10): 1619-1629.

Pando, D., Matos, M., Gutiérrez, G., & Pazos, C. (2015). Formulation of resveratrol entrapped niosomes for topical use. Colloids and surfaces B: Biointerfaces, 128: 398-404.

Paramanya, A., Sharma, S., Bagdat, R.B., & Ali, A. (2020). Recent practices of medicinal and aromatic plants in nanotechnology. In: Nanomaterials for Agriculture and Forestry Applications (pp. 435-467). Elsevier.

Patel, M.R., Patel, R.B., & Thakore, S.D. (2018). Nanoemulsion in drug delivery. In: Applications of nanocomposite materials in drug delivery (pp. 667-700). Woodhead Publishing.

Patel, R.P., & Joshi, J.R. (2012). An overview on nanoemulsion: a novel approach. International Journal of Pharmaceutical Sciences and Research, 3(12): 4640.

Patra, J.K., Das, G., Fraceto, L.F., Campos, E.V.R., Rodriguez-Torres, M.D.P., Acosta-Torres, L.S., ... & Shin, H.S. (2018). Nano based drug delivery systems: recent developments and future prospects. Journal of nanobiotechnology, 16(1): 1-33.

Peer, D., Karp, J. M., & Hong, S., Farokhzad, O.C., Margalit, R., Langer, R. (2007). Nanocarriers as an emerging platform for cancer therapy. Nano-Enabled Medical Applications, Taylor & Francis.

Pereira, M.C., Reshetnyak, Y.K., & Andreev, O.A. (2015). Advanced targeted nanomedicine. Journal of Biotechnology, 202: 88-97.

Priprem, A., Janpim, K., Nualkaew, S., & Mahakunakorn, P. (2016). Topical niosome gel of *Zingiber cassumunar* Roxb. extract for anti-inflammatory activity enhanced skin permeation and stability of compound D. Aaps Pharmscitech, 17(3): 631-639.

Rahman, H.S., Othman, H.H., Hammadi, N.I., Yeap, S.K., Amin, K.M., Samad, N. A., & Alitheen, N.B. (2020). Novel drug delivery systems for loading of natural plant extracts and their biomedical applications. International Journal of Nanomedicine, 15: 2439.

Rameshk, M., Sharififar, F., Mehrabani, M., Pardakhty, A., Farsinejad, A., & Mehrabani, M. (2018). Proliferation and in vitro wound healing effects of the microniosomes containing Narcissus tazetta L. bulb extract on primary human fibroblasts (HDFs). DARU Journal of Pharmaceutical Sciences, 26(1): 31-42.

Rawal, S., & Patel, M. (2021). Bio-nanocarriers for lung cancer management: Befriending the barriers. Nano-Micro Letters, 13(1): 1-54.

Schmitt, C., Lechanteur, A., Cossais, F., Bellefroid, C., Arnold, P., Lucius, R., ... & Hattermann, K. (2020). Liposomal encapsulated curcumin effectively attenuates neuroinflammatory and reactive astrogliosis reactions in glia cells and organotypic brain slices. International Journal of Nanomedicine, 15: 3649.

Sekar, V., Al-Ansari, M.M., Narenkumar, J., Al-Humaid, L., Arunkumar, P., & Santhanam, A. (2022). Synthesis of gold nanoparticles (AuNPs) with improved anti-diabetic, antioxidant and anti-microbial activity from *Physalis minima*. Journal of King Saud University-Science, 34(6): 102197.

Singh, R., & Lillard Jr, J.W. (2009). Nanoparticle-based targeted drug delivery. Experimental and Molecular Pathology, 86(3): 215-223.

Sotelo-Boyás, M., Correa-Pacheco, Z., Bautista-Baños, S., & y Gómez, Y.G. (2017). Release study and inhibitory activity of thyme essential oil-loaded chitosan nanoparticles and nanocapsules against foodborne bacteria. International Journal of Biological Macromolecules, 103: 409-414.

Srivalli, K.M.R., & Mishra, B. (2016). Drug nanocrystals: A way toward scale-up. Saudi Pharmaceutical Journal, 24(4): 386-404.

Steichen, S.D., Caldorera-Moore, M., & Peppas, N.A. (2013). A review of current nanoparticle and targeting moieties for the delivery of cancer therapeutics. European Journal of Pharmaceutical Sciences, 48(3): 416-427.

Sun, Y.W., Wang, L.H., Meng, D.L., & Che, X. (2017). A green and facile preparation approach, licochalcone A capped on hollow gold nanoparticles, for improving the solubility and dissolution of anticancer natural product. Oncotarget, 8(62): 105673.

Tas, A., & Keklikcioglu Cakmak, N. (2021). Synthesis of PEGylated nanographene oxide as a nanocarrier for docetaxel drugs and anticancer activity on prostate cancer cell lines. Human & Experimental Toxicology, 40(1): 172-182.

Tüylek, Z. (2021). Nanotıp ve Yeni Tedavi Yöntemleri. Avrasya Sağlık Bilimleri Dergisi, 4(2): 121-131.

ud Din, F., Aman, W., Ullah, I., Qureshi, O. S., Mustapha, O., Shafique, S., & Zeb, A. (2017). Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. International Journal of Nanomedicine, 12: 7291.

Valizadeh, A., Mikaeili, H., Samiei, M., Farkhani, S.M., Zarghami, N., Akbarzadeh, A., & Davaran, S. (2012). Quantum dots: synthesis, bioapplications, and toxicity. Nanoscale Research Letters, 7(1): 1-14.

Vashist, A., Vashist, A., Gupta, Y.K., & Ahmad, S. (2014). Recent advances in hydrogel based drug delivery systems for the human body. Journal of Materials Chemistry B, 2(2): 147-166.

Vidlářová, L., Romero, G. B., Hanuš, J., Štěpánek, F., & Müller, R. H. (2016). Nanocrystals for dermal penetration enhancement–effect of concentration and underlying mechanisms using curcumin as model. European Journal of Pharmaceutics and Biopharmaceutics, 104: 216-225.

Wang, Y., Wang, Y., Wang, X., & Hu, P. (2018). Tilianin-loaded reactive oxygen species-scavenging nano-micelles protect H9c2 cardiomyocyte against hypoxia/reoxygenation-induced injury. Journal of Cardiovascular Pharmacology, 72(1): 32-39.

CHAPTER 15

APPLICATIONS OF MEDICINAL AND AROMATIC PLANTS IN NANOTECHNOLOGY

Gamze TOPAL CANBAZ[1]

[1] Sivas Cumhuriyet University, Faculty of Engineering, Department of Chemical Engineering, Sivas, Türkiye, e-mail:gamzetopal@hotmail.com,
ORCID ID: 0000-0001-7615-7627

INTRODUCTION

Medicinal and aromatic plants (MAP) are plants that have many uses such as food, medicine, cosmetics and spices since the beginning of human history. While some of the MAP plants are collected from nature, some are produced by growing. The plants can be used as fresh or dry depending on the area of use. All organs of the plant's body, leaf, flower, seed, tuber and bark are used for different purposes and with different methods.

The therapeutic use of plants differs from country to country.While the rate of use of plants for therapeutic purposes is 80% in developing countries, the use of plants for therapeutic purposes reaches up to 95% in the Middle East, Asia and Africa (Acıbuca and Budak, 2018). According to the World Health Organization, 60% of the drugs available or tested on the market consist of components in MAP. Most anticancer, antimicrobial, and cardiovascular drugs are plant-based drugs. Aromatic compounds or essential oils obtained from them have been used for health and therapeutic purposes since ancient times, like medicinal plants, due to their high bioactivity, antibacterial, antiviral, anti-inflammatory, antifungal, antimutagenic, anticarcinogenic and antioxidant properties. (Shaaban et al., 2012). 10% of the 3000 most commonly known and used essential oils has a very important place in the production of medicine in the health sector, in the production of soap and perfume in the cosmetics sector. Aromatic oils obtained from MAP are applied in various ways due to their therapeutic effects. In oral applications, oils are diluted with olive oil, while in skin applications they are used with other solvents.

The use of MAP is restricted due to the low solubility, unstable nature or unknown toxic effects of the components consisting of flavonoids, alkaloids, terpenoids, polyphenolic compounds and essential oils. This can be a problem in synthesizing new drugsIt is thought that solving these problems with the wide possibilities offered by nanotechnology and meeting MAP and nanotechnology for the same purpose will contribute to the development of the diagnosis and treatment process.

1. MAP AND NANOTECHNOLOGY

1.1. Restrictions on The Use of MAP Antifungal, Antibacterial, Anticancer

The use of medicinal and aromatic plants in the diagnosis and treatment methods of diseases is gaining importance day by day. Although MAP is frequently used as tea, spice and food in daily life, some plants play an active role as active pharmaceutical ingredients. The oils or extracts of these plants are obtained by traditional methods and used by making creams in the treatment of wounds.

The chemical components present in the plant act as active ingredients in the medicinal formulation. Active components of plant extracts such as tannins, flavonoids, alkaloids, phenylpropanoids and terpenoids are soluble in water but show low absorption. As a result, the bioavailability and effectiveness of these components are reduced. Depending on the delivery of therapeutically active compounds to the site of action, the effectiveness of the drug is determined. In the literature, it was stated that plant-derived components showed activity in in-vitro studies, but could not achieve the same activity in in-vivo studies. The most common and most studied herb among MAP is Curcumin. It has been used in treatments such as diabetes, bronchitis, rheumatoid arthritis, cancer (Thangapazham et al., 2013). Despite its widespread use, it has limitations such as low solubility and bioavailability (Gao et al., 2015). Another commonly used ingredient is Camptothecin, which is used in traditional Chinese medicine and isolated from the bark and trunk of Camptotheca acuminata, a tree native to China. This component shows antitumor effect against prostate, lung, bladder cancers. However, its poor solubility and side effects such as nausea limit its use (Du et al., 2014) . As a result of oxidation of aromatic oils obtained from MAP, antimicrobial and antioxidant activities decrease. This is a factor limiting the use of aromatic oils (Kesarwani and Gupta, 2013).

1.2. MAP and Health

With the development of nanotechnology, it is aimed to produce nano-sized materials. Products produced with nanotechnology are used in the fields of medicine, food, agriculture, textile and biotechnology. Nanoparticle synthesis is carried out by physical, chemical and biological methods. The disadvantage of physical and chemical methods is that they are expensive and the chemicals necessary for synthesis harm the environment and living things. The biological method has recently become more preferred because it is environmentally friendly and inexpensive.

Plants, fungi, algae and bacteria are used as sources in the biological synthesis method (Agarwal et al., 2017). The use of plant extracts in the biological method is a simple and inexpensive method. All parts of the plant such as root, stem, leaf and flower are used in the synthesis of nanoparticles by biological method. Especially, its use as a reducing agent in the synthesis of metal nanoparticles attracts a lot of attention. The natural antimicrobial effects of MAPs increase when they are used as nanoparticles.

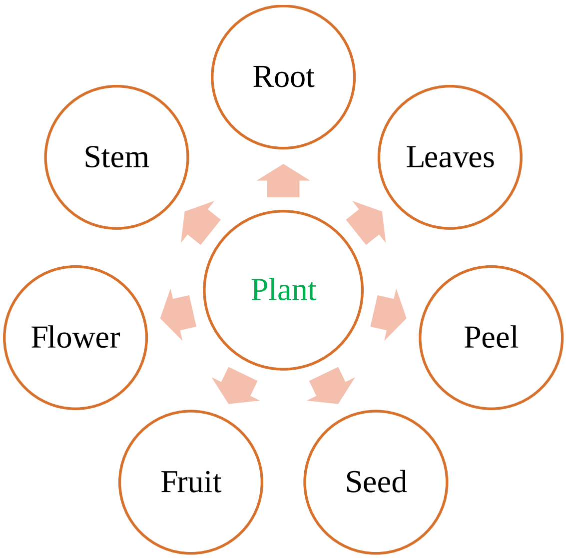


Figure 1: Plant Parts Used in Nanoparticle Synthesis

The exact mechanism of nanoparticle synthesis by plants and the compounds responsible for the synthesis have not been fully elucidated. In addition to proteins, amino acids and vitamins, components such as flavonides, alkaloids, polyphenols, terpenoids and polysaccharides are thought to play important roles in the reduction of metal salts.

With nanotechnological applications, these disadvantages mentioned above can be overcome and the limitations in the use of MAP can be eliminated. Studies on antibacterial and antitumor activities of nanoparticles synthesized using MAP are given in the table below.

Table 1: MAP-based nanoparticles and their applications

Plant	Nanoparticles	Application	Reference
Allium sp.	Ag np	Antibacterial	(Bouqellah et al., 2019)
Zingiber officinale	NiO np	Antibacterial	(Haider et al., 2020)
Thymus vulgaris	Ag np	Antioxidant Antimicrobial	(Aldosary et al., 2023)
Uncaria tomentosa	Polymeric np	Antitumor	(Ribeiro et al., 2020)
Acacia nilotica	ZnO np	Antibacterial	(Rasha et al., 2021)
Jatropha curcas	Ag np	Antibacterial	(Chauhan et al., 2016)
Vitis vinifera	Ag np	Antibacterial Anticancer	(Hashim et al., 2020)
Theobroma cacao	Ag np	Antimicrobial	(Efavi et al., 2022)
Passiflora subpeltata	Ag np	Antibacterial Antioxidant Anticancer	(Loganathan et al., 2022)
Melissa officinalis	Ag np Au np	Antimicrobial	(Fierascu et al., 2017)
Capsicum chinense *Cinnamonum verum*	Ag np Au np ZnO np	Antibacterial Antioxidant Antibacterial	(Lomelí-Rosales et al., 2022; Ansari et al., 2020)
Camellia sinensis	ZnO np	Antimicrobial	(Senthilkumar and Sivakumar, 2014)
Hibiscus sabdariffa	Ag np	Antibacterial	(Abdelsattar et al., 2022)

1.3. MAP and Food

Consumption of contaminated food leads to an increase in food-borne diseases. In the process from the production to consumption of the food, it is necessary to use appropriate packaging materials by keeping it well. (Pal, 2017). Depending on the properties of food packaging materials, product type and desired shelf life, industries have aimed to change and develop these properties by using nanotechnology.

Although plastic and its derivatives used in food packaging are preferred due to their effective barrier and mechanical properties, simple and inexpensive processing techniques, obtaining the packaging materials used from non-renewable sources provides a disadvantage. The problem with plastic packaging is not just sustainability. There are also ecological problems caused by them. Since these petroleum-derived plastic packages are not biodegradable, it takes many years to decompose in nature. Waste disposal or recycling of these packages is a costly process. It is thought that the mentioned problems can be solved by producing biodegradable packaging with nanotechnology.

As in many areas, there are nanotechnology applications in the food industry. Nanoparticles added to the package structure provide the improvement of the mechanical and thermal properties of the package. Nanoparticles added to the polymer package structure extend the shelf life of the food by providing antimicrobial properties. (Lagarón et al., 2005).

The main purpose of the new system food packaging is to increase the shelf life of foods by preventing deterioration. Nanotechnology is used in different ways in food packaging. With nanocomposite and nanosensor applications on packages, it prevents food spoilage by providing protection against leakage and pathogen formation in packages. Another application is to increase the barrier properties of the packaging by adding bionanoparticles to the packaging. (Sharma and Dhanjal, 2016). The shelf life of foods can be extended with bionanoparticles without the need for support from additional preservatives. In the table below, studies of MAP-derived bionanoparticle used in packaging are given.

Table 2: Map-Based Nanoparticles and Food Applications

Plant	**Nanoparticles**	**Application**	**Reference**
Cassia fistula	ZnO np	Nanocomposite Food packaging	(Kumar et al., 2020)
Urtica dioica (Nettle)	ZnO np	Nanocomposite Food packaging	(Zahiri Oghani et al., 2021)
Citrus sinensis	ZnO np	Extend shelf life	(Gao et al., 2020)
Malva parviflora	ZnO np	Extend shelf life	(Iqbal et al., 2022)
Sugarcane	Ag np	Nanocomposite Packaging film	(Ounkaew et al., 2021)

CONCLUSIONS

Medicinal and aromatic plants are natural resources with extraordinary biological activity. As a result of the joint work of MAP and nanotechnology in the literature, the production and use of new materials has increased in industrial areas such as health, food and cosmetics. These studies have shown that the use of MAP-based materials is promising for future studies.

REFERENCES

Abdelsattar, A.S., Toka A.H., Nouran, R., Warda M.F., Yara Y.H., Shrouk, M.G., & El-Shibiny, A. (2022). Green synthesis of silver nanoparticles using *Ocimum basilicum* L. and *Hibiscus sabdariffa* L. extracts and their antibacterial activity in combination with phage ZCSE6 and sensing properties. Journal of Inorganic and Organometallic Polymers and Materials, 32(6): 1951-1965.

Acıbuca, V., & Bostan Budak, D. (2018). Dünya'da ve Türkiye'de tıbbi ve aromatik bitkilerin yeri ve önemi. Çukurova Tarım Gıda Bilimleri Dergisi, 33(1): 37-44.

Agarwal, H., Venkat Kumar, S., Rajeshkumar, S. (2017). A review on green synthesis of zinc oxide nanoparticles – An eco-friendly approach. Resource-Efficient Technologies, 3(4): 406-413.

Aldosary, S.K., El-Rahman, S.N.A., Al-Jameel, S.S., & Alromihi, N.M. (2023). Antioxidant and antimicrobial activities of *Thymus vulgaris* essential oil contained and synthesis thymus (Vulgaris) silver nanoparticles. Brazilian Journal of Biology, 83: e244675.

Ansari, M.A., Murali, M., Prasad, D., Alzohairy, M.A., Almatroudi, A., Alomary, M.N., Udayashankar, A.C., Singh, S.B., Asiri, S.M.M., Ashwini, B.S., Gowtham, H.G., Kalegowda, N., Amruthesh, K.N., Lakshmeesha, T.R., Niranjana, S.R. (2020). *Cinnamomum verum* Bark extract mediated green synthesis of ZnO nanoparticles and their antibacterial potentiality. Biomolecules, 10(2): 336.

Bouqellah, N.A., Mohamed, M.M., & Ibrahim, Y. (2019). Synthesis of eco-friendly silver nanoparticles using Allium sp. and their antimicrobial potential on selected vaginal bacteria. Saudi Journal of Biological Sciences, 26(7): 1789-1794.

Chauhan, N., Tyagi, A.K., Kumar, P., & Malik, A. (2016). Antibacterial potential of Jatropha curcas synthesized silver nanoparticles against food borne pathogens. Frontiers in microbiology, 7: 1748.

Du, F., Meng, H., Xu, K., Xu, Y., Luo, P., Luo, Y., Lu, W., Huang, J., Liu, S., & Yu, J. (2014). CPT loaded nanoparticles based on beta-cyclodextrin-grafted poly(ethylene glycol)/poly (l-glutamic acid) diblock copolymer and their ınclusion complexes with CPT. Colloids and Surfaces B: Biointerfaces, 113: 230-236.

Efavi, J. K., Nyankson, E., Kyeremeh, K., Manu, G. P., Asare, K., & Yeboah, N. (2022). Monodispersed AgNPs Synthesized from the nanofactories of *Theobroma cacao* (cocoa) leaves and pod husk and their antimicrobial activity. International Journal of Biomaterials, Article ID 4106558.

Fierascu, I., Georgiev, M. I., Ortan, A., Fierascu, R. C., Avramescu, S. M., Ionescu, D., ... & Ditu, L. M. (2017). Phyto-mediated metallic nano-architectures via *Melissa officinalis* L.: Synthesis, characterization and biological properties. Scientific Reports, 7(1): 1-14.

Gao, M., Chen, C., Fan, A., Zhang, J., Kong, D., Wang, Z., & Zhao, Y. (2015). Covalent and non-covalent curcumin loading in acid-responsive polymeric micellar nanocarriers. Nanotechnology, 26(27): 275101.

Gao, Y., Xu, D., Ren, D., Zeng, K., & Wu, X. (2020). Green synthesis of zinc oxide nanoparticles using *Citrus sinensis* peel extract and application to strawberry preservation: A comparison study. Lwt, 126: 109297.

Haider, A., Ijaz, M., Ali, S., Haider, J., Imran, M., Majeed, H., ... & Ikram, M. (2020). Green synthesized phytochemically (*Zingiber officinale* and *Allium sativum*) reduced nickel oxide nanoparticles confirmed bactericidal and catalytic potential. Nanoscale Research Letters, 15(1): 1-11.

Hashim, N., Paramasivam, M., Tan, J.S., Kernain, D., Hussin, M.H., Brosse, N., ... & Raja, P.B. (2020). Green mode synthesis of silver nanoparticles using Vitis vinifera’s tannin and screening its antimicrobial activity/apoptotic potential versus cancer cells. Materials Today Communications, 25: 101511.

Iqbal, T., Raza, A., Zafar, M., Afsheen, S., Kebaili, I., & Alrobei, H. (2022). Plant-mediated green synthesis of zinc oxide nanoparticles for novel application to enhance the shelf life of tomatoes. Applied Nanoscience, 12(2): 179-191.

Kesarwani, K., & Gupta, R. (2013). Bioavailability enhancers of herbal origin: An overview. Asian Pacific Journal of Tropical Biomedicine, 3(4): 253-266.

Kumar, S., Mudai, A., Roy, B., Basumatary, I.B., Mukherjee, A., & Dutta, J. (2020). Biodegradable hybrid nanocomposite of chitosan/gelatin and green synthesized zinc oxide nanoparticles for food packaging. Foods, 9(9): 1143.

Lagarón, J.M., Cabedo, L., Cava, D., Feijoo, J.L., Gavara, R., & Gimenez, E. (2005). Improving Packaged Food Quality and Safety. Part 2: Nanocomposites. Food Additives and Contaminants, 22(10): 994-998.

Loganathan, S., Selvam, K., Padmavathi, G., Shivakumar, M.S., Senthil-Nathan, S., Sumathi, A.G., ... & Almutairi, S.M. (2022). Biological synthesis and characterization of *Passiflora subpeltata* Ortega aqueous leaf extract in silver nanoparticles and their evaluation of antibacterial, antioxidant, anti-cancer and larvicidal activities. Journal of King Saud University-Science, 34(3): 101846.

Lomelí-Rosales, D.A., Zamudio-Ojeda, A., Reyes-Maldonado, O.K., López-Reyes, M.E., Basulto-Padilla, G.C., Lopez-Naranjo, E. J., ... & Velázquez-Juárez, G. (2022). Green synthesis of gold and silver nanoparticles using leaf extract of *Capsicum chinense* Plant. Molecules, 27(5): 1692.

Ounkaew, A., Janaum, N., Kasemsiri, P., Okhawilai, M., Hiziroglu, S., & Chindaprasirt, P. (2021). Synergistic effect of starch/polyvinyl alcohol/citric acid films decorated with in-situ green-synthesized nano silver on bioactive packaging films. Journal of Environmental Chemical Engineering, 9(6): 106793.

Pal, M. (2017). Nanotechnology: A new approach in food packaging. Journal of Food: Microbiology, Safety & Hygiene, 2(2): 8-9 .

Rasha, E., Monerah, A., Manal, A., Rehab, A., Mohammed, D., & Doaa, E. (2021). Biosynthesis of zinc oxide nanoparticles from *Acacia nilotica* (L.) extract to overcome carbapenem-resistant *Klebsiella pneumoniae*. Molecules, 26(7): 1919.

Ribeiro, A.F., Santos, J.F., Mattos, R.R., Barros, E.G., Nasciutti, L.E., Cabral, L.M., & Sousa, V.P. (2020). Characterization and in vitro antitumor activity of polymeric nanoparticles loaded with *Uncaria tomentosa* extract. Anais da Academia Brasileira de Ciências, 92(1): e20190336.

Senthilkumar, S.R., & Sivakumar, T. (2014). Green tea (*Camellia sinensis*) mediated synthesis of zinc oxide (Zno) nanoparticles and studies on their antimicrobial activities. International Journal of Pharmacy and Pharmaceutical Sciences, 6

(6): 461-465.

Shaaban, H.A.E., El-Ghorab, A.H., & Shibamoto, T. (2012). Bioactivity of essential oils and their volatile aroma components: Review. Journal of Essential Oil Research. 24(2): 203-212.

Sharma, D. & Dhanjal, D.S. (2016). Bio-nanotechnology for active food packaging. Journal of Applied Pharmaceutical Science, 6 (9): 220-226.

Thangapazham, R.L., Shashwat, S., & Maheshwari, R.K. (2013). Skin regenerative potentials of curcumin. BioFactors, 39(1): 141-149.

Zahiri Oghani, F., Tahvildari, K., & Nozari, M. (2021). Novel antibacterial food packaging based on chitosan loaded ZnO nano particles prepared by green synthesis from Nettle leaf extract. Journal of Inorganic and Organometallic Polymers and Materials, 31(1): 43-54.

CHAPTER 16

BIOREMEDIATION OF HEAVY METAL CONTAMINATED SITES BY MEDICINAL AND AROMATIC PLANTS: PHYTOREMEDIATION BEHAVIOR

İlknur ŞENTÜRK[1]

[1] Sivas Cumhuriyet University, Faculty of Engineering, Department of Environmental Engineering, Sivas, Turkey e-mail: ilknurg.senturk@gmail.com
ORCID ID: 0000-0002-8217-2281

INTRODUCTION

Rapid urbanization and industrialization have brought environmental pollution. Pollution is even more significant in areas close to industrial areas. Among various organic and inorganic pollutants, heavy metal pollution poses a great threat to the current environment. Because heavy metals tend to stay in the environment for a long time. It takes a long time for them to disappear from nature as a result of chemical and microbial degradation. This feature increases the accumulation and this situation poses a great risk in terms of environment and animal health. Metal concentration above a certain threshold limit will have a toxic effect, thus reducing the quality of soil as well as agricultural products. Therefore, this problem should be handled in the best way and a sustainable environmentally friendly way for treatment should be followed.

It is a worldwide popular and accepted method used for cleaning especially heavy metal-contaminated areas with medicinal and aromatic plants due to its sustainability, non-toxicity, not being included in the food chain because they are not preferred as food due to their essential odor, aesthetic, and natural appearance, environmentally friendly and applicable, accepted by the local people as an aesthetic and safe strategy, and being a low cost and natural method.

Scientists dealing with medicinal and aromatic plants have shown interest in using these plants for phytoremediation purposes in polluted areas. For this reason, studies on this subject have been going on for a long time. In reality, it is used in the perfumery, fragrance, aromatherapy, etc. Such plants, which are of extreme economic importance in areas, are also an excellent choice for the remediation of heavy metal-contaminated areas. In this chapter, this subject will be examined in detail, and examples of work in this field will be given.

1. HEAVY METAL POLLUTION

Soil and water structures are under the influence of toxic heavy metals as a result of rapid industrialization, urbanization, agricultural use, and human activities. Toxic heavy metals such as cadmium (Cd), nickel (Ni), mercury (Hg), selenium (Se), chromium (Cr), lead (Pb), uranium (U), silver (Ag), copper (Cu), strontium (Sr), zinc (Zn), arsenic (As) are continuously left into the environment due to different anthropogenic activities (Figure 1). Industrial wastewater containing heavy metals is generally released into the environment. These wastewaters can cause serious damage to the environment and human health due to their heavy metal content. Because these metals do not undergo chemical and/or microbial degradation. Heavy metals cannot be chemically destroyed like organic pollutants (Keklikcioğlu Çakmak and Topal Canbaz, 2020). These characteristics allow them to accumulate and last longer in the environment. As a result, they pose a serious risk to both the environment and human health (Topal Canbaz et al., 2022). As a result of accumulation in the bodies of living organisms, they can cause teratogenic, mutagenic, and endocrine-disrupting effects (Pandey et al., 2019). The toxicity value of heavy metals may drop or it may take on a less complex structure as a result of the oxidation stage. But they continue to stay in the environment (Mishra and Chandra, 2022). Industrial sources of heavy metals are seen in Table 1.

Figure 1: Anthropogenic Sources (Alengebawy et al., 2021)

Table 1: Heavy Metals Released from Industrial Sources (Mishra and Chandra, 2022)

Heavy metal	Industrial sources
Cd	paint sludge, zinc smelting, waste batteries, fuel and incinerators
Ni	smelting operations, thermal power plants, battery industry
Cu	electroplating, mining, smelting operations,
As	geogenic/natural processes, fuel burning, smelting operations, thermal power plants
Hg	hospital waste, thermal power plants, chloral-alkali plants, fluorescent lamps, electrical appliances
Cr	leather tanning, mining, chromium salts manufacturing, industrial coolants
Pb	smelting, lead-acid batteries, bangle industry, paints, e-waste, ceramics

Today, one of the serious problems for the environment and agriculture is heavy metal pollution. As heavy metals accumulate in the environment, they both have a negative effect on production efficiency and accumulate in humans and animals through the food chain (Pirzadah et al., 2019). Therefore, it is necessary to use some traditional technologies such as isolation and immobilization, mechanical separation, pyrometallurgical, electrokinetic, biochemical, and, soil washing (chemical infiltration), etc. to reduce heavy metal pollution (Rahimi et al., 2022). But, conventional approaches to remediation of heavy metal-contaminated soils are time-consuming, require huge capital costs, and even currently available technologies are not fully successful. Therefore, renewable biological approaches come into prominence. One of these approaches is phytoremediation technology (Arthur et al., 2005).

This book chapter shows the advantages of using aromatic and medicinal plants (AMPs) and the possibilities of use in cleaning contaminated areas as they are high-value economic products. AMPs grown in contaminated soils with heavy metals are safe crops to use as they are not dramatically polluted by heavy metals.

2. PHYTOREMEDIATION

Phytoremediation is the process known as a green technology, in which plants are used to remove pollutants or toxic substances from contaminated environments such as water or soil. Other traditional methods are both very expensive and not very suitable for recovering other toxic substances and heavy metals from contaminated soil or water. Contrary to traditional methods, the main purpose of phytoremediation is the conversion of metals into less toxic or harmless forms without any financial loss or transition to the food chain. In addition, phytoremediation is a more practical and long-term option that improves soil quality with time compared to traditional methods (Mishra and Chandra, 2022). Therefore, the green approach of photo technology to remove toxic metals from polluted areas is seen as a cost-effective, efficient, practical, environmentally friendly, safe, in-situ, viable, publicly acceptable, sustainable, and promising alternative to maintaining soil health (Dar et al., 2020).

3. PHYTOREMEDIATION OF HEAVY METAL CONTAMINATED AREAS

Most plant species can grow in heavy metal-contaminated environments. With the help of these plants, pollutants can be destroyed or reduced through various natural, biophysical, and biochemical processes such as hyperaccumulation or transformation, adsorption, translocation, transport, and mineralization These plants must have special adaptations to survive in such regions (Gupta et al., 2013).

Between 1995 and 2009, a search on Scopus (www.scopus.com) clearly demonstrates how little attention is paid to aromatic plants for phytoremediation (Gupta et al., 2013). Due to the possibility that they could re-enter the human or animal body through the food chain, using edible plants for phytoremediation is neither rational nor practical. The use of aromatic and medicinal plants in the phytoremediation of metal-contaminated soils has been included since this scenario was established (in the last ten years), and the amount of study in this area has been growing daily.

Consumption of edible plants by animals and humans makes them inappropriate for heavy metal phytoremediation. Heavy metals that will accumulate in the tissues of these plants will be transported to the body of humans or animals through the food chain and will lead to unfavorable impacts on health. In other words, the living will be adversely affected by this metal pollution, even if we don't want it at all. Therefore, the use of non-edible plants (eg aromatic and medicinal plants, AMPs) for phytoremediation purposes should be encouraged (Gupta et al., 2013). Growing such plants (AMPs) in metal-contaminated areas will prevent heavy metals from entering the food chain (Figure 2) (Khajanchi et al. 2013; Lone and Gaffar, 2021). Because of the nice smell these plants emit, animals do not harm them as they do not prefer them as food. In this way, it is possible to grow them on a large scale (Dar et al., 2020). The production of essential oils does not contain any toxic metals and therefore prevents their entry into the food chain (Khajanchi et al. 2013). This method is an aesthetic technique that is both applicable and environmentally friendly.

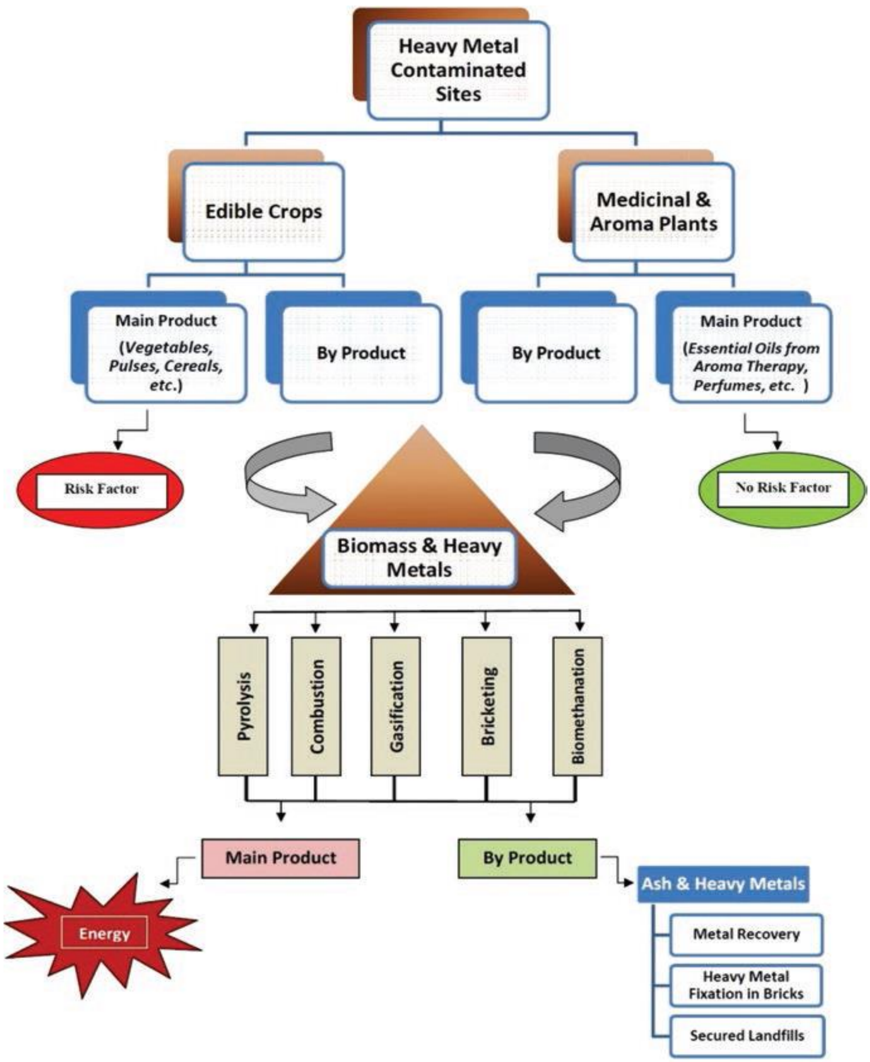


Figure 2: Diagram Showing Benefits of Phytoremediation by Non-Edible Plants Versus Edible Crops (Pirzadah et., 2019; Lone and Gaffar, 2021)

Heavy metal-contaminated soil can be treated using both edible and non-edible crops. Although the phytoremediation capacity of aromatic and medicinal plants may not be very great and they may not be accumulators, these plants can still be used in phytoremediation. As seen in Figure 3, there are many advantages of using AMPs for phytoremediation. AMP resources are quite plentiful and can be used on a large scale (Pirzadah et al., 2019).

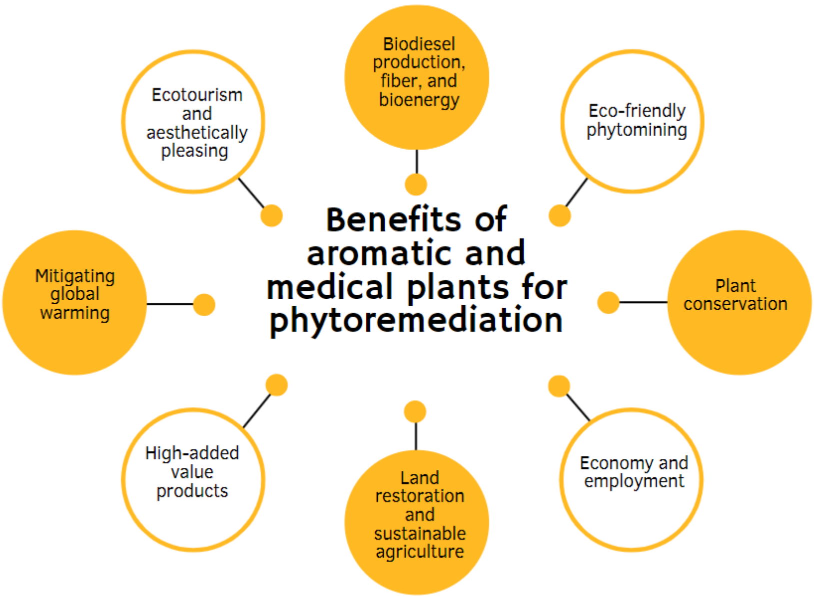


Figure 3: Benefits of Medicinal and Aromatic Plants for Sustainable Phytoremediation (Kumar et al., 2021; Mishra and Chandra, 2022)

Remediation of contaminated areas can be achieved by using different strategies by plant structure (Figure 4) (Rahimi et al., 2022). Each of these structures has a special importance for phytoremediation.

