

# A SYSTEMATIC REVIEW ON TRADITIONAL USE, PHYTOCHEMICAL AND PHARMACOLOGICAL PROPERTIES OF SOME MEDICINAL PLANTS GROWING IN KURDISTAN REGION – IRAQ

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## Abstract:

Many products labeled as "traditional herbal remedies" have a lengthy history of usage by definition of the term "traditional." Large segments of the population in many developing countries rely on traditional healers and their arsenal of medicinal plants to meet their healthcare requirements. Because of historical and cultural factors, herbal treatments are still widely used in modern medicine despite their antiquity. In industrialized nations, such things have become more accessible commercially. Current medical systems frequently recommend using chemicals in ways they weren't designed to be used. In certain parts of the world, the manufacture of herbal medicines are subjected to tight regulations, but this is not the case in other parts. In Germany Pharmacological goods are bound to the same criteria of efficacy, safety, and quality as herbal remedies, they are sold as "phytomedicines. On the other hand, most herbal products are marketed and monitored as food supplements in the United States, no pre-approval is required for this product category in the United Kingdom. As numerous academics in Iraq and the Kurdistan area have indicated, herbs have been utilized as a traditional cure for a wide range of illnesses in the past. Tribulus terrestris, Artemisia splendens Willd, Crataegus azarolus, Teucrium chamaedrys, Adiantum capillus-veneris and Matricaria chamomilla are the herbs discussed in this study, and their medicinal and traditional usage across the world, as well as some of the chemical components in these herbs' biological activity, are discussed.

**Keywords:** Medicinal Plants; Ethnopharmacology; Kurdistan-Iraq; Kodo Mountain; