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THE CHEMICAL COMPOSITION OF SALVIA FRUTICOSA GROWING IN NORTH CYPRUS

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DEPARTMENT OF PHARMACOGNOSY

EVALUATION OF OPINIONS OF TEACHERS

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Approval

We certify that we have read the thesis submitted by Muhammad Umar Mustapha titled **"THE CHEMICAL COMPOSITION OF *SALVIA FRUTICOSA* GROWING IN NORTH CYPRUS"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Educational Sciences.

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Declaration

I hereby declare that all information, documents, analysis and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

MUHAMMAD UMAR MUSTAPHA

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With sincere appreciation and a grateful heart.

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Abstract

Ethnopharmacological Relevance: *S. fruticosa* is utilized to cure a variety of chest and stomach conditions. The plant's essential oil or infusion is used to treat skin conditions, diabetes, hypertension, rheumatism, toothaches, and stomachaches.

Purpose of study and Significance of the study

The main objective of this study was to evaluate the chemical composition of *Salvia fruticosa* essential oil obtained from Cyprus and compare it with that of other Mediterranean regions. The purpose of the study was to determine whether there was a notable change in the chemical structure of the essential oil between various geographical regions in the region. The research also looks for any possible geographic characteristics that can lead to changes in the composition of the essential oils, finally determining whether one region has a better profile than the other. This study is important because it sheds light on how environmental factors affect the chemical makeup of essential oils, assisting in the selection of the best sources for potential applications in a variety of industries, including aromatherapy, natural products, and the pharmaceutical sector.

Results: The outcomes of the hydrodistillation procedure and subsequent examination of the essential oil extracted from *Salvia fruticosa*. Notably, 1,8-cineole (20.0%) and camphor (30.0%) were found to be the essential oil's main ingredients and were therefore designated as its main components. it was found that some specific chemical components were present in some geographical region but not in other regions. Additionally, there were significant differences in the percentage yield of different chemicals between the geographical regions, which was likely influenced by regional environmental conditions.

Keywords: Salvia fruticosa, 1,8-cineole, Camphor, Hydrodistillation, GC, GC-MS.

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CHAPTER I
Introduction

1.1 Background study of plant usage

Humans have undoubtedly benefited from the identification of food and medicine-useful medicinal and fragrant plants before the concept of history even existed. Early humans may progress civilization and improve their own and their society's health when they learnt to identify and consume particular plants. Every civilisation would adopt traditional medicine as a part of life support systems using medicinal and aromatic herbs extensively. To determine if a plant was useful for food or medicine, it is obvious that the range of accessible plant components would need to be tasted and evaluated. Today, people consume a wide variety of easily accessible herbs and spices, which continue to support optimum health. As the advantages of medicinal and aromatic plants become more widely known, humanity will increasingly rely on them. Natural products varied architectures and complex carbon skeletons are to blame for the significant role they play in drug development. Due to the fact that living systems have allowed secondary metabolites obtained from natural sources to evolve, we often consider them to exhibit greater "drug likeness and biological friendliness than totally synthetic molecules" (Koehn, 2005) making them promising candidates for drug development (Balunas, 2005) (Drahl, 2005).

According to fossil investigations conducted by (Solecki, 1975), The traditional medical systems initially appeared during the Middle Paleolithic which was about 60,000 years ago. The usefulness of plants as a technique of therapeutic compounds has been included into the primary mode of health care for over 65% of the global population, according to the (WHO) world health organisation. (Farnsworth, 1985). According to (Farnsworth, 1976) and (Raskin I, 2004), 25% of all medications prescribed today are derived from plants. The earliest record of the use of medicinal herbs for the production of pharmaceuticals is found on a Sumerian clay slab from Nagpur that is 5000 years old. More than 250 different plants were mentioned in its 12 drug preparation instructions, some of which contained alkaloids, such as mandrake, henbane, and poppy. (Kelly, 2009). By using plants as a source of traditional medicine, many disorders may be treated with fewer side effects (Bako, 2015). Plants that have chemicals with pharmacological activity can be exploited to make medicines commercially. The value of plant diversity in the treatment of illness has long been acknowledged. An examination of the literature indicates that more than 50,000 plant species are used in productive ways. In some developing countries, like the Turkish Republic of Northern Cyprus (TRNC), both contemporary drugs and herbal medicines are used in conjunction.

Due to the diverse spectrum of biological functions performed by *Salvia* species, much attention has been given to them (Askun, 2010) many researchers have concentrated on the pharmacological properties of the primary chemicals found in the essential oils made from *Salvia* species, such as their antibacterial, antispasmodic, antiseptic, cytostatic, antiviral, (Tada, 1994), antispasmodic, and antioxidant activities ((Janssen, 1987);(Gonzalez, 1989);(Darias, 1990),) activities. *Salvia* species are highly valued for their antioxidant,

antibacterial, anti-Alzheimer, and anticancer capabilities in the food, cosmetic, and pharmaceutical industries. (Senel, 2010), (Saricoban, 2004) and (Pavlidou, 2004).
Several kinds of plants belonging to the Lamiaceae family, popularly known as the mint family, are found in Cyprus. *Salvia fruticosa* (Greek sage), *Thymus capitatus* (Spanish oregano), and *Rosmarinus officinalis* (Rosemary) are a few of the Lamiaceae species that can be found in Cyprus. Numerous *Salvia* species are known to exist in the *Salvia* flora. *Salvia fruticosa* (Greek sage), *Salvia* judaica (Mediterranean sage), *Salvia* sclarea (clary sage), and *Salvia* verbenaca (wild clary sage) are the most well-known among them.

1.2 Lamiaceae family

The mint, deadnettle, and sage families are flowering plants that belong to the Lamiaceae or Labiatae family. Many of these plants have aromatic qualities throughout, and they include catnip, *Salvia*, bee balm, and other medical herbs in addition to commonly used culinary herbs like basil, mint, rosemary, sage, oregano, thyme, and others. The geographical distribution of the family is international. (Heywood, 2007) According to literature the enlarged Lamiaceae contain roughly 236 genera and 6,900–7,200 species, although the World Checklist lists 7,534. *Salvia* (900 species), are the largest genera, *Scutellaria* (360) follows, *Stachys* (300), *Plectranthus* (300), *Hyptis* (280), *Teucrium* (250), *Vitex* (250), *Thymus* (220), and *Nepeta* (200) and so on. In the past, there were about 400 species in the genus *Clerodendrum*, but by 2010, there were just about 150 left.
Lamiaceae family was said to comprise 8 subfamilies before, then this number increased to 10,
however, in recent years 2 more subfamilies have been added by the transfer of two new genera from the family Verbenaceae. Two of these subfamilies, Lamioideae and Nepetoideae, are wider than the others. In general, Nepetoideae contains mostly essential oil-rich genera. Numerous aromatic herbs and spices, including mint, thyme, oregano, and sage, are members of this subfamily. As a defense strategy against herbivores and pathogens, these plants produce essential oils, which are widely employed in medicine, food, or cosmetics.
The Nepetoideae subfamily of the Lamiaceae family is a fascinating group because of the wide variety of flowering plants it contains. This subfamily is a treasure trove of aromatic potency and has a great concentration of essential oils. *Salvia*, the sage genus, one of its prized members, emerges as a substantial contributor to its essential oil content in addition to being a member of the Nepetoideae family. *Salvia* is a prime example of the Nepetoideae subfamily's botanical prowess with its alluring scents and wealth of therapeutic potential.

1.3 Native location

Salvia (also often referred to as sage) gets its title from the Latin word salvare, which refers to healer. *Salvia* is a member of the Lamiaceae family and is regarded as one of its larger genera (Wu, et al., 2012). It consists of roughly 900 species that are found in South-West Asia, the Oriental Mediterranean, South Africa, and America (Tepe, 2008), (Maksimović, 2007). The family Lamiaceae, which has between 7,200 and 7,500 species, is a member of the Magnoliopsida subclass of flowering plants, also referred to as the dicots or flowering plant class. One of the two major classes of angiosperms (flowering plants), together with Liliopsida (monocots), is Magnoliopsida. Dicots are distinguished by their two cotyledons (seed leaves), net-like veins in their leaves, and often multiples of four or five in their arrangement of flower components. A significant family in the Magnoliopsida order is the Lamiaceae, which includes plants like mint, basil, rosemary, and lavender. With 88 species, 51 of which are indigenous, the *Salvia* genus of plants is among the most diverse in Turkey. The Lamiaceae family's aromatic perennial herb *S. triloba* L. (*S. fruticosa* Mill.), which is utilized both as a culinary and medicinal herb in Turkey, is regarded as the most economically significant *Salvia* species *S. triloba* L, often known as "Anatolian sage," is found in the countries of Albania, Cyprus, Greece, Italy, Syria, Lebanon, and Turkey in the eastern Mediterranean basin. (Hedge, 1892). Native to the Western and Eastern Mediterranean, which includes the region of North Africa, Italy, Turkey, Israel, Palestine, and the Canary Islands, *S. triloba* L. (syn. S. triloba L.fil.) is a member of the Lamiaceae family. According to the Kew checklist, *S. triloba* L has 19 synonyms in total. The World Checklist of Selected lists *S. triloba,* Three-lobed sage, *S. libanotica*, *S. lobryana,* and *S. cypria* among its commonly used names.

1.4 Highest essential oil yield

Several species of *Salvia* (sage), which belong to the Lamiaceae family, are known to contain essential oils. While the precise amount of essential oil might differ depending on a number of variables such plant type, growth environment, and extraction processes. One of the most commonly and frequently used species in the *Salvia* genus is *Salvia* officinalis (Common Sage). It is well known for having a significant amount of essential oil, especially in the leaves. *Salvia officinalis* essential oil is prized for its scent and medicinal qualities. *Salvia sclarea* and *Salvia lavandulifolia* come next.

1.5 History of *Salvia fruticosa*

Under the broad moniker of "elelisphakon," a particular plant's identity has been kept secret throughout historical documents. Sage's exact botanical classification, however, has been obscured by poor translations and misunderstandings, which has damaged its standing as a therapeutic herb. The restricted translation of the general name "elelisphakon" is frequently "garden sage" (*S. officinalis*). This imperfect translation, however, can be ascribed to recurrent errors that have led people to mistakenly attribute the intended species, *S. fruticosa*, rather than *S. officinalis*, with medicinal virtues. The "elelisphakos" referenced by Theophrastus (VI, 2, 5) in (Desfontaines, 1830) work is identified as *S. fruticosa*, which is further subdivided into wild and cultivated types. Given that *S. fruticosa* is the most common wild species in Greece and *S. officinalis* is quite rare in the wild, especially in areas south of Albania and Yugoslavia, this view gets plausibility. A Minoan fresco at Knossos on the island of Crete from around 1400 BCE shows *Salvia fruticosa.* Until it was determined that it was the same species described by Philip Miller in 1768, the plant was also known by the name *Salvia* triloba, given precedence by plant naming conventions to the earlier name given by Carl Linnaeus in 1781. (Clebsch, 2003). Due to its trifoliate leaves, which distinguish it distinctly from *S. officinalis*, A common name for it is three-lobed sage. The herb has been utilized in traditional medicine since 1400 B.C. ((Rivera, 1994.) and afterwards by Moroccan and Spanish herbalists. (Laguna, 1566) reported that this type of plant was regarded as the "holy herb" because it assisted women in becoming fruitful, referred to it as the "wild kind of sage,". According to (Wildeman, 1950), In the sixteenth century, the trifoliated sage that was grown in the botanical gardens of Belgium most likely originated in Spain. The value of *S. fruticosa* grown close to Salerno was noted in the saying "Cur moritur, qui Salvia crescit in horto," which means to "Why should he die who has sage in his garden?" (Pignatti, 1982)

Fig 1: *Salvia fruticosa* plant

1.6 Description of the plant

Greek sage is 2 feet (0.61 meters) tall and wide, and the stalks of flowers are at least 1 foot (0.30 meters) over the leaves. The plant has numerous different-sized leaves that grow in groups and is totally covered in hairs, giving it a shiny and hairy appearance. The whorls of pinkish-lavender, 0.5 in (1.3 cm) long blooms are held in a tiny, five-pointed, hairy calyx that is oxblood-red in colour. Although populations made up completely of *Salvia fruticosa* are not frequent in its natural habitat, it does thrive as a component of the Maquis shrubland and many other similar ecosystems. (Clebsch, 2003).

1.7 Chemical constituents

Salvia fruticosa, formerly known as *Salvia* triloba, is a three-lobed sage (Putievsky, 1986). The essential oil of three-lobed sage generally has low β- and α-thujone levels (less than 5%), and the primary components are 1,8-cineole (40-50%), camphor, (~10%), and α- and β-pinene (~10-20%) (Putievsky, 1986) (Laenger, 1996) (Lawrence, 1993). According to (Putievsky, 1986) *S. fruticosa*'s volatile oils contain monoterpene and sesquiterpene hydrocarbons (α-pinene, β-pinene, camphene, myrcene, and caryophyllene) as well as oxygenated monoterpenes (1,8-cineole, camphor, borneol, and α-terpinyl acetate). But not all *S. fruticosa* populations have the same essential oil composition. According to (Skoula, 2000), three populations of *S. fruticosa* growing naturally in the wild in Crete were genetically diverse, and this revealed significant variations in essential oil production and composition. In contrast to, (Putievsky., 1990) who found that the main volatile oils in *S. fruticosa* were 1,8- cineole, camphor, α-pinene, β-pinene, camphene, and myrcene. He did not identify α-thujone or β-thujone in other populations. The essential oil also known as apple oil, is taken from *S. fruticosa* foliage and stems devoid of galls and blossoms and contains between 55% and 62% 1,8-cineole (eucalyptol). *S. fruticosa* has been regarded as a highly prized medicine *Salvia* plant in the Mediterranean because of its high content of 1,8-cineol, even more so than *S. officinalis*. (Figueredo, 2012). By using GC and GCMS tests to examine the essential oil of the dried aerial parts, it was discovered that the monoterpene 1,8-cineol (eucalyptol) was a significant component of the oil. Other significant components of the oil included camphor, terpineol, sesquiterpene trans-caryophyllene, and the monoterpenes -pinene, -pinene, and -myrcene. These findings are in line with those of (Kosar, 2005)., who claimed 1,8-cineole is the main component of Salvia fruticosa essential oils native to Turkey, Greece, and Amman, Jordan. (Kosar, 2005) (Pitarokili, 2003), (Skoula, 2000), (Al-Kalaldeh, 2010), (Kosar, 2005). The main component of the essential oil of *S. fruticosa*, on the other hand, has reportedly been identified in some investigations as β-thujone (Longaray, 2007).

1.8 Phytochemical components of *Salvia* species

Diterpenoids, phenolic acids, triterpenoids, flavonoids, and saccharides are some of the main phytochemical components found in *Salvia* species (Zhou, 2009) (Zhang, 1994) . While phenolic acids and diterpenoids are primarily found in the roots of plants, flavonoids, triterpenoids, and monoterpenes are primarily dispersed in the aerial sections of plants, particularly in the flowers and leaves (Topcu, 2006). Diterpenoids and phenolic acids have distinctive distribution patterns among *Salvia* species, according to a phytochemical analysis.

1.9 Traditional uses

S. triloba, also known as "Adac ayi (sage)" or "Elma (apple)" because of the peasants' comparison of its galls to apples, it is used to treat a range of chest and stomach issues. Additionally, the plant's diuretic, stomachic, antibacterial, and wound-healing effects have been documented. Sage is grown and primarily utilized as a spice. This plant flourishes in profusion on the hills of Western Anatolia's mild climate. Elma yag (apple oil) is the name of the essential oil. The plant's essential oil or infusion is used to treat skin conditions, diabetes, hypertension, rheumatism, toothaches, and stomachaches (Baytop, 1999). This plant is used to treat a variety of skin, blood, and infectious diseases as well as ailments of the respiratory, digestive, circulatory, and osteomuscular systems (particularly the leaves) in the eastern Mediterranean region (Carmona, 2005) ; (Ali-Shtayeh, 2000) . According to (Pitarokili, 2003), It is additionally used to treat inflammation, hepatitis, and tuberculosis, as well as being a hypoglycemic plant. Additionally, they have antibacterial and antispasmodic properties and are commonly used in traditional medicine to treat gonorrhea, eye problems, and diarrhea. Additionally, *Salvia* species' essential oils are employed in cosmetics and perfumes as flavorings (Longaray, 2007); (kelen, 2008). The essential oil, also known as apple oil, is extracted from *S. triloba* foliage and branches devoid of galls and flowers. In the Mediterranean region, this *Salvia* species has been appreciated as a therapeutic herb even more highly than *S. officinalis* (Figueredo, 2012). Since ancient times, *Salvia* species have been offered for sale commercially for use as a spice to season meats like pig, sausage, and chicken. (Parry, 1969); (Stahl, 1973); (Rosengarten, 1973) (Morton, 1976). They are also used in therapy. Infusions made from the plant's essential oils and water extracts are sometimes applied topically to repair broken bones in addition to being inhaled in steam baths. No evidence has surfaced regarding any negative activity or toxicity symptoms related to the usage of this herb and all agreed that "if it does not benefit, it would not harm" (Interviews, 1998).

1.10 Limitations

Researching the chemical composition of *Salvia fruticosa* essential oil from diverse sources in Cyprus may be subject to a number of constraints. Some possible restrictions include:

- Sample Variability: The chemical make-up of the essential oil may naturally vary from place to place, depending on the soil, climate, and genetics of the plants. Finding samples that accurately reflect the whole population at each site might be difficult.
- Plant Material Availability: One potential drawback is the lack of *Salvia fruticosa* plants in the targeted places. It could be difficult to get to enough plants or to get samples when essential oil production is at its peak.
- External variables: The chemical makeup of essential oils can be impacted by external variables such climatic shifts, weather patterns, and environmental changes. These uncontrollable variables could introduce confounding variables that have an impact on the findings of the study.
- Time and Resources: Time, finances, and resources must be available for the sample collection, processing, and analysis phases of research initiatives. The size of the study or the number of samples that may be analyzed may be constrained by time constraints or resource constraints.
- Generalizability: The results of the study might only apply to the specific regions and circumstances in Cyprus. Care should be taken when extrapolating the findings to other areas or *Salvia fruticosa* species because variations in environmental conditions can have a major impact on the chemical makeup.

CHAPTER II
Literature Review

2.1 *Salvia fruticosa*

The Lamiaceae family are flowering plants, also referred to as the mint family, are enormous and diversified. (Raja, 2019). Typically, members of this family of plants are shrubs or herbs with aromatic compounds, such as essential oils, in their leaves or blooms. The medicinal properties of many geranium species are benefited from through the use of aromatherapy, cuisine, fragrance, and flavor. (Tamokou, 2017) A temperate to subtropical herbaceous family with over 40 species that can be found in Africa, Asia, and Europe. This shrub, formerly known as *Salvia* triloba L. fil., is classified as a member of the *Salvia* Section (=Eusphace Benth.), based on its staminal traits, the presence of gynostegium, and the more or less straight upper lip of the corolla. It is easily distinguishable from *S. officinalis* because to its trifoliate leaves. S. *interrupta* Schousboe, S. *pinnata* L., and S. *bracteata* Banks & Sol. are a few species with complex leaves that differ from it in that they are perennial plants or chamaephytes, not plants, and have pinnatisect or pointed leaves with five or more folioles. (Rosua, 1986) (Feinbrun-Dothan, 1978) (Hedge, 1972.). Additional suffruticose species were mentioned by (Boissier, 1879) from the Near East. At least the top leaves of this species, which have pointed leaves with small, linear, lanceolate lobes or folioles, encompass the inflorescence. Three-lobed sage exhibits diversity in terms of indumentum density, height, leaf shape, and spike length, according to (Hedge, 1972.) According to (Pignatti, 1982), The Murcian examples are notably different from the Palestinian examples in that they are slightly taller and have longer, greener leaves. (Feinbrun-Dothan, 1978). On the basis of leaf morphology, Murcian populations can be divided into two basic types: types with ovate-lanceolate leaves and types with ovate leaves.

According to (Bahadirli, 2022) the Thermo Scientific ISQ Single Quadrupole GC/MS (Gas Chromatography-Mass Spectrometry) equipment was used to examine the essential oils of *S. fruticosa* and S. *aramiensis*. Essential oil content from *S. fruticosa* and S. *aramiensis* was found to be 3.40 and 2.00 percent, respectively. 24 compounds, which amount to 99.35% of the essential oil of *S. fruticosa*, were discovered, while 13 compounds, which amount to 99.01% of the oil of S. *aramiensis*, were discovered. 1,8-cineole (29.04%) is one of *S.*

fruticosa's main constituents and 1,8-cineole(59.51%) is one of S. *aramiensis'* primary constituents.

The separation and identification of flavonoids were achieved using column chromatography of the crude extract from the aerial portion of S. chloroleuca. From this plant, several substances were initially isolated. Total phenolic content and FRAP value significantly correlated, and this finding is consistent with earlier *Salvia* research (Orhan I, 2007) . The potential antioxidant properties of *Salvia* species' aerial parts have already been proven using a number of techniques. Polyphenolic substances' capacity to stop lipid peroxidation and redox reactions is what gives them their antioxidant properties. Phytochemical substances with antioxidant properties belong to the class of flavonoids (Adom KK, 2002;). Therefore, it is plausible to suppose that the S. *chloroleuca* extract's reported antioxidant activity in our investigation may have been influenced by its flavonoid concentration. Low-density lipoprotein (LDL) oxidation is prevented by flavonoids, and they also lessen thrombotic tendencies, according to research. Flavonoids included in dietary plants may also reduce the incidence of coronary heart disease-related death in people (Hollman PC, 2010).

2.2 Phytochemical constituents of *Salvia* species

Salvia has a variety of chemical elements such as phenolic compounds, monoterpenes, flavonoids, diterpenes, organic acids, triterpenoids, essential oils, alkaloids (Bonito MC, 2011); (Bautista E, 2013); (Xue Y, 2014) (Pitarokili et al., 2003; Pavlidou et al., 2004), Al-Kalaldeh et al. (2010). Therefore, it is conceivable to conduct biological activity tests in the presence of these substances to look for biological effects like antioxidants, anti-inflammatory, antibacterial, antischistosomal pain relief in rheumatism and arthritis, constipation tonics, antinociceptive, or anticancer. Table 1 summarizes research on the various chemical elements of these phytochemicals discovered in Lamium species.

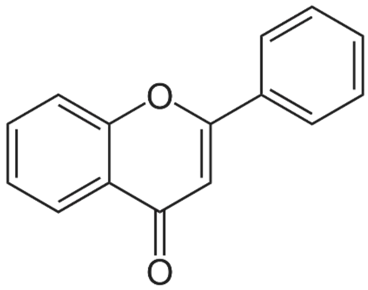
Table 1. Review studies of the phytochemicals present in *Salvia* species

Phytochemicals	Species	Compound	Reference
Phenolic compounds	*Salvia* officinalis	Rosmarinic acid	(Lu, 1999)
	Salvia miltiorrhiza	*Salvia*nolic acid	(Jung I, 2020)
	Salvia fruticosa	Carnosic acid	(Božić D, 2015)
Monoterpenes	*Salvia elegans*	Camphor	(Ali A,

			2015)
	Salvia sclarea	Linalool	(Kuźma L, 2009)
	Salvia lavandulifolia	1,8-Cineole (Eucalyptol)	(Porres-Martínez M, 2015)
Diterpene	*Salvia microphylla.*	Carnosic acid	(Aydogmus, 2006)
	Salvia miltiorrhiza	Tanshinones	(Jiang Z, 2019)
	Salvia divinorum	Salvinorin A	
Flavonoids	*Salvia officinalis*	Apigenin	(Aydogmus Z. Y., 2006)
	Salvia miltiorrhiza	*Salvia*nolic acids	(Jung I, 2020)
	Salvia hispanica	Quercetin	(Knez Hrnčič M, 2019)
Organic acids	*Salvia fruticose*	Carnosic acid	(Božić D, 2015)
	Salvia lavandulifolia	Rosmarinic acid	(Habán, 2019)
	Salvia officinalis	Rosmarinic acid	(Lu, 1999)
Essential oil	*Salvia sclarea*	linalyl acetate	(Kuźma L, 2009)
	Salvia fruticosa	α-thujone	(Schmiderer C, 2023)
	Salvia officinalis	α-pinene	(Ghorbani, 2017)

2.3 Flavonoids:

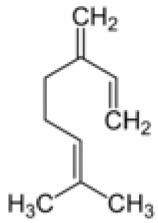
Flavonoids are a group of secondary polyphenolic metabolites that are present in plants. Chemically, flavonoids are composed of two phenyl rings (A and B) and a heterocyclic ring (C, the ring with the inserted oxygen), which together make up a 15-carbon skeleton. According to study, phenolic compounds have antiviral, anti-allergic, anti-inflammatory, and antioxidant activities. They are polyphenolic substances that may be found in nature, and depending on their chemical structure, flavonoids and other chemically structured substances (catechins, anthocyanidin, and chalcones) can be separated from them. Many of the flavonoids that have been discovered are found in foods such fruits, vegetables, and beverages. The molecular makeup of flavonoids dictates how effective they are as antioxidants. Among other biological roles, flavonoids offer defense against allergies, inflammation, platelet aggregation, microbes, ulcers, and cancer. (de Souza Farias SA, 2021).



2.4 Monoterpenes:

The class of terpenes known as monoterpenes, having the chemical formula C10H16, is made up of two isoprene units. These adaptable compounds can either be single-ringed (monocyclic) or fused (bicyclic) ring-structured, or they can be linear and unbranched (acyclic). Monoterpenoids are a subclass of monoterpenes that have undergone alterations, such as the removal of a methyl group or the addition of oxygen functionality. It is notable that there is such diversity among monoterpenes and monoterpenoids. Their importance is felt across many different businesses, including those that produce food, cosmetics, pharmaceuticals, and skincare. These substances are essential in creating the aromatic characteristics of many different natural sources. Their uses include developing alluring perfumes, powerful active chemicals, efficient insecticides, and delicious flavors, improving the caliber of goods and experiences in a variety of industries. (Breitmaier, 2006)

Monoterpenes are produced through biosynthesis from isopentenyl pyrophosphate units and are essential components in many natural sources. Acetyl-CoA is converted into this chemical building block by a sequence of reactions facilitated by the enzyme HMG-CoA reductase. The creation of isopentenyl pyrophosphate is guided by mevalonic acid's crucial function in this process. It's interesting to note that certain bacterial species and plant plastids have developed a different IPP production pathway known as the MEP (2-methyl-D-erythritol-4-phosphate) pathway. This unique route begins with C5 sugars and offers an unconnected route for IPP production. The enzyme known as isopentenyl pyrophosphate isomerase facilitates the conversion of IPP into DMAPP in either pathway, which is a crucial step in the production of monoterpenes. Myrcene is a well-known instance of a monoterpene chemical. As an acyclic structure, this particular monoterpene is categorized as an alkene hydrocarbon. Its existence demonstrates the intriguing diversity that monoterpene molecules can include, highlighting the complex and varied ways that these substances contribute to the natural world.



Myrcene

Another example of a monoterpenoid is linalool which is an acyclic monoterpenoid

linalool

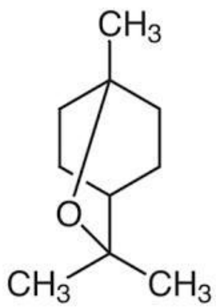
2.5 Primary component of *Salvia fruticosa*

Recent research has uncovered fascinating insights into the wide variation found in the amount and make-up of the essential oils present in different groups and clones of *Salvia fruticosa*. This plant miracle, also known as *Salvia fruticosa*, is remarkable for producing an enormous amount of essential oil, which is distinguished by a delicate pale-yellow tint. The complex composition of these oils has attracted a lot of interest, exposing a mix of different chemicals, each with special qualities of their own. However, camphor and 1,8-cineole, two important components, are at the core of this fragrant symphony. Among these essential oil constituents, 1,8-cineole stands out as a monoterpenoid that takes on the appearance of a colorless liquid and endows it with a feeling of purity.

2.6 1,8-cineole (Eucalytol):

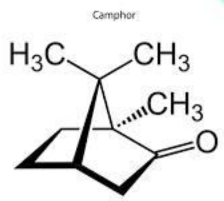
It has a bicyclic ether structure and emits a reviving camphor-like perfume that makes you think of nature's vigor. Despite being a liquid, this substance forms harmonious unions with a variety of organic solvents but does not dissolve in water. Its attractiveness is enhanced by the interaction between 1,8-cineole's chemical properties and its sensory appeal, which captures the essence of a multidimensional botanical gem.

The achiral component 1,8-cineole develops as an aromatic molecule with diverse botanical associations, frequently known as 1,8-cineole due to its presence in numerous plants. This amazing molecule has made itself at home in the leaves of many different plants, including the respected *Salvia* and the enduring Eucalyptus. Its new function as a rhizosphere volatile within the context of Arabidopsis has just come to light, adding to its already outstanding resume. The substance is referred to as a natural monoterpene, and its other name, "eucalyptol," reflects how commonplace it is in the Eucalyptus genus. 1,8-cineole, which has its roots in the oil of the Eucalyptus globulus, takes center stage as an important component of many plant essential oil compositions. When taken alone, this substance's unique properties stand out, especially for its substantial mucolytic and spasmolytic effects on the respiratory tract, an efficacy supported by clinical validation. Beyond these advantages for the respiratory system, 1,8-cineole also has therapeutic potential for inflammatory airway diseases like asthma and chronic obstructive pulmonary disease (COPD). These encouraging therapeutic benefits highlight the substance's complexity and position it as a natural medicine with the potential to improve wellbeing for those who are dealing with respiratory difficulties.

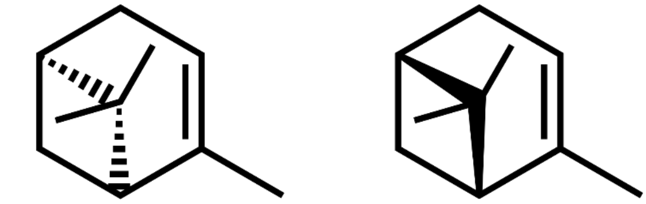


2.7 Camphor: A waxy, colorless solid with a strong fragrance, camphor is a compelling chemical with intriguing properties. The fact that it is classified as both a terpenoid and a cyclic ketone reflects the complexity of its several functions. The wood of the camphor laurel, formally known as Cinnamomum camphora, a large evergreen tree adorning the landscapes of East Asia, is where the alluring scent of camphor first appeared. The Dryobalanops genus tree known as the kapur tree, which is native to South East Asia, also contributes to the creation of this intriguing compound. Imagine camphor as a crystalline powder with a tint that reflects a spotless whiteness or colorlessness. However, its delicate exterior masks a strong olfactory identity that is similar to the unmistakable smell of mothballs. The physical characteristics of camphor, which have a density similar to water and a propensity to release volatile vapors at temperatures above 150 °F, highlight its fascinating complexity.

Camphor wears several hats in the realm of applications, demonstrating its value as a component in moth-proofing formulas, pharmacological concoctions, and flavor improvements. Camphor is a cyclic monoterpene ketone that has the structural characteristics of bornane while also accepting an oxo substituent in a particular place. Camphor is a plant metabolite that was created by nature and is carefully linked into the web of every other plant life. With its cyclic monoterpene ketone composition, this bornane monoterpenoid provides the world an alluring scent and is evidence of the amazing depths of nature's chemical symphony.

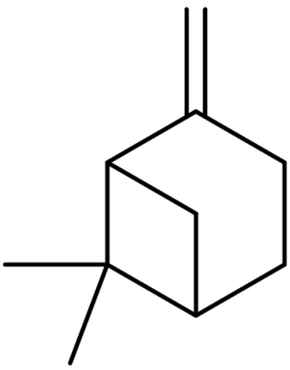


2.8 α-pinene*:* The pair of isomers known as pinene include alpha-pinene, a significant terpene component, as an organic molecule. Its presence in a wide variety of coniferous plants, most notably in the aromatic embrace of pine trees, distinguishes this terpene chemical component. α-pinene, a crucial component of these botanical wonders' alluring aromas, is tucked away in their oils where it works its olfactory magic. Alpha-pinene, which is well known for its aromatic attractiveness, frequently finds a beloved place inside essential oils, giving them a unique essence. These oils and diffusers take advantage of the chance to harness its delicious properties, improving the olfactory landscape. α-pinene claims its place as a key member of the monoterpene family, and plants liberally releases these chemicals into the atmosphere. These emissions, which are influenced by elements like temperature and light intensity, help maintain the delicate harmony of the olfactory tapestry of nature. α-pinene's voyage does not end with smell, though. This terpene engages in a lively ballet of chemical reactions as it interacts with the environment. It easily interacts with substances like ozone, the hydroxyl radical, and the NO3 radical, each of which has an impact on the complex chemistry taking on above. The interaction between alpha-pinene and its atmospheric counterparts weaves a story of chemical relationships that range from the realms of botany to the very heavens above, adding a layer of intricacy to the natural world.



(+)-α-pinene (−)-α-pinene

2.9 *β*-Pinene: an intriguing participant in the universe of organic compounds, tells its tale as a monoterpene that settles in the lively world of plants. It is one of the two unique isomers of the pinene family, together with its counterpart, *β*-pinene, and is considered a botanical gem. This colorless diamond dissolves easily in alcohol when it is liquid, yet it eludes water's grasp. The fact that *β*-pinene emits a perfume resembling the woodsy embrace of pine and fills the air with a verdant aura is evidence of its fragrant attractiveness. Going deep into the embrace of nature reveals that *β*-pinene is not alien to the lush kingdom. This essence stands out as one of the most prevalent among the many compounds weaved by forest trees, demonstrating its widespread presence. A fascinating transition happens when something is released into the air and mixes with oxygen. The development of the pinocarveol and myrtenol family is heralded by the oxidation of *β*-pinene, which results in a variety of compounds with allylic properties. In essence, -pinene weaves a tale of olfactory enchantment that reverberates over the vastness of woods and within the boundaries of plants. Its sophisticated chemistry and capacity to recall the aroma of pine serve as a showcase for the complex dance that occurs when organic compounds interact with the natural environment.



β-pinene

2.10 Biological activities of *Salvia* species

Sage (*Salvia* species) has been utilized for thousands of years as a herb having useful medicinal characteristics. Sage was frequently used in herbal tea blends before antibiotics were developed and was advised for tuberculosis patients to prevent sudation. Sage leaves also have a variety of biological properties, including being, micostatic, virustatic, antibacterial, astringent, and antihidrotic. (Anonymus, 1994).

2.11 Antimicrobial activity

Most frequently, the *Salvia* species essential oils with volatile monoterpenoids as their major constituents produce the most essential oils *S. officinalis* L., S. lavandulifolia Vahl., S. triloba L (*S. fruticosa* Mill.) are those that are most frequently claimed to have antibacterial activity.

Thujone (41.5%) and limonene (14.7%) make up the majority of the Egyptian sage essential oil, which exhibits antibacterial activity against yeast Saccharomyces cerevisiae (MIC 2.0 mg/1) and Gram-positive Sarcina spp., Staphylococcus aureus (MIC =1.0 mg/ml), and Staphylococcus aureus (MIC =1.0 mg/ml). Farag et al., 1989). According to (Kustrak, 1989), the composition of sage oil—specifically, the amounts of 1, 8-cineole, p-cymene, α- and β-thujone, and camphor—as well as the interactions between 1, 8-cineole, p-cymene, and ketonic compounds—determined the antibacterial activity (against Bacillus subtilis). Dalmatian sage oil's thujone concentration was said to be responsible for its antibacterial properties. (Jalsenjak, 1987) . Although there was a slight delay in reaching full activity, essential oil microencapsulation had no effect on antibacterial activity. Sage oil's antifungal activity was, however, hindered by microencapsulation.

Studies have shown Bacillus subtilis, Brevibacterium linens, Micrococcus luteus, and Seratia marcescens have all been reported to grow slowly in the presence of undiluted sage essential oil (*Salvia* officinalis). However, when tested against numerous types of bacteria and fungi, commercial sage essential oil, which may be a combination of *Salvia* triloba and *Salvia* lavandulifolia, showed no impact. (Biondi, 1993) . A similar lack of fungistatic effect was seen when *Salvia* triloba essential oil was tested against soilborne and foliar plant diseases. Malt Extract Agar (MEA) medium, which contains ground sage, did not exhibit any fungistatic activity against fungi that can contaminate food. (Schmitz, 1993) However, other research indicated that sage essential oil had a potent antifungal impact on Alternaria alternata and Aspergillus parasiticus. In these research, volatile oils typically displayed greater antifungistatic capabilities in comparison to studied extracts. (Crisan, 1975).

Significant growth inhibition of oral bacteria, including obligate anaerobes and capnophilic microaerophiles, has been observed for sage oil. (Farag., 1989b) It has demonstrated antibacterial action against a variety of bacteria, including Actinobacillus, Porphyromonas gingivalis, Peptostreptococcus anaerobius, Fusobacterium nucleatum, and Treponema denticola, among others. Only a few of the compounds are known to be accountable for the antibacterial properties including thujone and limonene. (farag., 1989a) , (Farag., 1989b) Additionally, sage essential oil has demonstrated a limited ability to inhibit the development of the bacteria Bacillus subtilis, Brevibacterium linens, Micrococcus luteus, and Seratia. Significant growth inhibition of oral bacteria, including obligate anaerobes and capnophilic microaerophiles, has been observed for sage oil. It has demonstrated antibacterial action against a variety of bacteria, including Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Peptostreptococcus anaerobius, Fusobacterium nucleatum, and Treponema denticola, among others. Some of the compounds suspected to be accountable for the antibacterial activity include thujone and limonene. Additionally, sage essential oil has demonstrated a limited ability to inhibit the growth of a number of bacteria, including Seratia marcescens, Micrococcus luteus, Brevibacterium linens, and Bacillus subtilis. However, compared to essential oils containing thymol or other chemicals with a phenolic-OH structure, its antibacterial effect is comparatively less potent.

Additionally, it has been noted that *Salvia* plebeia essential oil possesses fungitoxic potential and can stop the growth of the storage fungus Aspergillus flavus. (Mishra, 1990)

Additionally, a wider range of antibacterial potential is revealed by the field of botanical findings. Preparations made from additional *Salvia* species show promise outside the purview of *Salvia* officinalis. Diterpenoids and flavonoids, for example, compose a symphony of inhibitory power against bacterial and fungal foes inside their complex compositions. Particularly in this battle of the scents, *Salvia* apiana shows its strength. It has strong antibacterial and antifungal properties when taken as an extract, with carnosic acid, 16-hydroxycarnosic acid, and their derivatives taking the lead. These bioactive components of *Salvia* apiana's essence use their powerful inhibitory power to thwart the rogue advance of bacteria and fungus. But nuances still exist in this world of plants. Even though *Salvia* apiana's essential oil is esteemed in its own right, it has no effect on the tested organisms. The pair of oleanolic and ursolic acids, while each having merits of their own, have no effect on the organisms being studied. This complex interaction between plant components and microbial targets provides a window into the rich chemical fabric of nature. We are reminded that nature's pharmacopoeia is a symphony of intricacy, where specific combinations orchestrate various responses, as each component reveals its distinct tale of antimicrobial capability.(Dentali, 1992)

Investigating the dry methanolic extract of *Salvia* officinalis led to an unexpected discovery, despite the fact that it wasn't effective against Gram-negative bacteria. A remarkable efficacy against the threat posed by Gram-positive Staphylococcus aureus was included within its botanical essence. This specific extract, which comes from the illustrious *Salvia* officinalis, demonstrated its strength in the field of antibacterial action. However, its extraordinary impact was only apparent when dealing with Gram-positive bacteria. While Staphylococcus aureus, a renowned Gram-positive contender, was taking the stage, the curtain of antimicrobial action beautifully lowered upon it. Gram-negative counterparts were spared. This discovery emphasizes the complexity of interactions between different bacterial strains and plants. The ability to prevent bacterial development is not a property that all botanical entities share, but rather one that is carefully woven into the fabric of each botanical entity as nature's pharmacopeia unfolds its chapters. The dry methanolic extract of *Salvia* officinalis revealed its distinctive prowess against a particular bacterial adversary in the midst of this symphony of biochemical interactions, presenting us with an intriguing testimonial to the fascinating universe of natural substances. (Dobrynin, 1976) (Pavlenko, 1989).

2.12 Antioxidant activity

Sage leaves (*S. officinalis* L.) are recognized for their powerful antioxidant capacity based on phenolic structure. ((Chipault, 1956) ; (Farag, 1989) (Lamaison, 1991) ; (Schwarz, 1992) ; (Cuvelier, 1994). Sage extracts that are readily available commercially are mostly used in the food processing sector, although they may also be useful for human health. LDL oxidation was inhibited in a dose-dependent manner by all antioxidants. Carnosic acid, carnosol, and rosmarinic acid were the three most effective antioxidants in the HAEC system.

In a different investigation, column chromatography and HPLC were used to isolate the antioxidant components of sage oleoresin (Cuvelier, 1994). Six main chemicals were purified and recognized by IR, MS, and 1H NMR spectrometry: carnosol, carnosic acid, rosmadial, rosmanol, and methyl carnosate. All diterpenes—all but rosmadial—have two orthophenolic functionalities and one isopropyl group on the next carbon. They are all of the ferruginol type. They were found in sage and four commercial rosemary extracts, and an accelerated test was used to establish how effective they were at fighting free radicals (based on the disappearance of methyl linoleate in a lipophilic solvent under highly oxidizing circumstances). The most potent antioxidant was carnosic acid. The separation and purification of sage extracts using high-speed counter-current chromatography has also been successful (Fischer, (1991)) , and diets including rosemary or sage have yielded foods with enhanced quantities of carnosic acid. (Ternes, 1995). Sage was added to a unique mixture of seven herbal extracts to improve the immunological response in human haemolysate. This mixture decreased oxidative stress and malondialdehyde levels, which are indicators of free radical damage. In addition, antioxidant enzyme activity, particularly those of catalase and superoxide dismutase, rose. (Stajner, 1997) Sage cell suspension cultures are capable of generating rosmarinic acid, a naturally occurring antioxidant present in sage. The development and generation of rosmarinic acid by sage cells were found to be controlled by the kind of culture media by (Hippolyte, (1991).)(Hippolyte, Growth and rosmarinic acidproduction in cell suspension cultures of Salvia officinalis L.,, 1992) . The medium's composition could be improved to maximize the generation of rosmarinic acid. Cell growth kinetics and the timing of rosmarinic acid synthesis were both impacted by changes in the medium's composition

The bitter taste and potent perfume of aromatic plant extracts make them difficult to use as antioxidants in food products. However, a flavorless and odorless antioxidant made from sage and rosemary was created in 1977. In both animal and vegetable oils, it was shown to be an efficient antioxidant (Chang, 1977). Supercritical carbon dioxide extraction, a technique that allays worries about solvent residuals, was used to extract natural phenolic antioxidants from sage in a 1995 report. (Gerard, (1995).)

The appeal of natural antioxidants is growing in an environment where worries about the safety and acceptability of synthetic analogues loom large. This need, which is being driven by an increasing awareness of the source and effects of the chemicals we consume, highlights the promise provided by the products of nature. As potent equivalents for their synthetic counterparts, these include *Salvia* and a variety of aromatic and therapeutic herbs, ushering in a new era of safer alternatives. Antioxidants, those amazing substances that protect our bodies from oxidative stress, are in the midst of a revolutionary change. Natural sources are becoming more popular as customers want for confidence about the sources of the food they consume. There is a specific fascination to drugs made from plants that have long played important roles in traditional medicinal and culinary traditions. *Salvia* and its fragrant friends stand out as promising botanical jewels among this collection. This change involves adopting a worldview that mirrors the rhythms of nature itself, not just accepting a trend. The certainty of purity and safety reverberates with each twist of a leaf and each whisper of a herb's scent. *Salvia* and its relatives emerge as guardians of a new standard of wellbeing as the need for natural antioxidants increases, acting not only as substitutes but also as alternatives. They represent a link between contemporary sensibilities and nature's eternal wisdom, providing a way to make better decisions and ensure a more secure future.

2.13 Anti-inflammatory activity

Natural anti-inflammatory agents like carnosol have been proven to have an inhibitory effect on tumor-initiating activity in mice. (Huang, 1994) Additionally, sage contains substances like ursolic acid and oleanolic acid that may not have antioxidant action but have showed promise in studies on inflammation and cancer prevention. (Wu, 1998) These triterpenoids reduce inflammation and stop tumor growth in mouse skin. Recent research has further supported the anti-inflammatory properties of sage extracts, pointing to ursolic acid as the primary active component behind these effects. These discoveries expand the medicinal use of sage extracts. (Tokuda, 1986) . Naphthoquinones, which occur naturally and are substances implicated in the inflammatory process, have been highlighted for their medicinal potential. *Salvia* aethiopis naphthoquinone compounds have exhibited pharmacological similarities to non-steroidal anti-inflammatory (NSAI) drugs. In mouse models, a particular substance known as aethiopinone, an o-naphthoquinone diterpenoid found in the roots of S. aethiopis, showed potent anti-inflammatory and antinociceptive effects. It also prolonged bleeding in mice, similar to certain NSAI medications. Similar to reference NSAI medications like Aspirin, Ibuprofen, and Piroxicam, aethiopinone showed prevention of oedema production in mice models. Additionally, when given topically, it lessened ear oedema brought on by phorbolic ester. The substance demonstrated analgesic effects against painful heat stimuli, demonstrating both moderate peripheral and central analgesia. Despite having molecular similarities to antipyretic drugs like tanshinones, aethiopinone did not display antipyretic activity in yeast-induced hyperthermia testing in rats. (Hernández-Pérez, 1995)

Ursolic acid is a standout candidate in the complex field of curing diseases from the inside out. Against lymphatic leukemia cells (P-388 and L-1210) as well as human lung cancer cells (A-549), this extraordinary chemical has demonstrated its prowess, displaying a robust cytotoxicity that bears promise against these formidable foes. Ursolic acid reveals its dual function as a potent inhibitor of ornithine decarboxylase activity, a key participant in the intricate dance of tumor promotion caused by 12-O-tetradecanoylphorbol-13-acetate (TPA), similar to its counterpart carnosol. This dynamic action extends to the canvas of mouse skin, where TPA-induced tumor promotion occurs, and where its influence reverberates. Ursolic acid, a well-known inhibitor of tumor promotion, enters the complex orchestra of tumor prevention with an influence similar to that of retinoic acid. A symphony of trials shows that both ursolic acid and oleanolic acid take the lead in delaying the appearance of papillomas on the canvas of mouse skin when given prior to each TPA treatment. When compared to the control group, they not only reduce the occurrence of these undesirable formations, but also the typical number of papillomas per mouse. When given before to the initial TPA treatment, ursolic acid shines as a very strong force. Ursolic acid prefers to target the crucial cellular events in TPA-induced tumor promotion, as revealed by the complexity of its mechanism. It inhibits the growth of ornithine decarboxylase and polyamine levels similarly to retinoic acid and oleanolic acid, although its inhibitory mechanism is distinguished by subtle differences. The continual narrative of battling cancers and maintaining wellbeing weaves a vibrant tapestry of hope and possibility in this dance between substances, mechanisms, and outcomes. (Huang, 1994).

2.14 Antispasmodic activity

Additionally, it has been demonstrated that the extracts of sage (*Salvia* officinalis L. and *Salvia* triloba L.) exhibit antispasmodic effects in vitro, decreasing the contractions of smooth muscles induced by histamine, serotonin, acetylcholine, and barium chloride by 60 to 80%. However, a related experiment with extracts of vervain sage (S. verbenacea L.) revealed that this species enhanced the spasmogenic action of applied spasmogens on isolated smooth muscle segments of guinea pig ileum. (Todorov, 1984). Although some of sage. essential oil components like pinene (Taddei I., 1988) or borneol (in higher doses) (Cabo, 1986) show spasmogenic activity per se, dose-dependent antispasmodic activities of sage essential oil in vitro (guinea pig ileum) and in vivo (Giachetti, 1986) have been reported When tested for spasmolytic effect on isolated rat duodenum tissue, the S. lavandulifolia Vahl. essential oils were highly effective at inhibiting at least one of the chemical spasmogenic agents. ($BaCl_2$ and acetylcholine). (Cabo, 1986).

2.15 Hypoglycemic activity

Based on ethnopharmacological data and pharmacological studies, *S. officinalis* L. (Essway, 1995), S. lavandulifolia Vahl. ((Jimenez, 1986), S. triloba L (Yaniv, 1987) and S. aegyptyaca (Shabana, 1990) possess strong hypoglycaemic properties. In tests, it was discovered that *S. officinalis* essential oil (1950 mg/kg, i.p.) was hypoglicaemically active in both normal and alloxan-induced diabetic rats. The effects of S. lavandulifolia Vahl's aqueous extract on laboratory rats suggest that many synchronized processes may be responsible for the hypoglycemic action. (Zarzuelo, 1990) . These include enhanced peripheral glucose uptake, reduced intestinal glucose absorption, and potentiation of insulin release triggered by glucose. It has been suggested that the physiological basis for the hypoglycaemic activity of the S.

lavandulifolia aqueous extract in the case of prolonged administration is hyperplasia of pancreatic islet beta cells.

S. triloba leaf water extracts were tested on normoglycemic rabbits and on rabbits that had been administered alloxan to make them hyperglycemic. S. triloba is a plant that is commonly used in eastern Mediterranean folk medicine as a hypoglycemic agent. (Perfumi, 1991) . In alloxan-hyperglycemic rabbits, an oral dose of 0.250 g/kg body weight reduced blood glucose levels statistically significantly, but not in normoglycemic animals. In contrast, both normoglycaemic and alloxanhyperglycaemic rabbits that had been orally loaded with glucose experienced a hypoglycaemic reaction after a single dose of water extract. However, the plasma insulin levels in these animals were unaffected by the S. triloba extract. The hypoglycaemic effect of the medication was not observed in rabbits receiving intravenous glucose load. These findings imply that the S. triloba therapy causes hypoglycemia primarily via decreasing glucose absorption from the intestines.

2.16 Hypertoprotective effects

Strong antioxidant capacity has been shown by the methanolic extract of S. miltiorrhiza Bge. roots, as shown by its ability to scavenge 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and its ability to limit the production of free radicals. In cultured liver cells, it also demonstrates a cytoprotective action against t-BHP. Similar to this, it has been shown that the aqueous extract of S. miltiorrhiza roots possesses oxygen free radical scavenging action and protects against liver injury brought on by substances like carbon tetrachloride (CCl4). (Yang, 1990) (Yu, 1994) According to (Liu, 1992) , Salianolic acid (Sal A) has demonstrated the most powerful action against peroxidative damage in rat liver microsomes, hepatocytes, and erythrocytes among the phenolic compounds extracted from the aqueous extract. Sal A defends bio membranes by preventing lipid peroxidation's starting stage thanks to its many phenolic hydroxyl groups. Salianolic acid B (Sal B), a different polyphenolic antioxidant isolated from the roots of S. miltiorrhiza, has also demonstrated DPPH scavenging action. Sal B has demonstrated a number of positive effects, including the reduction of cholesterol in animals with hypercholesterolemia and the prevention of endothelial damage, increased vitamin E content in LDL, and suppression of LDL oxidative modification. (Wu, 1998).

Oleanolic acid and ursolic acid both have antihyperlipidemic characteristics and have been shown in animal experiments to be effective at preventing chemically induced liver damage. (Liu J. , 1995) . Although its hepatoprotective effects may differ depending on the specific toxicant, oleanolic acid has been shown to protect against a variety of hepatotoxicants, including CCl4, acetaminophen, cadmium, bromo-benzene-furosemide, colchicine, and Dgalactosamine. In contrast, ursolic acid is even more effective than oleanolic acid at preventing chemically induced liver damage. The suppression of liver cytochrome P-450 enzymes, which prevents the activation of toxins, as well as the augmentation of the body's defense mechanisms are the mechanisms behind hepatoprotection. These acids also promote liver regeneration and stop liver lesions from turning into fibrosis, which adds to their hepatoprotective properties. (Bombardelli, 1992)

CHAPTER III

Methodology

3.1 Methodology

The aim of this study was to determine the essential oil composition *of Salvia fruticosa* because of its possible therapeutic benefits, *Salvia fruticosa*, sometimes referred to as Greek sage or Jerusalem sage, is a medicinal herb that is frequently used in traditional medicine. The essential oil was distllated using the Clevenger Aparatus. *Salvia fruticosa* plant samples were gathered from their native habitat after ensuring the precise identification and authentication. Fig 3.1 The plant's volatile components, particularly its essential oil, were easier to separate with this distillation technique. A number of analytical methods, including gas chromatography-mass spectrometry (GC-MS), were used to evaluate the resultant essential oil in order to identify and measure the phytochemical components that were present. The goal of this study was to advance the knowledge about *Salvia fruticosa's* chemical composition in the Northern Cyprus and possible uses in a variety of fields, including pharmaceutical, scent, flavoring, and medicines. It might also serve as a starting point for more research into the biological effects and potential health advantages of *Salvia fruticosa* essential oil.

Figure 3.1: Air-dried *Salvia fruticosa* undergoing hydro-distillation

3.2 Materials and Methods

Plant material collection

To ensure a representative sample of botanical elements for further examination, the collection of leaves, flowers, and stems was carefully planned. *Salvia fruticosa* material was collected in the famous Northern Cyprus location of St. Hilarion Castle, which has the coordinates (35.308967, 33.250017). This location was carefully picked to capture the ecological diversity of the plant's native environment. The plant's phenological and reproductive stages were found to be best captured in April 2023, making the material that was gathered a true representation of the plant's biological makeup. The collection of the plant material was a painstaking process that was carried out with accuracy and respect for scientific integrity. For the delicate removal of leaves, blooms, and stems from the parent plant, specialized instruments like hand clipping scissors were used. The gathered material was carefully organized and shipped in a container so as to preserve its structural integrity and biological qualities. The herbarium sample, a representative of the gathered plant material, underwent thorough processing after successful acquisition to guarantee its taxonomic integrity and durability. To protect the sample from outside influences and prevent any potential degradation before taxonomic identification, a layer of newspaper was meticulously used. Asst. Prof. Dr. Azmi Hanoğlu, a recognized expert in botanical taxonomy, was tasked with the identification procedure, an essential component of botanical investigation. The herbarium sample was properly stored for future generations now that it had a taxonomically determined identity. The plant material dried in the shade and kept till distillation.

The voucher specimen kept in the Near East University Herbarium (NEUN), ensuring its accessibility for future scientific research, comparative studies, and taxonomic references.

3.3 Isolation of the essential oils

Salvia fruticosa essential oil distillation was pursued using a thorough methodology that involved a symphony of methods and tools. The use of the Clevenger apparatus, a recognized tool in the field of hydro-distillation, was essential to this endeavor. The thorough air-drying phase, which lasted 27 days, was the first step in this complex procedure. It started with the judicious curation of the plant material, which weighed 65 grams. The plant material was added to the Clevenger device along with one liter of water once it had dried to the desired stage. The use of this aqueous solution, which acts as a solvent to dissolve and transport the volatile chemicals present in plant material, facilitated the extraction of essential oils. With the application of controlled heat, the subsequent hydro-distillation process was started, causing the vaporization of water and the migration of volatile components, including the essential oil, through the apparatus. The essential oil was finally separated from the aqueous phase after a lengthy dance of vaporization and condensation inside the Clevenger device. Condensation made it easier for the essential oil to gather, separate from the water vapor, enabling its discrete collection. Over the course of three hours, the procedure was carefully carried out to ensure a balance between extraction effectiveness and preservation of the sensitive elements. Further investigation was done on this extracted essential oil, which is now a repository of the plant's fragrant and medicinal qualities. Chemical analysis was used to decipher its complex structure and identify the molecular ensemble that gave it its distinctive profile.

Figure 3.2: separated essential oil *Salvia fruticosa* from water

The essential oil was stored at (4^0C) until analysis. The oil yield was calculated as (2.1% w/v). The analytical effectiveness of Gas Chromatography-Mass Spectrometry (GC-MS) was used in the current work to reveal the complex chemical components cloaked inside the subject essential oils. By separating, identifying, and quantifying individual components, the GC-MS approach is hailed for its robustness and applicability in unraveling complicated mixtures in the broad field of analytical chemistry.

3.4 GC/MS Analysis

The GC/MS analysis was carried out with an Agilent 5975 GC-MSD system. Innowax FSC column (60 m x 0.25 mm, 0.25 μm film thickness) was used with helium as carrier gas (0.8 mL/min). GC oven temperature was kept at 60°C for 10 min and programmed to 220°C at a rate of 4°C/min, and kept constant at 220°C for 10 min and then programmed to 240°C at a rate of 1°C/min. Split ratio was adjusted at 40:1. The injector temperature was set at 250°C. Mass spectra were recorded at 70 eV. Mass range was from m/z 35 to 450.

3.5 GC- FID Analysis

The GC analysis was carried out using an Agilent 6890N GC system. FID detector temperature was 300°C. To obtain the same elution order with GC-MS, simultaneous auto-injection was done on a duplicate of the same column applying the same operational conditions. Relative percentage amounts of the separated compounds were calculated from FID chromatograms. Identification of the essential oil components were carried out by comparison of their relative retention times with those of certified standards or by comparison of their linear retention index (LRI) to series of n-alkanes. Computer matching against commercial (Wiley GC/MS Library, MassFinder3 Library) and in-house "Başer Library of Essential Oil Constituents" built up by genuine compounds and components of known oils, as well as MS literature data was used for the identification.

CHAPTER IV

Results and Discussion

A total of 32 elements, representing for 95.6% of the total essential oil, were identified and characterized thanks to the methodical application of these approaches. The study described here sheds light on the *Salvia fruticosa* essential oil's composition and reveals a substantial predominance of camphor (30.0%) compared to 1,8-cineole (eucalyptol) (20.0%). These two substances appear as the main components, and followed by borneol (10.5%), camphene (9.4%), and α-pinene (5.3%) following suit as important compounds.

Oxygenated monoterpenes were the major contributors to the percentage yield of the essential oil taking up (61.7%) with 1,8-cineole (eucalyptol) (20%) and camphor (30%) having the highest yield. Monoterpenes hydrocarbons such camphene (9.4%) and α-Pinene (5.3%) were the second major group with the highest yield followed by oxygenated sesquiterpenes (3.3%)

such as Caryophyllene oxide (1.6%), then sesquiterpenes hydrocarbon (3.1%) and Ester (2.1%).

These results support the compositional qualities reported here by (Putievsky E, 1992.) and (Askun, 2010) in their earlier research. The toxic properties of camphor have been emphasized by (Tirillini B, 1996) (Pattnaik S, 1997.), and (Tzakou O, 2001.) whereas the antibacterial significance of both 1,8-cineole (eucalyptol) and camphor has been reported. These findings are supported by the poisonous properties of camphor. Our investigation led to the discovery of 32 elements that together make up 95.6% of the total oil composition in the essential oil of *S. fruticosa*. The essential oil's yield was calculated to be (2.1%) (v/w). Surprisingly, a significant amount (61.7%) of the composition was made up of oxygenated monoterpenes, which can be attributable to the high concentrations of 1,8-cineole (20.0%), camphor (30.0%), and borneol (10.5%). Camphene (9.4%), α-pinene (5.3%), β-pinene (3.6%), limonene (2.7%), and myrcene (1.4%), all of which are categorized as monoterpene hydrocarbons, were additional important components. Additionally, traces of minor components that made up less than 1% of the total composition were found. It is interesting to note that 1,8-cineole (20.0%), camphene (9.4%), borneol (10.5%), camphor (30.0%), and α-pinene (5.3%) emerged as the major constituents in the *S. fruticosa* oil sample. These results correspond with those made by (Kosar, 2005) who determined that camphor and 1,8-cineole were the main components of Turkish *S. fruticosa* essential oil. (Pitarokili, 2003) identified comparable patterns for *S. fruticosa* from Greece. This thorough analysis highlights the major differences in the *S. fruticosa* essential oil composition across several geographic areas, deriving conclusions from both the body of current literature and significant empirical discoveries. These differences, according to (Perry, 1999) might be traced to a medley of environmental elements, such as meteorological circumstances, seasonal dynamics, geographic parameters, and genetic subtleties. Furthermore, it is widely known that the quantitative makeup of the oil is inextricably tied to the particular environment of the plant, as explained by (Karousou, (2005).) This study's main goal was to conduct a thorough analysis into the makeup of the essential oils found in *Salvia fruticosa* leaves. The essential oils from *S. fruticosa* leaves were effectively hydrodistilled, resulting in their peculiar yellowish colour and distinctive smell signature. We successfully outlined the qualitative and quantitative profiles of volatile components within the *S. fruticosa* leaf oil by using analytical techniques including Gas Chromatography with Flame Ionization Detection (GC-FID) and Gas Chromatography-Mass Spectrometry (GC-MS). A total of 32 elements, accounting for

95.6% of the composition overall, were identified and characterized thanks to the methodical application of these approaches.

Table 4.1: **Essential Oil Composition of *Salvia fruticosa***

RRI	Component	%
1014	Tricyclene	0.3
1032	α-Pinene	5.3
1035	α-Thujene	0.2
1076	Camphene	9.4
1118	β-Pinene	3.6
1132	Sabinene	0.1
1174	Myrcene	1.4
1188	α-Terpinene	0.2
1203	Limonene	2.7
1213	1,8-Cineole	20.0
1255	γ-Terpinene	0.3
1280	*p*-Cymene	tr
1298	Terpinolene	0.3
1437	α-Thujone	tr
1451	β-Thujone	0.5
1474	*trans*-Sabinene hydrate	0.2
1532	Camphor	30.0
1553	Linalool	0.5
1556	*cis*-Sabinene hydrate	0.2
1591	Bornyl acetate	2.1
1611	Terpinen-4-ol	0.9
1612	β-Caryophyllene	1.7
1628	Aromadendrene	1.4
1682	δ-Terpineol	0.1
1706	α-Terpineol	0.2
1719	Borneol	10.5

1864	*p*-Cymen-8-ol	0.2
2008	Caryophyllene oxide	1.6
2098	Globulol	0.4
2143	Rosifoliol	0.1
2144	Spathulenol	0.6
2257	*β*-Eudesmol	0.2
2324	Caryophylladienol II	0.2
2392	Caryophyllenol II	0.2
	Total	95.6

RRI: Relative retention indices calculated against *n*-alkanes; % calculated from total ion chromatogram (TIC); tr: Trace (tr<0.1 %),

Monoterpene hydrocarbon = 25.4%
Oxygenated monoterpene = 61.7%
Sesquiterpene hydrocarbon = 3.1%
Oxygenated sesquiterpene = 3.3%
Eester = 2.1%

The discussion below will provide data on the impact of various planting locations on three-lobed sage herb quantity characteristics and the comparison of essential oil content of the plant with the oil from other mediterranean region.

The essential oil produced from *Salvia* fruticosa in Northern Cyprus was extensively compared to equivalent products from Turkey, Libya, Egypt, Greece, and Italy in the current study. The goal of this thorough investigation was to clarify the complex connections between geographic locations and their effects on the percentage yield and phytochemical makeup of the essential oils. Intriguing differences in the discovered chemical compounds among nations are revealed by the systematic comparison. The large variance in the percentage yield of particular compounds further highlights how the geographic region affects the chemical composition of the essential oils. Notably, it was found that specific chemical components were present in some nations but not in others, demonstrating the distinctive phytochemical fingerprint of each location. Additionally, there were significant differences in the percentage yield of different chemicals between the nations, which was likely influenced by regional environmental conditions. Libya (49.34%), Greece (48.74%), and Egypt (44.70%) had the largest yields of 1,8-cineole, a substance with established medicinal value, among these variations. It should be noted that the essential oil from Cyprus stood out with a larger production of camphor (30%), highlighting the possible influence of geographic variations on the predominance of particular chemical elements. Additionally, when the various regions were compared, Egypt (5.66%), Cyprus (5.3%), and Libya (5.15%) contained more α-pinene than turkey (4.0%), greece (4.0%) and Italy (3.7%). This comparative study highlights the need for region-specific analyses when utilizing the potential advantages of these oils for various applications, as well as advances our understanding of the geographic influences on the composition of *Salvia* fruticosa essential oils. Camphene from Cyprus (9.4%), Greece (6.0%) and Egypt (8.72%) were found in abundant quantity while Turkey (4.4%), Libya (2.7%) and Italy (0.6%) possessed very little quantity. The chemical Myrcene, which had a concentration of (7.38%) in the Libyan sample, stood out among the studied locations in an amazing way. When analyzing the chemical makeup of essential oils, it's crucial to take the origin and environmental elements into account. This variance in chemical composition content between geographical regions proves this point. The complex interactions between geography, climate, and plant chemistry highlight the use of natural products in both therapeutic and industrial fields. The chemicals α-thujone and β-thujone are one of the major contributors to the essential oil of *Salvia* species but in the essential oil of *Salvia* fruticosa, little to no traces of them were detected.

Salvia fruticosa, commonly known as "Greek sage," has a variety of uses, including as a culinary herb, a component of traditional medicines, and a valuable resource in the food, pharmaceutical, and fragrance sectors (Rivera, 1994.) ; (Boelens. M. H. and Boelens, 1997) Greece, Turkey, Albania, and Cyprus are major suppliers of Greek sage, which is notable since it holds a crucial position in the global market (Putievsky E. R., 1986) . Greek sage essential oils have attracted a lot of attention due to their economic significance, which has prompted thorough examinations into their chemical make-up. The presence of l,8-cineole and/or camphor as distinctive components of *S. fruticosa* oils is highlighted by accumulated study data. The significant application of these oils in numerous fields highlights their relevance.

S. fruticosa plays a variety of functions in human pursuits, including culinary uses, therapeutic treatments, and the creation of fragrances and pharmaceutical goods. Due to the plant's extensive chemical capabilities, it has been incorporated into a variety of industries, benefiting both domestic and international businesses. Greek sage oils have become more well-known on the global market as a result of their distinctive chemical profiles, which have been thoroughly studied. The prevalence of particular chemical components, particularly l,8-

cineole and camphor, in *S. fruticosa* oils is supported by studies found across the literature. These oils' particular chemical makeup and geographic origin have undergone extensive study, revealing notable variances. It's interesting to observe that camphor emerges as a notable ingredient, frequently present in significant amounts in *S. fruticosa* essential oils. For example, camphor concentrations in wild populations from the island of Cyprus have been shown to reach up to 44.5% of the total oil content (Bellomaria, 1992) . This variety in composition emphasizes the botanical and chemical complexity of *S. fruticosa* as well as its significance in the local and global environment. These collective studies confirm the complex interactions between botany, chemistry, and practical uses. *S. fruticosa*'s multifarious qualities as the "Greek sage" are representative of its profound cultural and economic significance and serve as a witness to the complex relationships between nature, human use, and scientific investigation.

Beyond their practical uses, the constituents of this plant's essential oils have attracted significant study because of their diverse qualities, which include antioxidant, anticancer, anti-Alzheimer's, and antibacterial effects. These admirable qualities are not, however, immune from difficulties and complexity, which call for careful examination. Many human traditions have a long history of using *Salvia fruticosa*. Herbal tea is one way it enters our daily lives. It also contributes to the smells and scents that characterize the pharmaceutical sector and is used as an addition to make food goods more appealing. These various uses highlight the plant's and its constituents extensive influence in both practical and sensory spheres. Despite the appeal of its adaptable qualities, a few significant difficulties manifest. The biological activity that *S. fruticosa* imparts and its essential oil content are the main subjects of investigation. The ambiguity around the geographic provenance of the plant material used is a major problem in many investigations. The essential oil's chemical makeup may vary due to the absence of context, which could confuse the biological effects that have been noticed. The potential and ecological consequences of this plant may not be fully understood if agricultural concerns and conservation issues are neglected. Secondary metabolites, which are recognized for their sensitivity to degradation and instability, are the chemical components in charge of the biological actions that have been documented. Therefore, it is crucial to establish a strong link between the active substances and the resulting biological features. To do this, careful experimental design must be used, taking into account things like extraction techniques, seasonal fluctuations, and geographic affects. It is crucial to take on these difficulties in the quest to fully realize *Salvia fruticosa*'s medicinal potential. It is crucial to conduct thorough investigations that incorporate chemical, pharmacological, and botanical aspects. The entire potential of this plant can only be unlocked by thorough investigation, not just in terms of its use but also in terms of its ecological relevance and sustainable use.

CHAPTER V

Conclusion

The complex universe of phytochemistry and biological activity present in the native *Salvia fruticosa* Miller extracts from Cyprus have been elucidated by this ground-breaking research, in conclusion. Parallel to this, the thorough GC-MS analysis revealed the fascinating existence of 32 volatile chemicals, which together provided a diverse view into the chemical makeup of these extracts. The oxygenated monoterpenes, which made up a sizeable amount of the extract's composition (61.7%) were clearly the main component category. Notably, 1,8-cineole and camphor, two significant elements that play crucial roles in the intricate chemistry of these extracts, were added to the essential oil to enhance its potency. In the modern world, the idea of utilizing natural plants for medical purposes has gained more and more traction. Numerous studies have highlighted the therapeutic value of numerous plants, providing a compelling substitute for traditional treatment that is free from worries about side effects. Our thorough investigation reveals that *Salvia fruticosa* essential oil contains a wealth of phytochemicals that have the potential to be used as ointments or therapeutic agents. This is hugely important, especially now that researchers are working to transform medical paradigms without sacrificing adverse effects. Our research shows that *Salvia fruticosa* essential oil stands out as a strong contender with a variety of possible advantages. Analgesic, antibacterial, anti-inflammatory, antioxidant, antidiabetic, and anticancer qualities are only a few of its many beneficial qualities. The elevated levels of oxygenated monoterpenes, particularly 1,8-cineole (20%) and camphor (30%), are principally responsible for this range of effects, as well as the plant's potent medicinal properties. We have not only understood the complexity of *Salvia fruticosa* extracts but have also revealed a route for a future of alternative, successful, and side-effect-free medical therapies during this voyage of unlocking the mysteries of nature's gift. The exceptional qualities of this essential oil point to a bright future for improvements in healthcare that will be fueled by the fusion of ancient botanical knowledge and cutting-edge scientific research.

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Appendix X

Turnitin Similarity Report

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