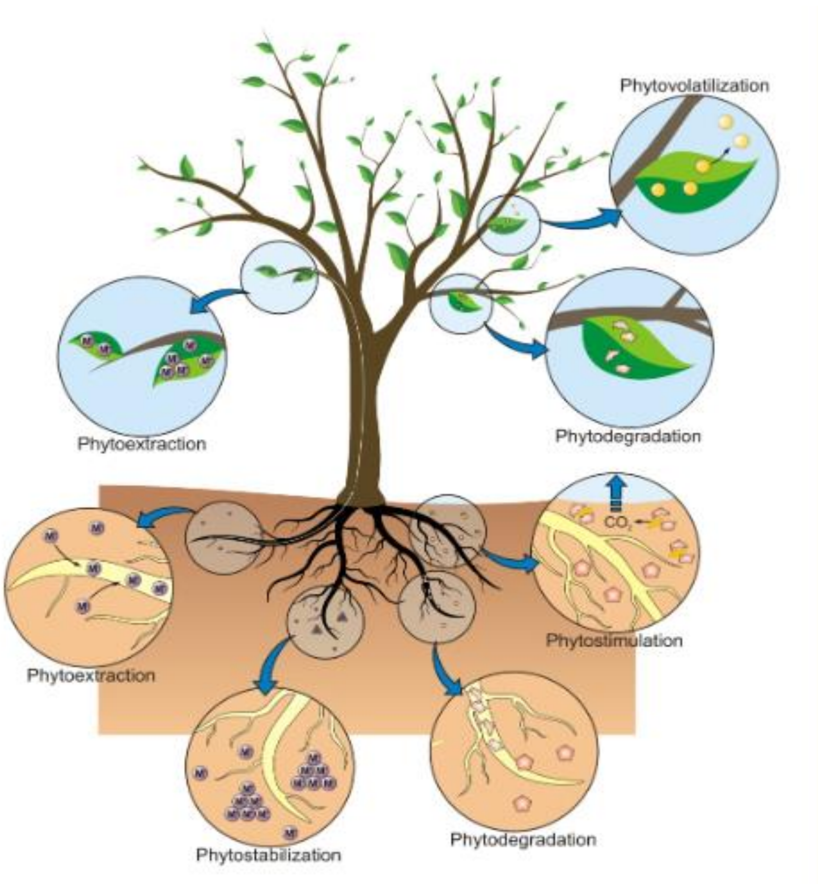


Figure 4: Different Phytoremediation Strategies Adapted by Aromatic Plants (J.C. Favas et al., 2014)

4. PHYTOREMEDIATION OF HEAVY METALS BY MEDICINAL AND AROMATIC PLANTS

Medicinal and aromatic plants are grown and commercially processed to obtain and process essential oils in their structures. Heavy metals absorbed by medicinal and aromatic plants during this process do not enter in the essential oils (Rahimi et al., 2022). A significant source of essential oil production is especially aromatic plants. The valuable oils obtained from here have a significant market share in the food processing, soaps, detergents, insect repellents, perfumery, cosmetic industry, and aromatherapy industries (Mishra and Chandra, 2022). It was observed that the percentage of essential oil increased gradually in some aromatic plants that were not seriously contaminated by heavy metals after heavy metal exposure. Due to the steam distillation technique applied to extract the essential oils in the structure of aromatic plants exposed to heavy metals, there are no dangerous heavy metals left in the oils. In this way, essential oils obtained from these aromatic plants used for phytoremediation may be acceptable in the marketplace (Wani et al., 2021; Mishra and Chandra, 2022).

Phytoremediation is not a stand-alone method. It is a holistic treatment mechanism consisting of the combination of different treatment strategies of the plant (Figure 4). Examples of studies using aromatic and medicinal plants in which different strategies are effective in phytoremediation are compiled in Table 2.

Table 2: Heavy Metal Removal with Different Phytoremediation Methods (Kumar et al., 2021). A: Aromatic, M: Medicinal plants

Phytoremediation method	**Plants used**	**A/M**	**Contaminants**
Phytostabilizer	*Dactylis glomerata* L.	M	As, Cd, Pb
	Chrysopogon zizanioides (L.) *Roberty* and *Vetiveria zizanioides* (L.) *Nash*	A/M	Cd, Pb, Cu, As, Hg, Fe, Cr, Ni, Sn, Zn
	Cymbopogon citratus (DC.) Stapf	A/M	Cd, Hg, Pb, Cu, Ni, Cr
	Cymbopogon winterianus Jowitt ex Bor.	A/M	Cd, Cr
	Ocimum basilicum L.	A/M	Cr, Cd, Ni, Pb, As, Zn
	Salvia officinalis L.	A/M	Cd, Pb, Cu
	Mentha × piperita L.	A/M	Pb, Ni, Cu, Cd
	Rosmarinus officinalis L.	A	Pb, As, Sb, Zn, Cu
	Zygophyllum fabago L.	M	Cd, Pb, Zn Cu
Rhizofiltration	*Helianthus annuus* L.	A	Radionuclides (Cs, U and Sr)
	Sagittaria montevidensis Cham. & Schltdl.	M	Al, V, Fe, As, Cu, Zn, Pb, Cd, Ni, Cr
	Eichhornia crassipes (Mart.) Solms	M	As, Cd Cr, Cu, Ni, Se
Phytoaccumulator	*Rosmarinus officinalis* L.	A	Ni. Hg, Pb, Cu, Zn, Cd, Ni, Fe, As, Sb
	Pelargonium roseum (Andrews) DC.	A	Cd, Ni, Pb, Zn
	Matricaria recutita (L.) Rauschert	A	Cd, Pb, Zn
	Portulaca oleracea L.	M	Cr
	Chrysopogon zizanioides (L.) Roberty	A	Mn, Cu
	Helianthus annuus L.	A	Pb, Cd, Zn, Cu, Fe, and As
	Cymbopogon martini (Roxb.) Wats.	A/M	Mn, Cu

Table 2 (Continued): Heavy Metal Removal with Different Phytoremediation Methods (Kumar et al., 2021). A: Aromatic, M: Medicinal plants

Phytoremediation method	Plants used	A/M	Contaminants
Phytodegradation	*Helianthus annuus* L.	A	Methyl benzotriazole
	Scirpus microcarpus J.Presl & C.Presl, *Phalaris arundinacea* L.	M	TNT, RDX
	Leucaena leucocephala (Lam.) de Wit	M	Tetrachloroethane (TCE), EDB
	Nicotiana tabacum L.	M	Perchlorate
	Canna indica L.	A/M	Simazine
	Arabidopsis thaliana (L.) Heynh.	M	TNT (2,4,6-trinitrotoluene)
	Kandelia candel (L.) Druce	M	Pyrene
	Chrysopogon zizanioides (L.) Roberty, *Phalaris arundinacea* L.	A/M	RDX, TNT
Phytostimulation	*Ceratophyllum deinersuin* L.	M	Atrazine
	Vetiveria zizanioides (L.) Nash, *Bidens pilosa* L., *Eleusine indica* (L.) Gaertn.	A/M	Petroleum hydrocarbons
	Ludwigia octovalvis (Jacq.) Raven	M	As
Phytovolatilization	*Nicotiana tabacum* L.	M	Methyl mercury
	Pteris vittata L.	M	As

The aromatic plant families Poaceae, Geraniaceae, Asteraceae, and Lamiaceae are the most effective ones for the phytoremediation of heavy metal-contaminated environments (Mishra and Chandra, 2022). Recently, due to their effectiveness, *Matricaria recutita* (chamomile), *Salvia officinalis* (sage,) and *Thymus vulgaris* (thyme) are recommended for phytoremediation (Kumar et al., 2021). These crops have high value with low input and can collect high amounts of toxic heavy metal in their tissues (Gupta et al., 2013). They can also take part in phytoremediation more successfully than other plants grown under the same conditions (Figure 5) (Bağdat and Eid, 2007). *Hypericum perforatum* L. (St. John's wort) for Cd and Cr, *Ocimum basilicum* L. (Basil), and *Beta vulgaris* L. cv. Fordhook Giant (Swiss chard) for Cu, Pb, and Zn and *Panax ginseng* for Cd, Pb, and Ni treatment have been used successfully in different studies (Bağdat and Eid, 2007).

Aromatic plants growing in heavy metal-contaminated areas can collect a remarkable quantity of toxic metals according to the level of pollution. Lydakis et al., (2016) studied with aromatic plants chamomile, sage, and thyme for their study. These plants flourish normally without showing any important morphological or physiological symptoms because of soil pollution, proving that they are tolerant of the wide concentration range of Cd, Pb, and Ni in the soil. Cultivation of medicinal and aromatic plants in heavy metal-contaminated areas will not provide complete cleaning of such areas but will provide a good solution. Of course, in such an area, besides certain heavy metals, other substances that may be more or less toxic can also be found in the soil. Such substances may damage the property and content of essential oils from aromatic plants. For this reason, a good soil analysis must be done before starting the cultivation of aromatic plants in a field contaminated with heavy metals. It is also an indisputable necessity to take all necessary precautions to avoid the consumption of aromatic plants by humans and animals.

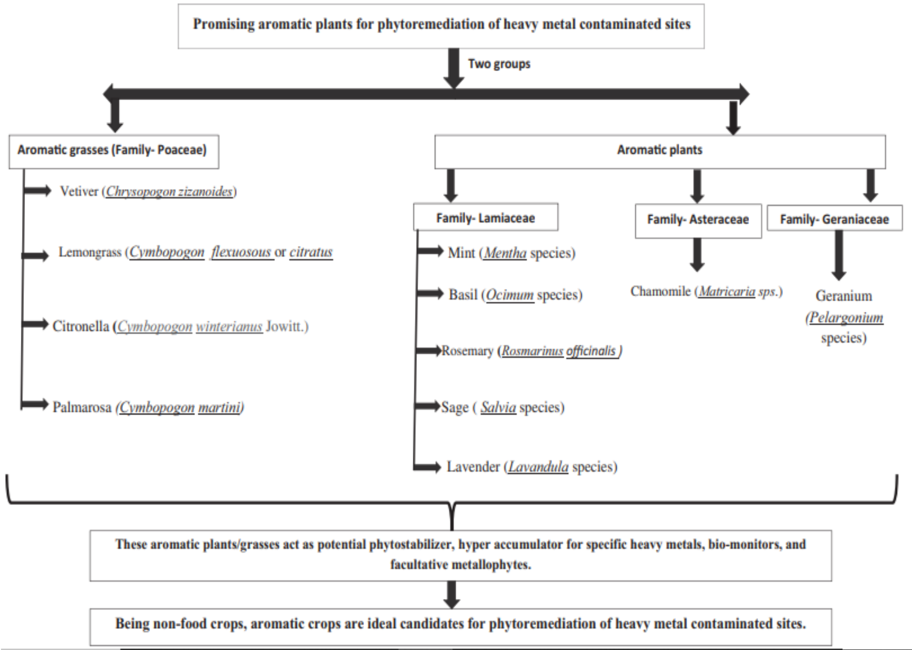


Figure 5: Encouraging Aromatic Plant Groups for Phytoremediation (Pandey et al., 2019)

5. CERTAIN MEDICINAL AND AROMATIC PLANTS HAVE HEAVY METAL ACCUMULATION

The research that has been done up to this point is reviewed in this section, along with the potential for phytoremediation and the efficiency of commonly grown medicinal and aromatic plants in removing heavy metals from the environment. This section reviews the research that has been done so far and looks at the phytoremediation potential of commonly grown medicinal and aromatic plants as well as the effectiveness of the medicinal and aromatic plants' ability to remove heavy metals from the environment. Table 3 presents the findings from the research that was conducted.

Table 3: Heavy Metal Removal with Medicinal and Aromatic Plants from Different Families (Lone and Gaffar 2021)

Name and family of the plant	Common name	Heavy metal
Vetiver or Khus **(Family – *Poaceae*)**	The most widely known species are *Chrysopogon zizanioides* or *Vetiveria zizanioides*.	Cd, Pb, Cr, Zn, etc.
Geranium **(Family − *Geraniaceae*)**	The most widely known species are *Pelargonium hortorum*, *Pelargonium roseum*, *Pelargonium graveolens,* etc. *Geranium* is the common name used for *Pelargonium* species.	Ni, Pb, and Cd
Lemon Grass **(Family – *Poaceae*)**	The most widely known species are *Cymbopogon flexuosus* and *Cymbopogon citratus*.	Cu, Pb, Cr, Fe, Mn, As, Ni, etc. Mn, Fe, and Cu besides accumulating Cr, Zn, As, Cd, Ni, Pb, and Al
Citronella **(Family – *Poaceae*)**	There are several species of citronella, and the widely known species of this plant is *Cymbopogon winterianus* Jowitt.	Cd, As, Fe, Ni, and Cu
Palmarosa **(Family – *Poaceae*)**	Palmarosa is the common name for the species of *Cymbopogon martini*.	Cr, Ni, and Cd
Mint **(Family – *Lamiaceae*)**	The most widely known species are *Mentha crispa* and *Mentha pulegium*. These species are popularly known as mint.	Cr, Cd, and Pb

Table 3 (Continued): Heavy Metal Removal with Medicinal and Aromatic Plants from Different Families (Lone and Gaffar 2021)

Name and family of the plant	Common name	Heavy metal
Rosemary **(Family – *Lamiaceae*)**	*Rosmarinus officinalis* is the well-known species of rosemary plant.	Pb, Zn, Cu, Cd, Ni, and Fe
Chamomile **(Family – *Asteraceae/Compositae*)**	Chamomile or camomile is the common name for several daisy-type plants of the Asteraceae family. The notable varieties of *Chamomilla* species include *Matricaria chamomilla* (German chamomile) and *Chamaemelum nobile* (Roman chamomile).	Cd, Cr, and Ni
Lavender **(Family – *Lamiaceae*)**	The most notable species of lavender is *Lavandula vera*.	Zn, Cd, and Pb.
Basil **(Family – *Lamiaceae*)**	The notable species of basil for phytoremediation methods include *Ocimum tenuiflorum* and *Ocimum basilicum*. Commonly known as the basil, the *Ocimum* species are used as phytostabilizers	Cr, Cd, and Pb
Sage **(Family – *Lamiaceae*)**	Sage is the common name used for *Salvia* species.	Cd, Pb, Zn, Cr, Ni, Fe

A lot of experiment and researches has been done in this area. The use of AMPs for treatment in heavy metal-contaminated areas was investigated. It has been revealed these plants are effective on which metal. An example of such research is given in Table 4.

Table 4: Medicinal and Aromatic Plants for the Phytoremediation of Different Heavy Metals (Pirzadah et al., 2019)

Plant	Metal	Plant	Metal
Cymbopogon citratus	Cd, As, Ni, Cu, Fe	*Vetiveria zizanioides*	Cd, Ni
Vetiveria zizanioides	Cd and Pb	*Cymbopogon citratus*	Ni
Ocimum basilicum	Cd	*Matricaria chamomilla*	Cd, Pb, Zn
Mentha arvensis	Cu, Zn	*Catharanthus roseus*	Cd, Pb, Ni, Cr
Vetiveria zizanioides	Cu, Pb, Sn, Zn	*Ocimum tenuiflorum*	As
Lemongrass	Pb, Cd, Zn	*M. chamomilla*	Cd, Pb
Euphorbia hirta	Cd	*Cymbopogon winterianus*	Cr
Cymbopogon citratus	Pb(II), Cd(II), Zn(II)	*Vetiveria zizanioides*	Cu, Zn, Pb
Ocimum basilicum	Cr, Cd	*Chrysopogon zizanioides*	Hg
Mentha crispa	Pb	*Aloe vera*	Cr
Mentha species	Ni, Cr, Cd, Al	*Ocimum basilicum*	Cr, Cd, Pb, Ni
Ocimum basilicum	Cd and Zn	*Pelargonium sps.*	Pb
Lavandula vera	Pb, Zn, Cd	*Hypericum sp.*	Cd
Rosmarinus officinalis	Cd and Pb	*Ocimum tenuiflorum*	Cr
Cymbopogon flexuosus	Cr	*Hypericum perforatum*	Cd
Euphorbia hirta	Radioactive waste	*Senecio coronatus*	Ni
Cymbopogon citratus	Pb	*Vetiveria zizanioides*	Cd, Ni
Ocimum basilicum	Cd, Pb, Zn	*Cymbopogon citratus*	Ni

Table 5 provides examples of research done with a different group of aromatic and medicinal plants that demonstrate phytoremediation capacity in addition to those presented in Tables 3 and 4 above. Table 6 lists the rate at which several aromatic and medicinal plants accumulate heavy metals.

Table 5: Promising Plants for Phytoremediation: Medicinal and Aromatic (Pruteanu and Muscalu, 2014; Lone and Gaffar, 2021; Hayat et al., 2022)

Name of the plant	Heavy metal	Name of the plant	Heavy metal
Aloe vera	Cr	*Hypericum perforatum*	Ni, Cr, Cd
Artemisia annua	As	*Matricaria chamomilla*	Ni
Bacopa monnieri	Fe	*Panax ginseng* Meyer	Cu
Brugmansia candida	Ag, Cd	*Phyllanthus amarus* Schum and Thonn	Cd
Catharanthus roseus	Cd, Pb, Ni, Cr	*Senecio coronatus*	Ni
Dioscorea bulbifera	Cu	*Trigonella foenum-graecum*	Cd, Co, Cr, Ni
Euphorbia hirta	Cd, radioactive waste	*Withania somnifera*	Cu
Thalspi caerulescens	Zn, Cd	*Artemisia vulgaris*	Zn, Cu, Pb, Cd, Ni
Catharanthus roseus	Cr	*Alyssum bertolonii*	Ni
Brassica juncea (indian mustard)	Se, Zn, Cu, Pb, Cd	*Mentha spicata*	Cr, Cu
Hypericum perforatum	Cu, Cd	*Hippophae rhamnoides*	Fe, Zn, Mn, Cu
Matricaria recutita	Cd, Zn	*Rinorea niccolifera*	Ni
Bacopa mannieri	Hg, Cd	*Aloe vera*	Cd, Cr, Pb, Co, Ag, Se, Hg
Achillea millefolium	Cu	*Cannabis sativa*	Pb, Cu, Zn, Cd, Ni
Salvia officinalis	Cd	*Urtica dioica*	Cr
Centaurea cyanus and Echinophora platyloba	Zn	*Taraxacum officinale*	Cd, Cu, Zn
Ocimum basilicum	Cd	*Astragalus racemosus*	Se
Centella asiatica and Orthosiphon stamineus	Zn, Cu, and Pb	*Cunila galioides Benth.*	Al
Pfaffia glomerata (Spreng)	Pb	*Mentha piperita*	As, Cd, Ni, Pb

Table 6: Heavy Metal Storage Capacity of Some Medicinal Plants (Nasim and Dhir, 2010; Fahimirad and Hatami, 2017)

Plant species	Heavy metal	Values
Amaranthus dubius	Cd	150 ppm
Amaranthus hybridus	Hg	336 ppm
Agave amaniensis	Cd	900 $\mu g\ g^{-1}$ dry wt
Costus speciosus	Cd, Pb	530 $\mu g\ g^{-1}$ dry wt
Matricaria chamomilla	Zn	271 $mg\ kg^{-1}$ dry wt
Ocimum tenuiflorum	Cr	419 $\mu g\ g^{-1}$ dry wt
Matricaria chamomilla	Zn	271 $mg\ kg^{-1}$ dry wt
Phyllanthus amarus	Cd	82 ppm
Hypericum sp.	Cd	0.5 $mg\ kg^{-1}$ dry wt
Cuminum cyminum	Fe	1.4 $mg\ g^{-1}$ dry wt
Bombax costatum	Fe	1.5 $mg\ g^{-1}$ dry wt
Hibiscus sabdariffa	Mn	243 $\mu g\ g^{-1}$ dry wt
Spilanthes oleracea	Zn	62.8 $\mu g\ g^{-1}$ dry wt
Bombax costatum	Zn	67.1 $\mu g\ g^{-1}$
Aesculus Hippocastanum	Pb	1480 $\mu g\ g^{-1}$
Tilia sp.	Zn	13.8–32.5 $mg\ kg^{-1}$
Sambucus nigra	Zn	30.8–49.9 $mg\ kg^{-1}$

5.1. Advantages of using AMPs for phytoremediation purposes

Phytoremediation is an aesthetically satisfactory mechanism that can reduce remediation costs and provide in-situ treatment/clean-up rather than burying pollution in-situ or moving the problem to another area.

With the help of green plants, this technology consists of a number of techniques for reducing, removing, degrading, or immobilizing environmental toxins. With inexpensive and readily available plants, the targeted metal can be significantly accumulated and tolerated (Şentürk et al., 2022). In addition to the treatment and cleaning process, more economical and sustainable results can be obtained when such plant species that produce large amounts of biomass for biofuel and energy production are used (Kumar et al., 2021).

Medicinal and aromatic plants have many different uses. For example, medicinal plants can be used for therapeutic purposes as well as for the elimination of environmental pollution as mentioned above (Figure 6) (Hayat et al., 2022). In addition, essential oils and secondary metabolism products obtained from these plants can meet the raw material needs of many industries such as pharma, perfumery, the cosmetic industry, and aromatherapy.

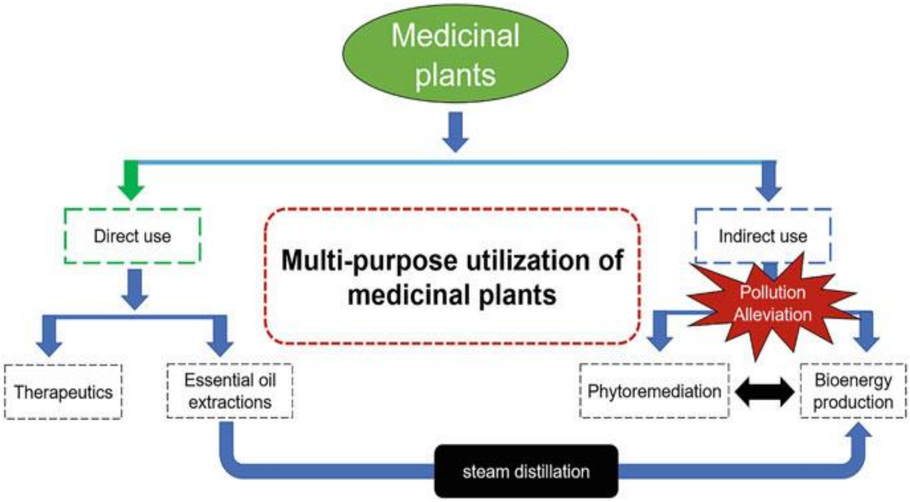


Figure 6: Multipurpose Uses of Medicinal Plants (Gupta et al., 2013; Hayat et al., 2022)

5.2. Disadvantage of Using AMPs for Phytoremediation Purposes

There are some disadvantages as well as possible advantages related to the use of AMPs for phytoremediation purposes. These are given below (Ali et al., 2013; Kumar et al., 2021):

- Phytoremediation using aromatic and medicinal plants gives results after a long period of time because the growth of plants takes a long time and plants with low biomass. It usually takes one or more harvest seasons for effective results.
- Since the treatment is limited to the depth that the roots of the plants can reach, it is not effective in very deep soil pollution.
- It is not widely used yet. Limited to pilot-scale field studies and research studies.
- Difficulty in mobilizing metal ions tightly bound to the soil.
- It is a more applicable method in low or moderately polluted areas, as plants will not grow due to toxic effects in heavily polluted areas.

CONCLUSIONS

The use of medicinal and aromatic plants instead of edible plants is an excellent solution for the remediation of heavy metal-contaminated sites. The advantage of this situation has been better understood recently. Phytoremediation by the use of aromatic and medicinal plants is, above all, a safe, environmentally friendly, economically viable, and sustainable approach. They also have an important market for aromatic oils, secondary metabolites, and bioenergy obtained from plants.

The only factor that compels practitioners here is time. It takes time for the plant to grow, and reach the desired plant biomass and the targeted phytoremediation potential. For more efficient and effective use of this method, methods and biotechnological approaches to solving these problems should be developed. Toxicity, which affects plant growth and survival at high metal concentrations, also inhibits the survival of local microorganisms in the contaminated area. It seems that more comprehensive biotechnological research is needed to fully and uninterruptedly benefit from the phytoremediation ability of AMPs.

REFERENCES

Alengebawy, A., Abdelkhalek, S. T., Qureshi, S. R., & Wang, M. Q. (2021). Heavy Metals and Pesticides Toxicity in Agricultural Soil and Plants: Ecological Risks and Human Health Implications. Toxics, 9(3): 42. https://doi.org/10.3390/ toxics9030042

Ali, H., Khan, E., & Sajad, M.A. (2013). Phytoremediation of Heavy Metals-Concepts and Applications. Chemosphere, 91(7): 869-881. https://doi.org/10.1016/ j.chemosphere.2013.01.075

Arthur, E.L., Rice, P. J., Rice, P. J., Anderson, T. A., Baladi, S.M., Henderson, K.L. D., & Coats, J. R. (2005). Phytoremediation-An Overview. Critical Reviews in Plant Sciences, 24(2): 109-122. https://doi.org/10.1080/07352 680590952496

Bağdat, R.B., & Eid, E.M. (2007). Phytoremediation Behaviour of Some Medicinal and Aromatic Plants to Various Pollutants. J. Field Crops Cent. Res., 16: 1–10.

Dar, F.A., Pirzadah, T.B., & Malik, B. (2020). Accumulation of Heavy Metals in Medicinal and Aromatic Plants. In: Aftab T., Hakeem K. R., (eds) Plant Micronutrients Deficiency and Toxicity Management. Springer Nature Switzerland AG, pp 113-128. https://doi.org/10.1007/978-3-030-49856-6

Fahimirad, S., & Hatami, M. (2017). Heavy Metal-Mediated Changes in Growth and Phytochemicals of Edible and Medicinal Plants. In: Ghorbanpour M, Varma A (Eds) Medicinal plants and environmental challenges. Springer, Cham, pp 189-214. https://doi.org/10.1007/978-3-319-68717-9

Favas, Paulo J.C., Pratas, J., Varun, M., D’Souza, R., & S. Paul M. (2014). Phytoremediation of Soils Contaminated with Metals and Metalloids at Mining Areas: Potential of Native Flora. In: M. C. Hernandez Soriano (Ed.), Environmental Risk Assessment of Soil Contamination. InTech. pp 485-517. http://dx.doi.org/10.5772/57469

Gupta, A. K., Verma, S. K., Khan, K., & Verma, R. K. (2013). Phytoremediation Using Aromatic Plants: A Sustainable Approach for Remediation of Heavy

Metals Polluted Sites. Environmental Science & Technology, 47(18): 10115-10116. https://doi.org/10.1021/es403469c

Hayat, K., Menhas, S., Hayat, S., Salam, A., Aftab, T., Zhou, Y., Afrdi, M.S., Khan, A.A., Zhou, P. (2022). Stress-Tolerant Species of Medicinal Plants and Phytoremediation Potential. In: Aftab, T. (eds) Environmental Challenges and Medicinal Plants. Environmental Challenges and Solutions. Springer, Cham. https://doi.org/10.1007/978-3-030-92050-0_18

Keklikcioğlu Çakmak, N., & Topal Canbaz, G. (2020). TiO_2 Nanopartikülü ve TiO_2/Aktif Çamur Sentezi ile Sulu Çözeltiden Cu (II) İyonlarının Adsorpsiyonu. Gümüşhane Üniversitesi Fen Bilimleri Enstitüsü Dergisi, 10(1): 86-98. https://doi.org/10.17714/gumusfenbil.514285

Kumar, J., Malik, N.A., & Atri, N.S. (2021). Aromatic and Medicinal Plants for Phytoremediation: A Sustainable Approach. In: Aftab T, Hakeem K. R (Eds) Medicinal and Aromatic Plants Healthcare and Industrial Applications. Springer Nature Switzerland AG, pp 485-544. https://doi.org/10.1007/978-3-030-58975-2

Khajanchi, L., Yadava, R.K., Kaurb, R., Bundelaa, D.S., Khana, M.I., Chaudharya, M., Meenaa, R.L., Dara, S.R., & Singha, G. (2013). Productivity, essential oil yield, and heavy metal accumulation in lemon grass (*Cymbopogon flexuosus*) under varied wastewater groundwater irrigation regimes. Ind Crop Prod 45:270–227.

Lydakis-Simantiris, N., Fabian, M., & Skoula, M. (2016). Cultivation of Medicinal and Aromatic Plants in Heavy Metal-Contaminated Soils. Global NEST Journal, 18(3): 630-642. https://doi.org/10.30955/gnj.001829

Lone, I.A., & Gaffar, M. (2021). Phytoremediation Potential of Medicinal and Aromatic Plants. In: Aftab T, Hakeem K. R (eds) Medicinal and Aromatic Plants Healthcare and Industrial Applications. Springer Nature Switzerland AG, pp 741-760, https://doi.org/10.1007/978-3-030-58975-2

Mishra, B., & Chandra, M. (2022). Evaluation of Phytoremediation Potential of Aromatic Plants: A systematic review. Journal of Applied Research on

Medicinal and Aromatic Plants, 31, 100405. https://doi.org/10.1016/j.jarmap.2022.100405

Nasim, S. A., & Dhir, B. (2010). Heavy Metals Alter the Potency of Medicinal Plants. Rev Environ Contam Toxicol, 203:139-149.

Pandey, J., Verma, R. K., & Singh, S. (2019). Suitability of aromatic plants for phytoremediation of heavy metal contaminated areas: A review. *International* Journal of Phytoremediation, 21(5): 405-418. https://doi.org/10.1080/15226514.2018.1540546

Pirzadah, T.B., Malik, B., & Dar, F.A. (2019). Phytoremediation Potential of Aromatic and Medicinal Plants: A Way Forward for Green Economy. Journal of Stress Physiology & Biochemistry, 15: 62-75.

Pruteanu, A., & Muscalu, A. (2014). Phytoremediation Using Medicinal Plants-A Review. Annals of the University of Craiova-Agriculture, Montanology, Cadastre Series, 44(2): 186-193.

Rahimi, A., Abdalı, R., & Abbasi, M. (2022). Phytoremediation using Medicinal Plants. In: Özyazıcı G, (eds) New Development on Medicinal and Aromatic Plants-II. İksad, pp 175-208. ISBN: 978-625-8213-33-1

Şentürk, İ., Eyceyurt Divarcı, N.S., & Öztürk, M. (2022). Phytoremediation of nickel and chromium-containing industrial wastewaters by water lettuce (Pistia stratiotes). International Journal of Phytoremediation, 1-12. https://doi.org/10.1080/15226514.2022.2092063

Topal Canbaz, G., Açikel, U., & Sağ Açikel, Y. (2022). ZnO-Kitosan Kompoziti ile Ağır Metal Giderimi. European Journal of Science and Technology, 35: 603-609. https://doi.org/10.31590/ejosat.1094734

Wani, M. S., Malik, N. A., Wani, N. A., & Tantray, Y. R. (2021). Environmental Pollutants and Their Remediation Using Medicinal and Aromatic Plants. In: Aftab T, Hakeem K. R (E&ds) Medicinal and Aromatic Plants Healthcare and Industrial Applications. Springer Nature Switzerland AG, pp 545-570.

CHAPTER 17

USE OF ALKANET (*Alkanna tinctoria* (L.) Tausch) PLANT AS NATURAL HERBAL

Hülya KAYNAR[1]
Emine TONUS[2]

[1]Sivas Cumhuriyet University, Faculty of Architecture, Fine Arts and Design, Sivas, Türkiye, e-mail: hkaynar@cumhuriyet.edu.tr, ORCID ID: 0000-0002-9442-6162
[2] Sivas Cumhuriyet University, Sivas Vocational School of Technical Sciences, Department of Handicrafts, Sivas, Türkiye, e-mail: eminetonus@cumhuriyet.edu.tr, ORCID ID: 0000-0001-5065-1643

INTRODUCTION

There are many plants used in the dyeing process in the vegetation grown in our country. Today, vegetable dyes have gained importance again. Herbal dyeing, which has been dealing with for centuries, has been abandoned with the emergence of chemical dyes, but today it has become preferred again. In this study, the colors resulting from the natural dyeing process made with the aeronautic plant (*Alkanna tinctoria*), which is among the medicinal aromatic plants, and the friction fastness, water drop and light fastness values on these colors were determined.

It has been scientifically determined that the dyeings made using materials obtained from nature first date back to 3000 BC. At this time, natural dyes are mentioned in a Chinese source and it is stated that not only dyes were obtained but also mordant substances were known in Egypt during the Middle Kingdom period (Uğur, 1988).

Various dyeing and patterning processes have been done throughout history with natural dyestuffs obtained from many plants and living things. B.C. Various print samples were found in the textile remains of the 2500s (Akbostancı, 2014). The times when natural dyes were the only option for textile coloring began to end tragically with the invention of the first synthetic dye by Perkin in 1856 (Shahid et al., 2013). With the increasing environmental awareness in recent years, discussions on the use of synthetic dyes have increased due to environmental pollution, toxic effects that harm human health and waste problems caused by synthetic dyes (Ali et al., 2007, Deveoğlu et al., 2011). Along with the increasing awareness of synthetic dyes, there is an increasing interest in the use of natural dyes that are renewable, cause minimal environmental pollution, and generally do not have a harmful effect on human health (Mansour, 2013, Gulrajani, 2001, Rungruangkitkrai et al., 2012). The natural dye market is becoming an increasingly growing and demanding sector (Kayahan et al., 2016). With this increasing interest towards natural dyes, the application of coloring textile surfaces with natural printing techniques that people have used since ancient times has become more common. Flowers, leaves, etc. in ecological textile print design. By using plant parts, colorful designs can be obtained on textile surfaces in natural ways (Bilir, 2018).

Natural dyes obtained from plants, animals and some metals, which have been used in dyeing for thousands of years from the first ages to the 19th century, have quickly left their place to synthetic dyes. Due to the development of the chemical industry and the cheap and easy cost of synthetic dyes, synthetic dyes have been replaced very quickly. Although there are many reasons for people to prefer chemical dyes, the feedback that emerged as they were used started to give negative results. The dyeing process and the dyed materials have a direct effect on human health. As a result of scientific research; It has been understood that the chemicals we use, the things we eat, drink and even the air we breathe carry carcinogenic substances that affect the human body and cause very serious diseases. Since medical science is advancing at the same pace, chemical dyes, which enter our lives with a dazzling effect and rapidly, have started to leave their place to more natural dyeing and dyeing methods, as their negative effects are understood.

In today's world, where concepts such as green world and green textile are spreading rapidly, it has been understood that the waste water resulting from the chemical dyeing process also causes harm when mixed with nature. Although chemical dyes cannot be completely abandoned, the search for methods and raw materials that cause less harm to the world, nature and human life has begun. With the increase in environmental awareness, researchers accelerated interdisciplinary studies and searched for new alternatives to chemical dyes. Along with natural dye, studies have been initiated to expand the production and use of natural fiber. When producing fiber, the way of using the waste parts of plants (artichoke stem, banana peel) has been chosen to reduce the cost.

Research continues on many plants in order to contribute to natural dyeing studies. In order for the colors obtained from the plant to be treated with natural fibers such as wool, cotton, silk and used as a dyestuff, their effects on the fibers and their fastness values should be measured. In this study, Alkanet plant grown in Sivas province and its surroundings was preferred as a dyestuff source. Dyeing processes were carried out using Alkanet plant and different mordant materials. Fastness values, which are important for the use of the obtained colors in the textile sector, were determined.

1. GENERAL CHARACTERISTICS of THE AEROBIC PLANT (*Alkanna tinctoria* (L.) Tausch)

Aviator (*A. tinctoria* (L.) Tausch) plant is in the Tubiflorae order, Boraginaceae (Hodangiller) family, Alkanna genus. Plants of this genus have a hairy and hairy structure. The leaves are straight-edged, not divided into segments, straight-edged, mostly rectilinear, less often arranged in opposite directions. It is a perennial plant, herbaceous in character and grows up to 10-30 cm. Blue flowers of the genus Alkanna bloom in April and July (Anonymous, 1991, Eyüboğlu et al., 1983, Seçmen et al., 1989). There are 4 subfamilies of the borage family, around 100 genera, and about 2000 species. Species of this plant have been found in Sivas (Kangal), Kayseri, Eskişehir and Ankara in Central Anatolia (Anonymous, 1991).

The 2 most important compounds found in the root of the plant are alkannin and shikonin. Shikonin *Lithospermum erythrorhizon* is a red naphthoquinone pigment produced from plant cells. Alkannin is the first pigment substance isolated from the root of the aerial plant and accepted as the main component of dark red pigments. In 1935, extracts from shikonin and alkannin were found to be enantiomers of each other. For the last 25 years, alkannin and shikonin and their derivatives have been known to have antitumor activity that prevents tumor formation in some skin cancers in cancer treatment. The aerobic plant is used in the pharmaceutical industry, cosmetics, and dyeing liquors. In addition, the extract prepared with aerobics, fennel, cinnamon, rosemary, cumin, black pepper and olive oil is used in rheumatic diseases (Tabata et al., 1999).

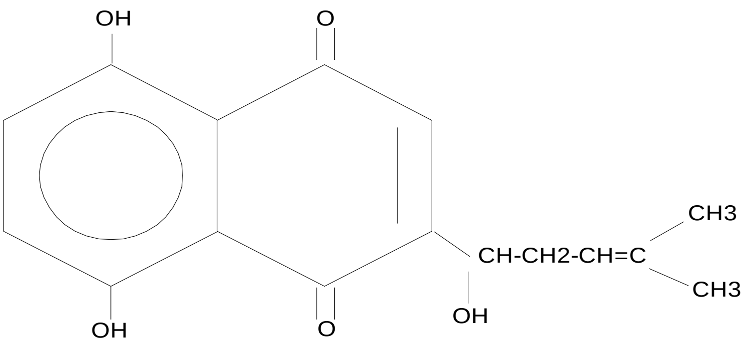


Figure 1: Clear formula of alkannin substance (Anonymous, 1991)

From a chemical point of view, there is 5-6% alkanine (Anchusine) dye in the aerial roots. The clear formula of alkanine is given in figure 1. It is mostly found in the flowers and roots of the aerialist. It is also found in some oils and resins, as well as Alkane (Anchuzin). It is divided into two acids, anchosine acid. Both Alkanna acid, Anchusine $C_{14}H_{14}O_4$ (or $C_{15}H_{12}O_4$) Anchuse acid has been used as a coloring agent for a long time. When these acids are left under sunlight, they lose their shine, darken and darken and become dull. Alkanine, on the other hand, dissolves in ether, vinegar, oils and chloroform, completely disintegrating at 220°C. It is also insoluble in water. It consists of two kinds of substances that give red color to Alkanna acid, which dyes alkalis blue, and Anchuzin acid, which dyes them green. Care must be taken when boiling, as Anchusa acid is quite easy to replace with Alkanna acid (Korur, 1937, Anonymous, 1991).

A. tinctoria (L.) Tausch root was dissolved in different solvents and the solutions were run on TLC plates, and different dyestuff extractions were obtained from the aerial root. Some components (alkannin, shikonin and teracrylalkannin) in dyestuff extractions have been determined (Von et al., 2003; Spyros et al., 2005; Öztav, 2009).

2. MATERIALS AND METHODS

As material, underground shoots of Alkanet (aviator) plant, threads (white and 2.5 Nm) and 10 different mordant substances were used. Havaciva was collected from the rural area of Kangal county, Sivas province, and dried by laying on cloth or paper material in an airy place. These mordants are; We can count as Iron II sulfate, Copper sulfate, Citric acid, Acetic acid, Copper II sulfate, Zinc chloride, Potassium aluminum sulfate, Potassium bi chromate, Sodium hydrosulfite, Tartaric acid.

Dried Alkanet plant roots and dye extracts were prepared, the wool yarns were pre-mordanted with each mordant substance, the fastness measurements (light, friction, wet and dry water drop) of the dyed wools were made.

During the mordanting process, 2% and 4% mordant material was prepared according to the weight of the wool yarns. Mordant water was obtained by mixing the selected mordant into the warm water prepared in a ratio of 1 to 20 in proportion to the amount of wool. The moist wools, which were kept in water for a while and the excess water was removed, were put into the mordant water and the boiling process was started. At the end of the one hour boiling period, it was left to cool in the same boiler, and after cooling, it was slightly squeezed and dried.

While preparing hot extract; Underground shoots of the plant (*A. tinctoria* (L.) Tausch) are cut into small pieces or ground into powder. It is prepared with wool yarn and dry plant rate of 100%. In cases where the plant is not dried, 500% of the plant is taken according to the wool in order to contain the same amount of dyestuff. Plants are boiled for 1 hour in water 20 times the amount of wool. The hot extract, which is separated from the plant residues by filtering after cooling, is ready for dyeing.

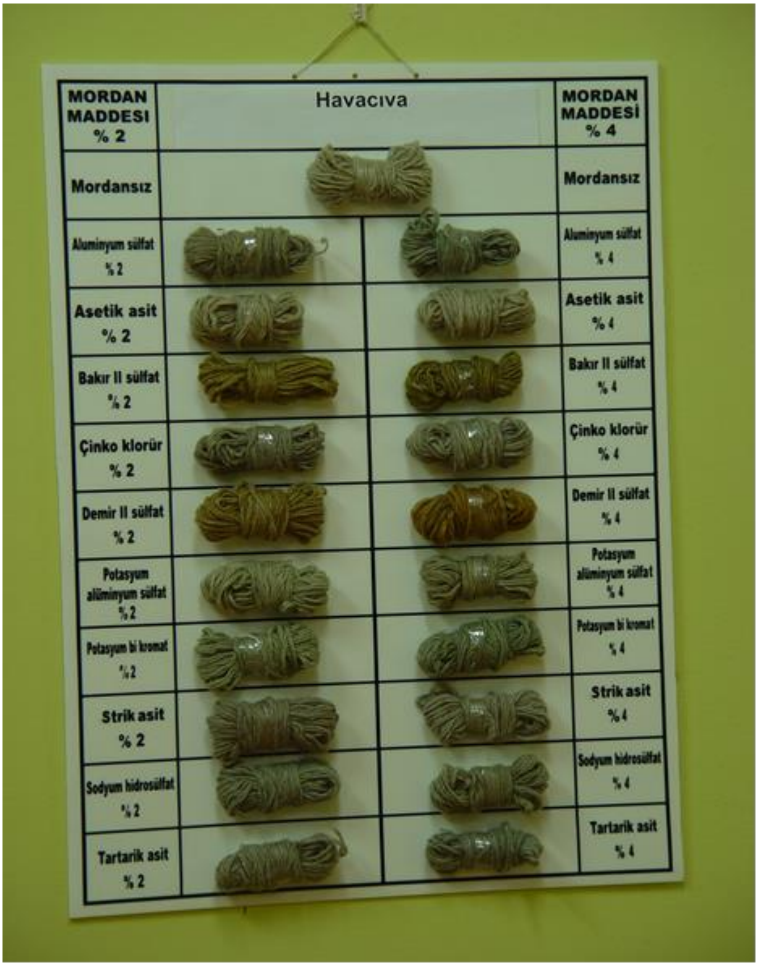
Painting process; The white wools to be dyed are skeined and soaked in warm water for at least one hour before dyeing. A dyed extract of 20 times the wool is prepared. The soaked wools are squeezed lightly and the excess water is removed, and the dyed extract is placed in it and boiled for 1 hour. After it comes to the boiling point, normal water is added instead of the water that is lost by evaporation. When the boiling process is finished, the wool is kept in the dye boiler until it cools. It is rinsed with plenty of cold water and hung in an airy place to dry. Completely dried wools are ready for fastness tests.

While measuring the light, friction and water drop fastnesses, it was taken from the sources belonging to the Turkish Standards Institute. Light fastness is made in accordance with TS 867 (Anonymous

1984a) and DIN 5033 (Anonymous 1978a) methods. While determining the friction fastness, according to TS 717 (Anonymous 1978a) and TS 423. While determining the water drop fastness, which is important in textile products, fastness tests were completed based on TS 399 (Anonymus 1978b) and TS 423 (Anonymus 1984b) prepared by TSE, and the results were prepared in a table and discussed comparatively.

3. RESULTS

Different color tones were obtained from 21 dyed wools in dyeing made with hot extract method by using 1 dyeing and 10 mordant substances in different ratios, with 100% ratio of air-dye according to wool and 10 mordant substances. Looking at Photograph 1, colors called cream, coffee bean, beige, light potato skin, baked apple (dark), shades of green, dark coffee foam, green, henna green are seen.



Photograph 1: The distribution of colors obtained from plant roots (*Alkanna tinctoria* (L.) Tausch*)* (Kaynar, 2011)

In this study, the colors obtained from dyeing with (*A.tinctoria* (L.) Tausch) plant roots were compared with the results obtained from previous studies. Harmancıoğlu (1955), experimented with different mordants (potassium aluminum sulfate, calcium oxide, sodium carbonate, sulfur tin chloride) by using the roots of the aerialist plant, and reported that he obtained eggplant color, dirty violet, red and blackish colors.

In Anonymous (1991), it is stated that brown is obtained in dyeing with Alkanet plant without using mordant. Sönmez (1992), on the other hand, used potassium aluminum sulphate (alum), copper, iron, chromium as mordant and reported that colors such as tan, blue-green, mustard green, red and purple were obtained.

As a result of the comparison; It was observed that there are similarities between the colors obtained in this study and the colors obtained by Anonymous (1991), Harmancıoğlu (1955) and Sönmez (1992). Different colors were found with different mordants. In this study, the light, friction and wet-dry fastness levels obtained as a result of dyeing with (*A. tinctoria* (L.) Tausch) plant roots are given in Table 1.

In Table 1, it was seen that the light fastness value varied between 3 and 5 as a result of dyeing with the roots of the Alkanet (Havaciva) plant. In the dyeing experiment performed without using mordant, the light fastness was obtained at the value of 4. It is seen that the light fastness value also changes when the mordants and their ratios change.

Table 1: Fastness Values Obtained From (*Alkanna tinctoria* (L.) Tausch) Plant Fastness Grades

SN	Used Mordant Substances and their proportions	light	friction	wet water drop	dry water drop
1	Asetic asid% 2	4	4	4	4/5
2	Asetic asid % 4	4	4	3/4	4
3	Copper II sulfate % 2	5	4	4/5	5
4	Copper II sulfate % 4	5	5	4/5	5
5	Zinc chloride % 2	4	4	4	4/5
6	Zinc chloride % 4	4	4	4	4/5
7	Ferrous II sulfate % 2	5	5	1/2	4
8	Ferrous II sulfate % 4	5	5	1	4/5
9	Potassium aluminum sulfate % 2	3	3	4/5	5
10	Potassium aluminum sulfate % 4	3	3	4	4/5
11	Potassium bichromate % 2	3	3	4/5	5
12	Potassium bichromate % 4	3	3	4/5	5
13	Citric acid % 2	4	4	4	4/5
14	Citric acid % 4	4	4	3/4	4
15	Sodium hydrosulfite 2%	4	4	4	4/5
16	Sodium hydrosulfite 4%	3	3	4	4/5
17	Tartaric acid 2%	3	4	4	4/5
18	Tartaric acid 4%	4	3	4	4/5
19	Copper sulfate 2%	5		4	4/5
20	Copper sulfate 4%	5		4	4/5
21	without mordant	4	4	4	4/5

Özbek (1996) found light fastness rates between 3-4 in his study with the roots of the Alkanet plant. In the experiments conducted by

Harmancıoğlu (1955) using 50% mordant with Alkanet plant roots, values between 1 and 2 were found in light fastness measurements. Light fastness values of 3 to 5 were determined in this study. The results of this study show similarities with Özbek (1996).

Friction fastness values of dyed wool obtained with different mordant substances of the aerobic plant; It is seen between 3 and 5, and the friction fastness values of dyeing without mordant are seen as 4.

Özbek (1996) found the fastness values (wet and dry water drops) of the colors formed as a result of dyeing experiments with Alkanet plant using different mordants between 4-5. The fastness values obtained in this study (wet and dry water drop) were found to be between 4-5. It is compatible with Özbek (1996). In addition, Akan et al., (2021), in his natural dyeing study with a plant belonging to the Boraginaceae family (*Alkanna strigose* Boiss. and Hohen.) belonging to the genus Alkanet, brown, light brown, dark brown, green, light green, milky brown and light earthy colors has achieved found the light fastness to be 4 and the friction fastness to be between 2-3. When compared, it provides a great similarity in terms of the colors obtained. Light fastness value is compatible. On the other hand, close values were found for rubbing fastness.

CONCLUSIONS

Today, chemical dyes in textile products are replaced by natural or nature-friendly dyes that give importance to human health. By choosing the herbal dyes included in the natural dyes, it is ensured that the plants included in the natural plant flora are evaluated, the residues of vegetables, fruits and other plants used in the industry are evaluated and added to the production again, these plants are cultivated, and new employment is created with the labor force required during all these processes.

In this study, natural herbal dyeing studies were carried out with the Alkanet plant, which is located in the natural vegetation of our country and is used in many areas other than dyeing. Wool yarns were chosen as dyeing material. Dried plant roots were taken with the amount of wool at a ratio of 100% to 1:1 and boiled for 1 hour with different mordants at 2% and 4% ratios. Fastness measurements (wet/dry water drop fastness, light and rubbing fastness) were applied to the colored wool yarns obtained from these dyeings in accordance with the standards. A color chart was created with the colors obtained in order to inform the people and institutions that will dye in the field of textile. From the roots of the Alkanet plant; Colors such as beige, light and dark green, cream, coffee foam tones, dark baked apples, potato skins, and coffee beans were obtained. It can be said that it would be appropriate to use yarns dyed with the air civa plant in the field of textiles and especially in hand-woven carpets and rugs.

REFERENCES

Akan, H., & Balos, M.M. (2021). *Alkanna strigosa* Boiss. & Hohen. (Boraginaceae) Kökünden Doğal Boya Eldesi. International Journal of Life Sciences and Biotechnology, 4(2): 224-234.

Akbostancı, İ. (2014). 20. The Changing Definition of Textile Printing Design and Production in the 21st and 21st Centuries, Art Design Magazine, 31.

Ali, S., Nisar, N., & Hussain, T. (2007). Dyeing Properties Of Natural Dyes Extracted From Eucalyptus. Journal of Textile Institute, 98(6): 559-562.

Anonymous, (1978 a). Color Fastness Test Methods for Dyed or Printed Textile Products - Color Fastness to Friction Test Methods - Determination of Color Fastness to Friction**.** Turkish Standards Institute Publications TS 717, Ankara.

Anonymous, (1978 b). Color Fastness Test Methods for Dyed or Printed Textile Products-Determination of Color Fastness to Water Drops**.** Turkish Standards Institute Side TS 399 / March. Ankara.

Anonymous, (1984 a). Color Fastness Test Methods for Dyed and Printed Textile Products-Method for Determination of Color Fastness to Light. Turkish Standards Institute Publications TS 867/October Ankara.

Anonymous, (1984 b). Methods of Using Gray Scales for Evaluation of Stains (Dye Bleeding) and Fading (Discoloration) in Color Fastness Determination of Textile Products.. Turkish Standards Institute Publications, TS 423/March. Ankara.

Anonymous, (1991). Dyeing of Wool Fibers with Dyes Obtained from Plants**,** Ministry of Industry and Trade, General Directorate of Small Arts and Industrial Zones and Sites, p:167. Ankara.

Bilir, M. Z., (2018). Multicolored Surface Design Based on Ecological Painting Yedi Sanat Design and Science Journal Issue 20: 63 ISSN: 1307-9840.

Deveoğlu, O. & Karadağ, R. (2011). An Overview: Natural Dyes, Marmara University Journal of Science, 1: 23-30.

Eyüboğlu, Ü., Okaygün, İ., & Yaraş, F. (1983). Wool Dyeing with Natural Dyes, Özkur Press, Istanbul.

Gulrajanı, M. L., Srivastava, R. J. & Goel, M. (2001). Colour gamut of natural dyes on cotton yarns, Coloration Technology, 117(4): 225-228.

Harmancıoğlu, M. (1955). Fastness Levels of Colors Obtained from Important Plant Dyes in Turkey Against Various Effects on Wool. Ankara University Publications: 77/41. Ankara University Press. 212 p. Ankara.

Kayahan, E., Karaboycı, M. & Dayık, M. (2016). Ecological Dyeing for Wool, Cotton and Regenerated Soybean Fibers Using Vegetable Wastes, Journal of Textiles and Engineer, 23(102): 112-125.

Korur, R.N. (1937). Vegetable Dyes in Turkey**.** Higher Institute of Agriculture Studies 41. Y.Z.E. Printing house. 83 p. Ankara.

Mansour, H. (2013). Textile Dyeing: Environmental Friendly Osage Orange Extract on Protein Fabrics. In: M.Günay (Ed.). Eco-Friendly Textile Dyeing and Finishing, pp.207-231.

Rungruangkitkrai, N. & Mongkholrattanasit, R. (2012). Eco-Friendly of Textiles Dyeing and Printing with Natural Dyes. The 4. RMUTP International Conference: Textiles & Fashion, 92, 1.

Ozbek, H. (1996). A Research on Colors Obtained from Some Dye Plants Growing in Sivas Region and Their Fastness Degrees on Wool Carpet Yarns. Gazi University, Institute of Science and Technology, Master Thesis (Unpublished) pp.33-35. Ankara.

Öztav, F. (2009). The Investigation Of Useage Of The Plant Of Alkanet (*Alkanna tinctoria*) As Cellulosic And Protein Fiberic Dyestuff. Gaziosmanpasa University. Graduate School of Natural and Applied Sciences Doctoral Thesis (Unpublished).p.95

Shahid, M., Shahid-ul-Islam, & Mohammad, F. (2013). Recent advancements ın natural dye applications: A Review, Journal of Cleaner Production, 53*:* 310-311.

Seçmen, Ö., Gemici, Y., Görk, G., Bekat, L., & Leblebici, E. (1989). Tohumlu Bitkiler Sistematiği. 2. baskı. Ege Üniversitesi Fen Fakültesi Yayını, (116) Bornova-İzmir.

Sönmez, Y., (1992). The Usability of *Verbascum asperiloides* (Cattle Tail) and *Arnebia densiflora* (Alkanna) Plant Extracts in Wool Dyeing, Unpublished Doctoral Thesis, Cumhuriyet. Univ., Sivas.

Spyros, A., Assimopoulou, A.N., & Papageorgiou, V.P. (2005). Structure determination of oligomeric alkannin and shikonin derivatives. Biomedical Chromatography, 19(7),: 498-505.

Tabata, M., Honda, G., Sezik, E., & Yesilada, E. (1993). A Report on Traditional Medicine and Medicinal Plants in Turkey (1990, 1991). Kyoto, Japan: Faculty of Pharmaceutical Sciences of Kyoto University.

Uğur, G. (1988). Türk Halılarında Doğal Renkler ve Boyalar**,** Türkiye İş Bankası Culture Publications General Publication No: 289, Art Series: 42, Ankara**.**

Von, V., & Katja, D. (2003). Naturstoffe aus farbe und heilplanzen. Geboren in Mülheim a.d. Ruhr, Bayreuth.

CHAPTER 18

EVALUATION OF CAROB (*Ceratonia siliqua* L.) FROM MEDICINAL AROMATIC PLANTS AS A DYEING IN TEXTILE FIBERS

Hülya KAYNAR[1]
Emine TONUS[2]

[1]Sivas Cumhuriyet University, Faculty of Architecture, Fine Arts and Design, Sivas,Türkiye, e-mail: hkaynar@cumhuriyet.edu.tr, ORCID NO: 0000-0002-9442-6162
[2]Sivas Cumhuriyet University, Sivas Vocational School of Technical Sciences, Department of Handicrafts, Sivas,Türkiye, e-mail: eminetonus@cumhuriyet.edu.tr, ORCID NO: 0000-0001-5065-1643

INTRODUCTION

The words organic, ecological and green, which have gained importance recently, have taken their place in the textile sector, and organic/ecological textile and green textile studies have accelerated in parallel with the development of the health sector. Ecology, known as environmentalist studies since the beginning of the 1990s, has closely interested the textile industry and aimed to produce the most suitable products for human health and the least harmful to the environment in all kinds of products and production stages.

Recently, ecological textile (Eko-Teks) constitutes the main lines regarding human health and environmental effects such as chemicals, waste water, workplace conditions, flue gas, noise level, used in the entire process from the acquisition of raw materials to the final product of textile products (Anonymous, 2022). In this context, new dyeing experiments are carried out with the thought that medicinal aromatic plants, which have been a source of life for thousands of years, will be useful in dyeing textile fibers due to their known effects.

Recently, medicinal aromatic plants have been used as dyestuffs in many fields such as food coloring, medicine, cosmetics, after the most basic need of nutrition. These plants are plants that grow on their own in nature, but according to the place and purpose of use, they have been cultured and produced over time. An important part of the medicinal and aromatic plants used for the treatment of diseases are collected from nature. The most striking and researched properties of medicinal and aromatic plants are their therapeutic properties. Herbal treatment; It has been used in many countries of the world in the form of traditional, complementary and natural treatment and still continues to be used.

The first records of the use of plants for therapeutic purposes date back to BC in Mesopotamia civilization. It has been determined that it belongs to the 5000s and 250 herbal drugs were used (Demirezer, 2010).

Medicinal and aromatic plants are divided into two as those collected from nature and those that are cultivated. Medicinal and aromatic plants collected from nature; There may be parts of plants such as fruits, stems, leaves, flowers that grow spontaneously in places such as forests, pastures, and unused agricultural lands, and sometimes weeds that grow in agricultural lands (FAO, 2020).

In this study, carob plant, which is not included in the known herbal natural dyes group, was selected from medicinal aromatic plants in order to provide layers to the organic/eco textile field. It is known that carob fruit is good for many diseases, carob extract is used as a therapeutic drug and is traded. In addition, dyeing studies with carob plant were not found. By using the fruits of the carob tree and different mordant substances as binders, dyeing experiments were carried out with woolen threads, which have a very important place in the textile industry. Fastness measurements were made on the dyed wool obtained as a result of the study, and as a result, the use of this plant in the field of textiles was interpreted.

1. CAROB (*Ceratonia siliqua* L.) PLANT

Carob (*Ceratonia siliqua* L.) is an evergreen belonging to the legume family, mainly grown in Mediterranean countries (Zhu et al., 2019; Donmez et al., 2022; Ouahioune et al., 2022). Carob is a maquis with high heat and light demand, drought-resistant and sensitive to frost. Because of these features, temperature is an important ecological factor that determines the distribution of carob (Günal, 2013). According to Durupınar (2015), the carob plant is a tree species that grows in semi-arid environments. It is botanically called *Ceratonia siliqua* L. Since ancient times, the carob plant has been found in abundance in all Mediterranean countries. It is also produced in most Mediterranean countries such as Spain, Cyprus and Italy. Carob production takes place in some North-South African and Asian countries such as Morocco, Greece, Algeria, Turkey, Israel, India and Pakistan. Carob is a long-lived and evergreen tree. After sprouting, they can reach 10 meters in length in 10-15 years, and they start to produce a good amount of fruit from the age of 15. A large tree can produce approximately 500 kg of fruit per year. Carob fruit is dark brown, sickle-shaped, 10-20 cm long and 2-4 cm wide (Rowe et al. 2006). Carob fruit is shown in Picture 1. 315,000 tons of carob seeds are produced annually from approximately 200,000 hectares of land in the world. 38% of this production is done in Morocco, 28% in Spain, 8% in Italy, 8% in Portugal, 6% in Greece, 6% in Turkey and 2% in Cyprus (Batal et al., 2013; Durupınar, 2015).

2. MATERIALS AND METHODS

Ripe fruits of the carob plant were used as material (Photograph 1). Carob fruit was collected from Mersin province, Silifke district, the fruits were dried in a suitable environment and divided into small pieces. As dyeing material, white and 2.5 Nm wool carpet yarn and 10 different (Iron II sulfate, Copper sulfate, Citric acid, Acetic acid, Copper II sulfate, Zinc chloride, Potassium aluminum sulfate, Potassium bi chromate, Sodium hydrosulfite, Tartaric acid,) mordant materials were used.

Photograph 1: Distribution of Colors Obtained From Carob (Kaynar, 2011)

Hot extract preparation, mordanting (pre-mordanting), dyeing of mordanted threads, naming of dyed threads, measurement of light, friction and water drop fastness were made. Mordanting process: Based on the amount of carpet yarns (2.5 Nm. wool) to be used in the trials. 2% and 4% mordant material was taken from the yarn amount and dissolved in warm water. It is important to dissolve the mordant in water to prevent abrasion on dyed wool. The prepared mordant material is mixed in water up to 20 times the weight of the wool yarn to be dyed, the pre-moistened wool is boiled with mordant water for one hour. Hot extract preparation process; Carob plant is prepared at a ratio of 1/1 with wool yarn. Plants are boiled for 1 hour in water 20 times the amount of wool. The hot extract, which is separated from the plant residues by filtering after cooling, is ready for dyeing. Painting process; The white wools to be dyed are skeined and soaked in warm water for at least one hour before dyeing. The wool thread is placed in the dyed extract prepared at a ratio of 1/20 and boiled for 1 hour after it reaches the boiling point. When the boiling process is finished, the wool is kept in the dye boiler until it cools. After rinsing with plenty of cold water, the drying process is started.

While measuring the light, friction and water drop fastnesses, prepared by the Turkish Standards Institute; Light fastness is made in accordance with TS 867 (Anonymous, 1984a) and DIN 5033 (Anonymous, 1978a) methods. While determining the friction fastness, the fastness tests were completed based on TS 717 (Anonymous, 1978a) and TS 423 (While determining the water drop fastness which is important in textile products, TS 399 (Anonymous, 1978b) and TS 423 (Anonymous, 1984b) which was also prepared by TSE) The results were prepared in tabular form and interpreted.

3. RESULTS AND DISCUSSION

In the dyeings made with the dye extract prepared from the carob plant, a total of 21 dyeings were made. Photograph 2 shows the colors obtained as a result of dyeing. These colors are; Light and dark coffee bean with acetic acid, light and dark aqua green with Iron II Sulphate, buff 1 with Potassium Aluminum Sulphate, buff 2, Coffee with milk 1 with Tartaric Acid, coffee with milk 2, light coffee bean, olive green with Oxalic Acid 1, olive green 2, brown coffee foam colors were obtained by dyeing without mordant.

Mordant	Painting Example	Obtained Colors
Acetic acid 2%		Light coffee bean
Acetic acid 4%		Dark Coffee bean
Copper II sulfate 2%		Aqua green 1
Copper II sulfate 4%		Dark aqua green
Ferrous sulfate 2%		Brown color 1
Ferrous sulfate 4%		Brown color 2
Potassium aluminum sulfate 2%		Baked apple 1
Potassium aluminum sulfate 4%		Baked apple 2
Potassium bichromate 2%		Camel hair 2
Potassium bichromate 4%		Camel hair 2
Sodium Sulphate 2%		Beige 1
Sodium Sulphate 4%		Beige 2
Tartaric acid 2%		Coffee with milk 1
Tartaric acid 4%		Coffee with milk 2
Oxalic acid 2%		Olive oil green 1
Oxalic acid 4%		Olive oil green 2
without mordant		Coffee foam

Photograph 2: The Distribution of Colors Obtained From Carob (Kaynar, 2011)

Light and friction fastness values obtained from dyeing with carob plant fruit are given in Table 1.

Table 1: Fastness Values Obtained From Carob Plant (*Ceratonia siliqua* L.)

No	**Used Mordant Substances And Their Proportions**	**Light**	**Friction**
1	Asetic asid% 2	5	3
2	Asetic asid % 4	5	3-4
3	Copper II sulfate % 2	6	2
4	Copper II sulfate % 4	6	2
5	Zinc chloride % 2	4	3
6	Zinc chloride % 4	4	2
7	Ferrous II sulfate % 2	6	2
8	Ferrous II sulfate % 4	6	1-2
9	Potassium aluminum sulfate % 2	6	3
10	Potassium aluminum sulfate % 4	6	3
11	Potassium bichromate % 2	4	4-5
12	Potassium bichromate % 4	5	3
13	Citric acid % 2	4	2-3
14	Citric acid % 4	5	3
15	Sodium hydrosulfite 2%	4	3
16	Sodium hydrosulfite 4%	5	3
17	Tartaric acid 2%	5	3
18	Tartaric acid 4%	5	3
21	without mordant	5	2-3
	Minimum	4	1.5
	Maximum	6	3.5
	Ortalama	5	2.6
	Standart sapma	0.7	0.5

In Table 1, it was seen that the light fastness value changed between a minimum of 5 and a maximum of 6 as a result of dyeing with the carob plant. In the dyeing experiment without using mordant, the light fastness value of 5 was obtained. Values of 5 and above are considered "good" when evaluating light fastness measurements. When the friction fastness values are examined, it is seen that there are values between a minimum of 1-2 and a maximum of 3-4. The colors obtained from this plant can be used in the field of textiles.

CONLUSIONS

Green production and green marketing have become one of the issues that the producers that contribute to the country's economy attach importance to. In particular, measures are taken to produce, develop and promote products that are recyclable and compatible with the environment. In this context, the preferred environmentally friendly dyes have started to take their place in every field of the textile industry. Many plants in the natural flora in our country are included in medicinal aromatic plants, increasing their preference rates in different areas of use. As people's awareness of choosing natural products for the environment and healthy life increases, the interest in these products increases. As a result, both preferred products emerge and new labor needs arise in many areas such as the supply, processing and re-cultivation of plants used in dyeing, contributing to the country's economy and the creation of new employment areas.

In this study, natural herbal dyeing studies were carried out with the Carob (*C. siliqua* L.) plant, which is located in the natural vegetation of our country and is used in many areas other than dyeing. Among the textile fibers, woolen yarns, which give the best results with vegetable dyeing, were chosen as the dyeing material. Dried plant roots were taken with the amount of wool in a ratio of 100% in a 1-to-1 ratio, boiled with different mordants at 2% and 4% for 1 hour, and fastness measurements (light and friction fastness) were applied to the obtained colored wool yarns. A color chart was created with the colors obtained in order to inform the people and institutions that will dye in the field of textile. In dyeing made with dye extract prepared from carob plant; Colors of coffee coffee foam were obtained with light and dark coffee beans, dark aqua green, Potassium, Buff 1, Buff 2, milk coffee 1, milk coffee 2, Light coffee bean, olive green 1, olive green 2, and coffee. In this study, it was concluded that the “colors of nature” preferred in products called nature-friendly green textiles were obtained, and carob fruit could be preferred in herbal dyeing.

REFERENCES

Anonymous (1978 a). Color Fastness Test Methods for Dyed or Printed Textile Products - Color Fastness to Friction Test Methods - Determination of Color Fastness to Friction**.** Turkish Standards Institute Publications TS 717, Ankara.

Anonymous (1978 b). Color Fastness Test Methods for Dyed or Printed Textile Products-Determination of Color Fastness to Water Drops**.** Turkish Standards Institute Side TS 399 / March. Ankara.

Anonymous (1984 a). Color Fastness Test Methods for Dyed and Printed Textile Products-Method for Determination of Color Fastness to Light. Turkish Standards Institute Publications TS 867/October Ankara.

Anonymous (1984 b). Methods of Using Gray Scales for Evaluation of Stains (Dye Bleeding) and Fading (Discoloration) in Color Fastness Determination of Textile Products.. Turkish Standards Institute Publications, TS 423/March. Ankara.

Anonymous (2022). Ecological Textile Products. https://www.ekoetiket.com/ sektorel/ekoloji-tekstil-urunleri/, (Access date: 15.12.2022).

Batal, H.E., Hasib, A., Ouatmane, A., Boulli, A., Dehbi, F., & Jaouad, A. (2013). Yield and composition of carob bean gum produced from different Moroccan populations of carob (*Ceratonia siliqua* L.). Journal of Materials and Environmental Science, 4: 309-314.

Demirezer, L.Ö. (2010). Our Responsibilities Regarding the Use of Plants in Medicine. Herbal Treatment Symposium 5-6 June, Zeytinburnu, Istanbul Proceedings Book, p: 87-88.

Donmez, A., Erunsal, S.C., & Sahin, S.N. (2022). Impact of locust bean gum/xanthan gum addition on new generation snack design from carob fruit byproducts. The Journal of Food, 47(4): 690-704.

Durupınar, Ü. (2015). Application of Carob Seed Based Coatings to Extend the Shelf Life of Turkish Delight. Afyon Kocatepe University, Institute of Science and Technology, Master Thesis (Unpublished).

FAO, (2020). Trade in Medicinal Plants, (http://www.fao.org/faostat/en/#data) (Accessed date: 09.12.2022).

Günal, N. (2013). Geographical Distribution, Ecological and Floristic Properties of Carob (Ceratonia Siligua L.) in Turkey. Marmara Journal of Geography, (2) , 65.

Ouahioune, L.A., Wrona, M., Becerril, R., Salafranca, J., Nerín, C., & Djenane, D. (2022). *Ceratonia siliqu*a L. kibbles, seeds and leaves as a source of volatile bioactive compounds for antioxidant food biopackaging applications. Food Packaging and Shelf Life, 31: 100764.

Rowe, R., Sheskey, P., & Owen, S. (2006). Handbook of Pharmaceutical Excipients, 5th ed., Pharmaceutical Press, London.

Zhu, B.J., Zayed, M.Z., Zhu, H.X., Zhao, J., & Li, S.P. (2019). Functional polysaccharides of carob fruit : A review. Chinese Medicine, 14(1): 1-10.

CHAPTER 19

THE USE OF MEDICINAL AND AROMATIC HERBS IN THE TREATMENT OF ENDOMETRIOSIS

Dilara ÜLGER ÖZBEK[1]

[1]Advanced Technology Research and Application Center, Sivas Cumhuriyet University, Sivas, Türkiye, e-mail: dilaraulger@cumhuriyet.edu.tr
ORCID ID:0000-0002-6834-020X

INTRODUCTION

Medicinal and aromatic plants are utilized as medication for the remedy of diseases, protection from them, and maintaining a healthy life (Faydaoğlu et al., 2011). Humanity has been utilized herbs for the treatment and counteraction of ailments since from the past. The usage of medicinal plants for therapeutic purposes today is called 'alternative medicine'. Treatment methods are developed by utilizing the essential nutrients contained in plants and important active substances formed by their metabolism. Endometriosis is also a disease that is desired to be cured with these herbs.

1. ENDOMETRIOSIS

Endometriosis is a serious problem that 15 % of women suffer from breeding age. It is specified as the adhesion of endometrial tissues outside the uterine, often in the ovaries, Douglas pouch, abdominal cavity, and rectovaginal septum, and less frequently in the intestines, external genitalia, and abdominal surgical scars (Dull et all.,2019). Symptoms of dysmenorrhea, pelvic pain, dyspareunia, and infertility are among the most well-known complaints (Carlos et al., 2009). The most important things in the treatment of endometriosis are to relieve the pain involved in the complaint, to provide and maintain fertility, and to delay and prevent recurrence or progression in endometriotic targets. In general, despite the medical and preventive treatments of endometriosis, the annual recurrence rate of the disease is 5-10 %, and this problem is encountered again in roughly 50 % of the cases (Clayton et al., 1999). Endometriosis is an estrogen-dependent disease, therefore a decrease in estrogen causes a decrease in complaints. For this reason, medical treatments have been developed that reduce the release of estrogen (Bieber et al., 2006).

1.1. *Achillea biebersteinii*

Achillea biebersteinii is a traditional medicinal herb called 'Sarıçiçek' in Turkish and utilized for gastrointestinal, abdominal pain and wound healing. It is known to have antimicrobial and antioxidant effects (Bariş Ö et al., 2006). In the experimental animal model with endometriosis, *Achillea biebersteinii* extracts given them. As a result, the endometriosis remnants were reduced and the adhesion was removed (Demirel et al., 2014).

1.2. *Alchemilla*

It has been reported that *Alchemilla vulgaris*, which belongs to the *Alchemilla* species, plays an active role in the treatment of gynecological diseases and it is known to be often utilized for this reason by women living in the countryside (D'Agostino et al., 1998). In a study conducted with the application of above-ground extracts of *Alchemilla mollis* and *Alchemilla persica* in an endometriosis rat model, it was observed that cystic formation and cytokine levels were significantly decreased. It has been explained that these effects are due to the strong antioxidant activities and phenolic compounds of *Alchemilla persica* and *Alchemilla mollis* (Küpeli et al., 2015).

1.3. *Calligonum comosum*

Calligonum is a class of plants in the *Polygonaceae* family with approximately 80 species (Ranjbarfordoei et al., 2013). In traditional medicine, *Calligonum comosum* is utilized for the treatment of unusually weighty or drawn-out monthly cycle and menstrual spasms. It has additionally been suggested for the cure of gynecological conditions that cause infertility, such as polycystic ovary syndrome (Tahmasebi et al., 2018). *Calligonum comosum* has a broad range of mechanisms of action with antioxidant, anti-inflammatory, and anti-cancer activity (El-Hawary et al., 1990; Abdallah et al., 2014). Again, it was found that *Calligonum comosum* extract, applied to endometriotic rat model, is a potent antiangiogenic and regresses the growth of endometriotic lesions, cyst-induced vascularization, and immune cell penetration (Kiani et al., 2019).

1.5. Curcumin

Curcumin is a polyphenolic component embedded in the rhizomes of *Curcuma longa* (Turmeric). Curcumin regulates many signaling pathways, and affect biochemical pathways such as oxidative damage, inflammation, angiogenesis, and cellular proliferation. In studies on endometriosis, curcumin has been reported to alleviate chronic pelvic pain, the intensity of dysmenorrhea, pain markers, and dysuria (Singh et al., 2021).

1.6. *Cyperus rotundus*

Rhizomes of *Cyperus rotundus* are one of the significant medicinal plants generally utilized in the cure of 388ynaecological diseases in the Asian continent. In some regions, *Cyperus rotundus* has been reported to be consumed by boiling for the cure of reproductive disorders and dysmenorrhea in women with endometriosis (Zhou et al., 2009). Immortalized human endometriotic epithelial cells (12Z), *Cyperus rotundus* extracts were applied to the cell line generated from tissues of women with active endometriosis. As a result, this medicinal plant inhibited cell adhesion and neutrophin expression by negatively affecting Akt and NF-kB pathways in endometriotic cells. Thus, the inhibitory effect of *Cyperus rotundus* on endometriosis has been demonstrated (Ahn et al., 2022).

1.7. *Teucrium chamaedrys*

Teucrium chamaedrys L. (Lamiaceae), whose called ‘Kısamahmut’ in Turkish, is used in the treatment of infections, wounds, gastrological problems, rheumatism, and gynecological infections (Rader et al., 2007). In one study, the benefit of *Teucrium chamaedrys* extract applied for the treatment of experimental animals with endometriosis was demonstrated. It was determined that the size of the endometriosis localizations and macroscopic adhesion regressed significantly in the groups given *Teucrium chamaedrys* extract (Özel et al., 2020).

1.8. *Malva neglecta*

Malva neglecta is a medicinal herb in the *Malvaceae* family. Consuming the plant's fresh leaves by boiling them has been used to cure dysmenorrhea and infertility (Günbatan et al., 2016). It has been explained that the polyphenols in the composition of *Malva neglecta* extracts applied to the endometriosis rat model show high activity against endometriosis due to their antiestrogenic activities and cytokine inhibitory effects. It has been proposed that an option in the treatment of endometriosis (Akkol et al, 2022).

1.9. *Melilotus officinalis* (L.) Pall

Melilotus officinalis (L.) Pall is known as "yellow melilot, yellow sweet clover, and medicinal sweet clover" (Udayama et al., 1998) and is a medicinal herb commonly used for hemorrhoids, bronchitis, kidney stones, painful menstruation, uterine hardening, and swelling (Kang et al., 1987). Administration of glycosylated flavonoids obtained from *Melilotus officinalis (L.) Pall* to a rat model of endometriosis is thought to result in decreased endometrial focal areas and cytokine levels, due to its anti-angiogenic property (Ilhan et al., 2020).

1.10. *Viburnum opulus*

The genus *Viburnum* is a member of the *Caprifoliaceae* family. and most of its species are endemic. The genus *Viburnum opulus* is referred to by different neighborhood names, for example, gilaburu, gilaboru, and gilda in the Flora of Türkiye (Karacelik et al., 2015). *Viburnum* *opulus* fruit extracts were applied to the rat model in which endometriosis was created surgically. It was found that the endometriotic volumes were significantly reduced in the groups used. No adhesion was observed in reference and extract applied groups. There was an exceptional lessening in the degrees of TNF-α, VEGF, and IL-6 in the extract-administered groups (Saltan et al, 2016).

CONCLUSIONS

Briefly, in the literature, there is a great deal of information on the impact of many medicinal and aromatic plants on the treatment of endometriosis. In many regions, it was seen that these herbs were traditionally used extensively to reduce the complaints of endometriosis.

REFERENCES

Abdallah, H.M.I., Asaad, G.F., Arbid, M.S., & Abdel-Sattar, E.A. (2014). Anti-inflammatory, antinociceptive, antipyretic and gastroprotective effects of *Calligonum comosum* in rats and mice. International Journal of Toxicological and Pharmacological Research, 6: 26-33.

Akkol, E.K., Karpuz, B., Türkcanoğlu, G., Coşgunçelebi, F.G., Taştan, H., Aschner, M., & Sobarzo-Sánchez, E. (2022). The phytochemical profile and biological activity of *Malva neglecta* Wallr. in surgically induced endometriosis model in rats. Molecules, 27(22): 7869.

Ahn, J.H., Choi, J.M., Kang, E.S., Yoo, J.H., Cho, Y.J., Jang, D.S., & Choi, J.H. (2022). The Anti-endometriotic effect of cyperi rhizoma extract, inhibiting cell adhesion and the expression of pain-related factors through Akt and NF-kB pathways. Medicina, 58(3): 335.

Bariş Ö., Güllüce, M., Şahin, F., Özer, H., Kiliç, H., Özkan, H., & Özbek, T. (2006). Biological activities of the essential oil and methanol extract of *Achillea biebersteinii* Afan(Asteraceae). Turkish Journal of Biology, 30(2): 65-73.

Bieber, E.J, Sanfilippo, J.S, & Horowitz, I.R. (2006). Clinical Gynecology 1th Ed. Philaladelphia: Churchill Livingstone, Elsevier Nc, 159-179.

Carlos, P., Marisa, T., Carolina, G., Hugo, S., M. Angelica, B., Ariel, F., & M.Cecilia J. (2009). Nuclear factor kB pathway and interleukin-6 are affected in eutopic endometrium of women with endometriosis. Reproduction, 137: 727-737.

Clayton, R.D., Hawe, J.A., Love, J.C., Wilkin Son, N., & Garry, R. (1999). Recurrent pain after hysterectomy and bilateral salpingoopherectomy for endometriosis. Evaluation of laparoscopic excision of residual endometriosis. British Journal of Obstetrics and Gynaecology, 106: 740-744.

D'Agostino, M., Dini, I., Ramundo, E., & Senatore, F. (1998). Flavonoid glycosides of *Alchemilla vulgaris* L. Phytotherapy Research, 12: 162–163.

Demirel, M.A., Suntar, I., Ilhan, M., Keles, H., & Akkol, E.K. (2014). Experimental endometriosis remission in rats treated with *Achillea biebersteinii* Afan.:

histopathological evaluation and determination of cytokine levels. European Journal of Obstetrics & Gynecology and Reproductive Biology, 175: 172-177.

Dull, A.M., Moga, M.A., Dimienescu, O.G., Sechel, G., Burtea, V., & Anastasiu, C.V. (2019). Therapeutic approaches of resveratrol on endometriosis via anti-inflammatory and anti-angiogenic pathways. Molecules, 24(4): 667.

El-Hawary, Z.M., Kholie, T.S. (1990). Biochemical studies on some hypoglycemic agents (II) effect of *Calligonum comosum* extract. Archives of Pharmacal Research, 13(1): 113-116.

Faydaoğlu, E., Sürücüoğlu, M.S. (2011). History of the use of medical and aromatic plants and their economic importance. Kastamonu University Journal of Forestry Faculty, 11(1): 52-67. (In Turkish).

Günbatan, T., Gürbüz, İ., & Özkan, A.M.G. (2016). The current status of ethnopharmacobotanical knowledge in Çamlıdere (Ankara, Turkey). Turkish Journal of Botany, 40(3): 241-249.

Kang, S.S., Lim, C.H., & Lee, S.Y. (1987). Soyasapogenols B and E from *Melilotus officinalis*. Archives of Pharmacal Research, 10(1): 9-13.

Karaçelik, A.A., Küçük, M., Iskefiyeli, Z., Aydemir, S., De Smet, S., Miserez, B., & Sandra, P. (2015). Antioxidant components of *Viburnum opulus* L. determined by on-line HPLC–UV–ABTS radical scavenging and LC–UV–ESI-MS methods. Food chemistry, 175: 106-114.

Kiani, K., Rudzitis-Auth, J., Scheuer, C., Movahedin, M., Lamardi, S.N. S., Ardakani, H.M., & Laschke, M.W. (2019). *Calligonum comosum* (Escanbil) extract exerts anti-angiogenic, anti-proliferative and anti-inflammatory effects on endometriotic lesions. Journal of Ethnopharmacology, 239: 111918.

Küpeli, Akkol E., Demirel, M.A., Bahadır Acıkara, O., Süntar, I., Ergene, B., Ilhan, M., & Tekin, M. (2015). Phytochemical analyses and effects of *Alchemilla mollis* (Buser) Rothm. and *Alchemilla persica* Rothm. in rat endometriosis model. Archives of Gynecology and Obstetrics, 292(3): 619-628.

Ilhan, M., Ali, Z., Khan, I.A., Taştan, H., Akkol, E.K. (2020). The regression of endometriosis with glycosylated flavonoids isolated from *Melilotus officinalis*

(L.) Pall. in an endometriosis rat model. Taiwanese Journal of Obstetrics and Gynecology, 59(2): 211-219.

Özel, Ş., Süntar, İ., Gökay, N.E., Türkmenoğlu, T.T., & Demırel, M.A. (2020). The effectiveness of *Teucrium chamaedrys* L. extracts on endometriotic implant regression in rat endometriosis model. In Veterinary Research Forum, 11(4): 305-309.

Rader, J.I., Delmonte, P., & Trucksess, M.W. (2007). Recent studies on selected botanical dietary supplement ingredients. Analytical and Bioanalytical Chemistry, 389(1): 27-35.

Ranjbarfordoei, A., Vandamme, P., & Samson, R. (2013). Some ecophysiological characteristics of artà (*Calligonum comosum* Lʼ Hérit) in response to drought stress. Forest Science and Practice., 15: 114–120.

Saltan, G., Süntar, I., Ozbilgin, S., Ilhan, M., Demirel, M.A., Oz, B.E., & Akkol, E.K. (2016). *Viburnum opulus* L.: A remedy for the treatment of endometriosis demonstrated by rat model of surgically-induced endometriosis. Journal of Ethnopharmacology, 193: 450-455.

Singh, A., Dasgupta, S., Bhattacharya, A., Mukherjee, G., & Chaudhury, K. (2021). Therapeutic potential of *curcumin* in endometrial disorders: Current status and future perspectives. Drug Discovery Today.

Tahmasebi, F., Movahedin, M., & Mazaheri, Z. (2018). Antioxidant effects of *Calligonum* extract on ovarian tissue of PCO model: An experimental study. International Journal of Reproductive BioMedicine, 16(10): 641-648.

Udayama, M., Kinjo, J., Yoshid, N., & Nohara, T. (1998). A new oleanene glucuronide having a branched-chain sugar from *Melilotus officinalis*. Chemical and Pharmaceutical Bulletin, 46(3): 526-527.

Zhou, J., Qu, F. (2009). Treating gynaecological disorders with traditional Chinese medicine: a review. African Journal of Traditional, Complementary and Alternative Medicines, 6(4):494-517.

CHAPTER 20

HERBAL TREATMENT METHODS USED IN THE TREATMENT OF BREAST CANCER

Bahar TÜRKMENOĞLU[1]
Ayşe SARI[2]
Betül Eylül ÇİÇEKLİYURT[3]

[1]Sivas Cumhuriyet University, Hafik Kamer Örnek Vocational School, Sivas,Türkiye, e-mail: baharturkmenoglu@cumhuriyet.edu.tr,
ORCID ID: 0000-0001-5631-3215
[2] Sivas Cumhuriyet University, Health Services Application and Research Hospital Oncology Center Executive Nurse, Sivas, Türkiye, e-mail: aasari@cumhuriyet.edu.tr, ORCID: 0000-0003-0621-4838
[3] Anadolu University, Department of Culinary, Eskişehir, Türkiye
e-mail: eylulcicekliyurt@hotmail.com, ORCID: 0000-0002-8480-9944

INTRODUCTION

Today, cancer is a serious threat to human health. Cancer is frequently seen all over the world and is a health problem that occurs when cells in the living body get out of control. The most common type of cancer in the world is lung cancer, followed by breast cancer in the second place and mostly seen in women (Anonymous, 2020a; Anonymous, 2020b). The incidence of breast cancer increases with advancing age, and 70% of newly diagnosed women are 50 years or older (Anonymous, 2020b). GLOBACAN according to the 2020 result, it has been announced that breast cancer is the most diagnosed cancer type worldwide with 11.7%, seen in the sum of both genders (Globocan, 2020). Surgery, chemotherapy, radiotherapy and hormonal therapy are used as treatment methods in patients diagnosed with breast cancer. In addition to these treatments, breast cancer patients resort to herbal treatment methods as in other cancer types (Kurt et al., 2013). While the use of herbal treatment methods is increasing in general populations, it is also increasing in cancer patients. Among the reasons for this increase; Difficulty in the care and treatment process of the disease, the increase in chronic diseases and malignant diseases, the high costs of new technological devices in the treatment process, and then the relatively difficult access to these opportunities, the inability of healthcare professionals to spare enough time for their patients, the concern about current treatment methods and the existing medical can be listed as the side effects that occur as a result of the application of the treatment (Turan et al., 2010).

1. CANCER

Cancer describes a group of diseases characterized by the uncontrolled growth and spread of cells in the body. Cancer ranks second in death rankings in the world and is the cause of one in six deaths. In order for cancer cells to multiply uncontrollably and to provide the necessary energy; it needs to change and reprogram its current metabolic pattern (Maniam and Maniam, 2020).

Research on cancer draws attention to six characteristics of all cancer types. These features are; growth by signaling incessantly, avoidance of factors inhibiting cell division, resistance to cell death, tendency to vascularization (angiogenesis), dissemination (metastasis), and immortality. Two more features were added in later studies. These; immune system and altered energy metabolism (Kato et al., 2017).

It is estimated that more than 20 million new cancer patients will be diagnosed each year worldwide by 2030, in line with the improvement in welfare and an aging population (Nilsson at al., 2019). Looking at these statistics for our country; According to 2020 data, the most common cancer types are respectively; lung cancer, breast cancer, colorectal cancer, prostate cancer and thyroid cancer. These data are; It covers people of both sexes and all ages and accounts for more than 50% of all cancers. The most common types of cancer in women are; are listed as breast, thyroid, colorectal, lung and uterine cancers (Globocan, 2020).

The World Health Organization (WHO) emphasized that most cancer deaths are due to five factors of behavioral and dietary risk and defined these five factors as high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco and alcohol consumption (WHO, 2015).

1.1. Breast Cancer

Breast cancer is the most common type of cancer in women in the world and in Türkiye. In 2018, approximately 2 million new cases were diagnosed in the world (Andersen et al., 2019). Although it is the cancer type that causes the most death in women, the survival and treatment rate increases by 90% with early diagnosis (Griva et al., 2009; Bray at al., 2018). Breast cancer constitutes 24.4% of female cancers in Türkiye, and a total of 22 345 new breast cancer cases were diagnosed in 2018 (Globocan, 2018). Global cancer statistics report that breast cancer cases are increasing and this increase is occurring more rapidly in middle- and low-income countries (George et al., 2019).

According to the data of 2020; In our country, the number of new cancer cases among women of all ages was reported as 101 018, and among female cancers, breast cancer ranked first with 24 175 (23.9%) (Globocan, 2020). Breast cancer is a disease that is also seen in men and constitutes approximately 1% of all cancers in men (White, 2010).

Breast cancer is an important public health problem and risk factors for its development are both hereditary and environmental (Galván-Salazar et al., 2015). A number of risk factors have been identified in the pathogenesis of breast cancer tumors; It is known that most of these factors are related to diet and lifestyle. Risk factors associated with increased incidence of breast cancer are age, lack of physical activity, reproductive and hormonal factors, individual lifestyle factors, such as alcohol consumption and obesity, are associated with higher disease risk (Hagen et al., 2018; Ferrini, 2015; Zang et al., 2015). On the other hand, among the risk factors; estrogen use and whether there is a family history of breast cancer are important (Hagen et al., 2018).

It is estimated that nutrition in breast cancer accounts for 50% of deaths from this disease. A healthy diet can reduce the risk of breast cancer, but an unbalanced diet can increase it in different ways by disrupting the hormonal balance (Maliou and Bitam, 2015).

The development of breast cancer is highly affected by reproductive hormones, estrogen and progesterone. Foods and nutrients that affect these hormones are of interest in terms of breast cancer cases and prognosis. Early diagnosis and treatment of breast cancer have a great impact on survival, and breast cancer survival rate can be affected by lifestyle and nutritional factors (Andersen et al., 2019).

In the treatment of breast cancer; surgery, radiotherapy, chemotherapy, biological therapy and hormone therapy methods are used. Cancer patients search for alternative treatments along with known treatment methods after diagnosis. She is concerned about the known side effects of current treatments and seeks to contribute to both side effects and cancer treatment. In the last few years, the use of certain types of complementary medicine, such as phytotherapeutic products and nutritional supplements, has increased significantly by women with a history of breast cancer. The risks that the use of such approaches in oncological processes may be a problem and may change the effectiveness of standard cancer treatment should not be ignored (Lopes et al., 2017).

On the basis of alternative searches by breast cancer patients; Activating the immune system, curing cancer and alleviating the symptoms associated with the side effects of existing cancer treatments, increasing the quality of life (Wanchai et al., 2010; Vidal et al., 2013).

2. PLANT SPECIES USED IN BREAST CANCER

2.1. *Cimicifuga racemosa* (Black Cohosh)

Black cohosh is a plant species native to North America and comes from the Ranunculaceae family. It is usually grown in Canada, China and Europe. It is also known as black cohosh, insect grass, rattle grass, snake root, redwood root or rheumatism grass. (Gardner, 2013). Root and rhizome of black cohosh; It is used in rheumatic diseases, malaria, sore throat, colds and complications related to childbirth. (Predny et al., 2006). It has been used for centuries by Europeans for the treatment of menopausal symptoms. (Borrelli and Ernst, 2002; Wuttke et al., 2003). Black cohosh is widely used to reduce menopausal symptoms such as hot flashes, night sweats, sleep disturbance, dizziness, irritable mood, mood disorders, and vaginal dryness, which are common in postmenopausal women (Leach and Moore, 2012). It has been found that black cohosh extracts enriched with triterpene glycosides have a chemopreventive effect and can be used successfully in patients with breast cancer without causing a negative effect on breast tissue (Einbond et al., 2012). However, one of the systematic reviews concluded that there was no association between black cohosh and a reduction in hot flashes in breast cancer patients due to insufficient evidence, but more research is requested (Fritz et al., 2014).

2.2. *Camellia sinensis* (Green tea)

The tea tree is a shrub or small tree belonging to the Theaceae family. Teas are known by names such as white, green, matcha, black, oolong depending on their processing method, taste, color, aroma and biological effects (Rothenberg et al., 2018; Tang et al., 2019). Tea contains microelements borate, cobalt, copper, iron, manganese, molybdenite and lead, pigments, polysaccharides, alkaloids, free amino acids and saponins (Karak et al., 2017; Tang et al., 2019). EGCG and theaflavin, which are found in the composition of tea and show antioxidant properties, come to the fore in the relationship between tea and cancer. These components can prevent the formation, growth and proliferation of cancer cells, especially due to the antioxidant properties of tea (Çelik, 2006; Sharangi, 2009; Öğünç, 2016). It is reported that polyphenols in the composition of green tea can inhibit angiogenesis. It is stated that while tea polyphenols affect the cancer cell cycle in this way, they do not have these effects in normal cells (Oak et al., 2005; El Bedoui, 2005). Studies show that the consumption of green tea is inversely related to the risk of developing breast cancer. In a study conducted with 103 postmenopausal women, 400 mg of green tea catechin epigallocatechin gallate (EGCG) was given to one group and 800 mg to the other group once a day for 2 months. EGCG has been shown to have beneficial effects on LDL-cholesterol concentration and blood sugar level. The prevention of weight gain after breast cancer treatment has been investigated, thanks to its potential to control weight and prevent cardiovascular disease with the consumption of green tea. Improvement in carbohydrate metabolism, mild decrease in weight and increase in HDL values were observed in overweight breast cancer patients. These clinical data and in vitro and in vivo results support the use of tea polyphenols as chemopreventive agents in adjuvant therapy in breast cancer (Wu et al., 2003; Wu et al., 2012; Stendell-Hollis et al., 2010; Luo et al., 2010).

2.3. *Curcuma longa* (Turmeric, Indian saffron)

It is widely cultivated in tropical regions. *Curcuma longa*, a species native to southwestern India and commonly referred to as turmeric, is used in a variety of medicinal applications. The rhizomes give turmeric its bright yellow color. Turmeric is used for medicinal purposes as well as in the cosmetic industry and paint industry (Omosa et al., 2017). Although turmeric is a rich source of vitamin D, it is the type of plant that is used against cancer and has the most evidence in the literatüre (Biswas et al., 2010; Bar-Sela et al., 2010). Also contains metabolites of curcumin and its derivatives, which have anticancer properties. Turmeric; While destroying the formed cancer cells, it also supports healthy cells. In addition, by providing antiangiogenesis, it prevents the blood flow necessary for the growth of the cancerous cell. More specifically, turmeric inhibits the proliferation of tumor cells, reduces inflammation, prevents cells from turning into tumors, and inhibits protein synthesis, which is known to have an effect on the formation of tumors (Bachmeier et al., 2010; Sikora et al., 2010). Turmeric also interferes with the production of dangerous advanced glycation end products that trigger inflammation that can lead to cancerous mutations (Sajithlal et al., 1998). Turmeric alters cellular signaling to improve healthy control over cellular replication, tightly regulating the cellular reproduction cycle and helping to stop the uncontrolled proliferation of new tissue in tumors (Ravindran et al., 2009). Promotes apoptosis in rapidly proliferating cancer cells without affecting healthy tissue (Vallianou et al., 2015; Zhang et al., 2010) and restrain tumor growth by making tumors more vulnerable to pharmacological cell-killing treatments (Vallianou et al., 2015; Clark et., 2010). In a case-control study, 60 patients diagnosed with breast cancer took turmeric supplements over a 21-day period. When the follow-up period was over, it was found that there were significant improvements in health status, symptom scores (fatigue, nausea-vomiting, pain, loss of appetite, insomnia) and hematological parameters (Kalluru et al., 2020).

2.4. *Silybum marianum* L. (Milk Thistle)

The thistle plant has been used traditionally for over 2000 years. (Tamayo and Diamond, 2007). Thistle can grow successfully even in heavy clay soils, including sandy soils. Thistle is sown directly into the ground and planting is done in autumn and spring. Due to its rapid adaptation to poor quality soils and different growing conditions, the nutritional needs of this plant range from low to moderate. Thistle seeds contain a lot of silymarin and all are used for medicinal purposes. Its therapeutic properties are formed by the presence of silymarin, which is a mixture of three flavonolignans (silybin-silydianin-silycristin) (Karkanis et al., 2011). Recent experimental and clinical studies have shown that milk thistle has a protective effect against cancer, diabetes and heart diseases (Tamayo and Diamond, 2007). It is seen that thistle extracts have positive effects on the toxic side effects of chemotherapy drugs used for treatment in patients diagnosed with breast cancer. On the other hand, it has been reported that some components in milk thistle extract synergize with paclitaxel (PTX) to activate apoptosis and regulate the cell cycle, thereby stopping breast cancer formation activity (Espinosa-Paredes et al., 2020). In addition, it has been found that thanks to the phytochemicals (lycopene, beta-carotene and cucurbitacin E) in its content, it contributes to the stopping of the cycle of cancerous cells in breast cancer (Gloria et al., 2014).

2.5. *Panax Ginseng*

Ginseng ranks fourth among the best-selling herbal medicinal products worldwide. It is extensively included in pharmacopoeias in Europe, Germany, Austria, England and America (Wu et al., 2012). Ginseng is used in the treatment process of breast cancer to increase energy, increase physical and psychomotor performance, as well as improve health in general (Bao et al., 2012). Studies show that ginsenosides in ginseng are good for stress and fatigue and also have anticancer effects.

The active ingredients in *Panax ginseng* roots reduced and blocked the development of tumor necrosis factor in mouse skin. It is stated that ginseng, which blocks the metastasis and progression of cancer cells and stimulates cell differentiation, can stop tumor development by interfering with DNA synthesis in studies indicating that it reduces the risk of cancer in humans (Coleman et al., 2003). According to the data obtained as a result of follow-up of breast cancer patients for about five years, no effect of ginseng in terms of quality of life was observed in breast cancer patients (Cui et al., 2006). Ginseng had no effect on quality of life, but statistically significant results were found in mental states (Ganz et al., 2002). It has been determined that ginseng taken 1000-2000 mg daily for eight weeks is effective in cancer-related fatigue (Barton et al., 2010). Combinations of ginseng longan, panax ginseng radix are used in herbal medicines prescribed for breast cancer patients in Taiwan (Lai et al., 2012).

2.6. *Allium sativum* L. (Garlic)

The homeland of garlic, which is among the ancient cultivated plants, is considered to be Central and Western Asia. The height of the garlic can reach 25-100 cm. While the flower may be white or pink, it is a cultivar with root, stem, leaf, tooth and flower parts. This plant, which is very important from a medical point of view; Because of its pungent smell, appetizing feature and burning flavor, it is used in foods and gives flavor to them. There are more than 200 chemical compounds in the content of garlic, and the most important of them are essential oils and enzymes, carbohydrates, minerals, amino acids, A, B1, B2, Niacin and vitamin C, which are composed of sulfur-containing compounds (Kütevin and Türkeş, 1987; Baytop, 1999). Another active ingredient in garlic is ajoenes. It has been found that ajoenes delay the formation of cancer thanks to the presence of selenium, which has an antioxidant effect. It also inhibits the formation of cancer cells and kills them by stopping macrophages and lymphocytes (Nicastro et al., 2015). Diallyltrisulfide (DATS) is an organosulfite toxic to cancer cells, but its effect on cancer initiation is not yet known. In this study, the mechanisms including inhibition of cancerous cell proliferation, regulation of cell cycle, weakening of the formation of free oxygen compounds and inhibition of DNA damage and the effects of these mechanisms were investigated. Although DATS has been found to be an effective attenuator against breast cancer in vitro, it has been stated that it contributes to the effectiveness of garlic as a chemical preservative and its use as an isolate may be effective in preventing cancer caused by environmental conditions (Nkrumah-Elie et al., 2012).

CONCLUSIONS

Millions of people lose their lives every year from cancer, which has become one of the most important health problems today, and the incidence of cancer and the death rate are still increasing. Especially the frequent occurrence of breast cancer, which is increasing day by day, and its increasing incidence, its early detection and high treatment success, increase the importance of breast cancer. However, during the treatment process of breast cancer, resistance to drugs may occur, so patients may turn to herbal treatment methods. For this reason, plants have been used for a long time in the treatment of breast cancer. For this reason, it is necessary to further investigate the effects of breast cancer preventive agents from plant sources and to reveal the effectiveness of plants that can be used in the treatment of breast cancer.

REFERENCES

Andersen, J.L.M., Hansen, L., Thomsen, B.L.R., Christiansen, L.R., Dragsted, L.O., Olsen, A. (2019). Pre- and post-diagnostic intake of whole grain and dairy products and breast cancer prognosis: the Danish Diet, Cancer and Health cohort. Breast Cancer Research and Treatment, 179(3): 743-53.

Anonymous (2020a). American Cancer Society recommendations for early breast cancer detection in women without breast symptoms. (http://www.cancer.org/cancer/breastcancer/screening-tests-and-earlydetection.html.) (Accessed date: 11.12.2022).

Anonymous (2020b). Türk Meme Vakfı. (https://www.memekanseri.org.tr/) (Accessed date: 20.08.2022)

Bachmeier, B. E., Mirisola, V., Romeo, F., Generoso, L., Esposito, A., Dell'Eva, R., ... & Pfeffer, U. (2010). Reference profile correlation reveals estrogen-like trancriptional activity of curcumin. Cellular Physiology and Biochemistry, 26(3): 471-482.

Bao, P.P., Lu, W., & Cui, Y. (2012). Ginseng and Ganoderma lucidum use after breast cancer diagnosis and quality of life: a report from the Shanghai Breast Cancer Survival Study, PLoSOne, 7(6), e39343.

Bar-Sela, G., Epelbaum, R., & Schaffer, M. (2010). Curcumin as an anti-cancer agent: review of the gap between basic and clinical applications. Current Medicinal Chemistry, 17(3): 190-197.

Barton, D. L., Soori, G. S., Bauer, B. A., Sloan, J. A., Johnson, P. A., Figueras, C., ... & Loprinzi, C. L. (2010). Pilot study of Panax quinquefolius (American ginseng) to improve cancer-related fatigue: a randomized, double-blind, dose-finding evaluation: NCCTG trial N03CA. Supportive Care in Cancer, 18(2): 179-187.

Baytop T. (1999). Türkiye'de Bitkilerle Tedavi. Nobel Tıp Kitabevi, İstanbul, ISBN No: 9754200211.

Biswas, J., Sinha, D., Mukherjee, S., Roy, S., Siddiqi, M., & Roy, M. (2010). Curcumin protects DNA damage in a chronically arsenic-exposed population of West Bengal. Human & Experimental Toxicology, 29(6): 513-524.

Borrelli, F., Ernst, E. (2002*). Cimicifuga racemosa*: A systematic review of its clinical efficacy. European Journal of Clinical Pharmacology, 58: 235-241.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., & Jemal, A. (2018). Global cancer statistics. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: Cancer Journal of Clinicians, 68: 394-424.

Coleman, C. I., Hebert, J. H., & Reddy, P. (2003). The effects of Panax ginseng on quality of life, Journal of Clinical Pharmacy and Therapeutics, 28(1): 5-15.

Cui, G. H., Tang, X. J., & Huang, L. Q. (2006). Application of multiplex allele-specific PCR for authentication of Panax ginseng and P. quinquefolius. Zhongguo Zhong yao za zhi= Zhongguo Zhongyao Zazhi= China Journal of Chinese Materia Medica, 31(23):1940-1943.

Çelik, F. (2006). Tea (*Camellia sinensis*); composition, the preventive effects on health and consumption: review. Turkiye Klinikleri Journal of Medical Sciences, 26(6): 642-648. (In Turkish).

Clark, C., Zheng, Z., Zhang, X., Carbo, D., Nathan, C. A., & Lvov, Y. (2010). Sonication-assisted synthesis of polyelectrolyte-coatedcurcumin nanoparticles. Langmuir, 26(11): 7679-7681.

Einbond, L. S., Soffritti, M., Degli Esposti, D., Tibaldi, E., Lauriola, M., Bua, L., ... & Wu, H. A. (2012). Chemopreventive potential of black cohosh on breast cancer in Sprague-Dawley rats. Anticancer Research, 32(1): 21-30.

El Bedoui, J., Oak, M., Anglard, P., & Schini-Kerth, V.B. (2005). Catechins prevent vascular smooth muscle cell invasion by inhibiting MT1-MMP activity and MMP-2 expression. Cardiovascular Research, 67: 317-325.

Ferrini, K., Ghelfi, F., Mannucci, R., & Titta, L. (2015). Lifestyle, nutrition and breast cancer: facts and presumptions for consideration. Ecancermedicalscience, 9: 557.

Galván-Salazar, H.R., Arreola-Cruz, A., Madrigal-Pérez, D., Soriano-Hernández, A.D., Guzman-Esquivel, J., Montes-Galindo, D.A., López-Flores, R.A., Espinoza-Gomez, F., Rodríguez-Sanchez, I.P., Newton-Sanchez, O.A., Lara-Esqueda, A., Martinez-Fierro, M.L., Briseño-Gomez, X.G., & Delgado-Enciso, I. (2015). Association of milk and meat consumption with the development of breast cancer in a western mexican population. Breast Care (Basel), 10(6): 393-396.

Ganz, P. A., Desmond, K. A., & Leedham, B. (2002). Quality of life in breast cancer survivors. J. Nat. Cancer Inst, 94: 39-49.

Gardner, Z.E., & McGuffin, M. (2013). American Herbal Products Association's Botanical Safety Handbook, 2nd ed.; CRC Press: Boca Raton, FL, USA, ISBN 9781466516953.

George, T.O., Allo, T.A., Amoo, E.O., & Olonade, O. (2019). Knowledge and attitudes about breast cancer among women: a wake-up call in Nigeria. Open Access Macedonian Journal of Medical Science, 7: 1700-1705.

Globocan (2018). Turkey Source: Internatıonal agency for research on cancer, Ed: World Health Organization.

Globocan (2020). International Agancy for Research on Cancer, 2020. Breast cancer, Estimated incidence, mortality and prevalence worldwide in 2020. Pupulation fact sheet in turkey. (http://globocan.iarc.fr/Pages/fact sheets population.aspx?country=792) (Accessed date: 20.08.2022)

Griva, F., Anagnostopoulos, F., & Madoglou, S. (2009). Mammography screening and the theory of planned behavior: suggestions toward an extended model of prediction. Women Health, 49: 662-681.

Hagen, K.B., Aas, T., Kvaløy, J.T., Søiland, H., & Lind, R. (2018). Diet in women with breast cancer compared to healthy controls - What is the difference? European Journal of Oncology Nursing, 32: 20-24.

Kalluru, H., Kondaveeti, S. S., Telapolu, S., & Kalachaveedu, M. (2020). Turmeric supplementation improves the quality of life and hematological parameters in breast cancer patients on paclitaxel chemotherapy: A case series. Complementary Therapies in Clinical Practice, 41: 101247.

Karak, T., Kutu, F.R., Nath, J.R., Sonar, I., Paul, R.K., Boruah, R.K., Sanyal, S., Sabhapondıt, S., & Dutta, A.K. (2015). Micronutrients (B, Co, Cu, Fe, Mn, Mo, and Zn) content in made tea (*Camellia sinensis* L.) and tea infusion with health prospect: A critical review. Critical Reviews Food Science and Nutrition, 57(14): 2996-3034.

Karkanis, A., Bilalis, D., & Efthimiadou, A. (2011). Cultivation of milk thistle (*Silybum marianum* L. Gaertn.), a medicinal weed. Industrial Crops and Products, 34(1): 825-830.

Kato, Y., Maeda, T., Suzuki, A., & Baba, Y. (2018). Cancer metabolism: new insights into classic characteristics. Japanese Dental Science Review, 54(1): 8-21.

Kurt, H., Keşkek, Ş. Ö., Çil, T., & Canataroğlu, A. (2013). Complementary/alternative therapies in patients with breast cancer. Turkish Journal of Oncology, 28(1): 10-15.(In Turkish).

Kütevin, Z., & Türkeş, T. (1987). Sebzecilik ve Genel Sebze Tarımı Prensipleri ve Pratik Sebzecilik Yöntemleri. İnkilap Kitabevi, Ankara cad: 95, İstanbul

Lai, Y. H., So, P. K., Lo, S. C. L., Ng, E. W. Y., Poon, T. C. W., & Yao, Z. P. (2012). Rapid differentiation of Panax ginseng and Panax quinquefolius by matrix-assisted laser desorption/ionization mass spectrometry. Analytica Chimica Acta, 753: 73-81.

Leach, M. J., & Moore, V. (2012). Black cohosh (*Cimicifuga* spp.) for menopausal symptoms. Cochrane Database of Systematic Reviews, 12:CD007244.

Lopes, C. M., Dourado, A., & Oliveira, R. (2017). Phytotherapy and nutritional supplements on breast cancer. BioMed Research International, Article ID 7207983.

Luo,T., Wang, J., Yin, Y., Hua, H., Jing, J., Sun, X., Li, M., Zhang, Y., & Jiang, Y. (2010). (-)- Epigallocatechin gallate sensitizes breast cancer cells to paclitaxel in a murine model of breast carcinoma. Breast Cancer Research, 12(1):R8.

Maliou D, & Bitam A. (2015). Implication of milk and dairy products consumption through insulin-like growth factor-I in induction of breast cancer risk factors in women. Nutrition Clinique et Métabolisme, 29(4): 219-225.

Maniam S, & Maniam S. (2020). Cancer cell metabolites: Updates on current tracing methods. ChemBioChem, 21(24): 3476-3488.

Nicastro, H.L., Ross, S.A., & Milner, J.A. (2015). Garlic and onions: Their cancer prevention properties. Cancer Prevention Research (Philadelphia), 8(3): 181-189.

Nilsson, L.M., Winkvist, A., Esberg, A., Jansson, J. H., Wennberg, P., Van Guelpen, B., & Johansson, I. (2020). Dairy products and cancer risk in a Northern Sweden population. Nutrition and Cancer, 72(3): 409-420.

Nkrumah-Elie, Y. M., Reuben, J. S., Hudson, A., Taka, E., Badisa, R., Ardley, T., ... & Darling-Reed, S. F. (2012). Diallyl trisulfide as an inhibitor of benzo (a) pyrene-induced precancerous carcinogenesis in MCF-10A cells. Food and Chemical Toxicology, 50(7): 2524-2530.

Oak, M.H., El Bedoui, J., & Schini-Kerth, V.B. (2005). Antiangiogenic properties of natural polyphenols from red wine and gren tea. The Journal of Nutritional Biochemistry, 16: 1-8.

Öğünç, A.V., Şehirli, A.Ö., Laçin, B.K., Ercan, F., Güçlü, H., & Topçu, G. (2016). Effect of green tea extract and whey proteins on experimental gastric ulcer model in rats. Academic Food Journal, 14(2): 111-122. (In Turkish).

Omosa, L. K., Midiwo, J. O., & Kuete, V. (2017). *Curcuma longa*. In: V.Kuete (Ed.). Medicinal Spices and Vegetables from Africa. Elsevier.

Predny, M.L. (2006). Black cohosh (*Actaea racemosa*): An annotated bibliography (Vol. 97). Southern Research Station.

Ravindran, J., Prasad, S., & Aggarwal, B. B. (2009). Curcumin and cancer cells: how many ways can curry kill tumor cells selectively? The AAPS journal, 11(3): 495-510.

Rothenberg, D. O. N., Zhou, C., & Zhang, L. (2018). A review on the weight-loss effects of oxidized tea polyphenols. Molecules, 23(5): 1176.

Sajithlal, G. B., Chithra, P., & Chandrakasan, G. (1998). Effect of curcumin on the advanced glycation and cross-linking of collagen in diabetic rats. Biochemical Pharmacology, 56(12): 1607-1614.

Sikora, E., Scapagnini, G., & Barbagallo, M. (2010). Curcumin, inflammation, ageing and age-related diseases. Immunity & Ageing, 7(1): 1-4.

Stendell-Hollis, N.R., Thomson, C.A., Thompson, P.A., Bea, J.W., Cussler, E.C., & Hakim, I.A. (2010). Green tea improves metabolic biomarkers, not weight or body composition: a pilot study in overweight breast cancer survivors. Journal of Human Nutrition and Dietetics, 23(6):590-600.

Sun, D., Zhuang, X., Xiang, X., Liu, Y., Zhang, S., Liu, C., ... & Zhang, H. G. (2010). A novel nanoparticle drug delivery system: the anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes. Molecular Therapy, 18(9): 1606-1614.

Tamayo, C., & Diamond, S. (2007). Review of clinical trials evaluating safety and efficacy of milk thistle (*Silybum marianum* [L.] Gaertn.). Integrative Cancer Therapies, 6(2): 146-157.

Tang, G. Y., Meng, X., Gan, R. Y., Zhao, C. N., Liu, Q., Feng, Y. B., ... & Li, H. B. (2019). Health functions and related molecular mechanisms of tea components: An update review. International Journal of Molecular Sciences, 20(24): 6196.

Turan, N., Öztürk, A., & Kaya, N. (2010). A new responsibility in nursing: Complementary therapy. Maltepe Üniversitesi Hemşirelik Bilim ve Sanatı Dergisi, 3(1): 103-108.

Vallianou, N. G., Evangelopoulos, A., Schizas, N., & Kazazis, C. (2015). Potential anticancer properties and mechanisms of action of curcumin. Anticancer Research, 35(2): 645-651.

Vidal M., Carvalho C., Bispo R. (2013). Use of complementary and alternative medicine in a sample of women with breast cancer. SAGE Open. 3(3):1-4.

Wanchai A., Armer J. M., Stewart B. R. (2010). Complementary and alternative medicine use among women with breast cancer: a systematic review. Clinical Journal of Oncology Nursing, 14(4):E45–E55.

White J, Kearins O, Dodwell D, Horgan K, Hanby AM, Speirs V. (2011). Male breast carcinoma: increased awareness needed. Breast Cancer Res., 13(5):219.

WHO. (2015). World health statistics 2015. World Health Organization.

Wu, A.H., Spicer, D., Stanczyk, F.Z., Tseng, C., Yang, C.S., & Pike, M.C. (2012). Effect of 2-month controlled green tea intervention on lipoprotein cholesterol, glucose, and hormone levels in healthy postmenopausal women. Cancer Prevention Research, 5(3): 393- 402.

Wu, A.H., Yu, M.C., Tseng, C., Hankin, J., & Pike, M.C. (2003). Green tea and risk of breast cancer in Asian Americans. International Journal of Cancer, 106(4): 574-579.

Wu, G., Lu, J., Guo, J. (2012).“Ganoderic acid DM, a naturaltriterpenoid, induces DNA damage, G1 cell cycle arrest and apoptosis in human breast cancer cells. Fitoterapia, 83(2): 408-414.

Wuttke, W., Seidlova-Wuttke, D., & Gorkow, C. (2003). The cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. Maturitas, 44: S67-S77.

Zang J, Shen M, Du S, Chen T, Zou S. (2015). The association between dairy intake and breast cancer in Western and Asian Populations: A systematic review and meta-analysis. Journal of Breast Cancer, 18(4):313-22.

İKSAD Publishing House
ISBN: 978-625-6955-52-3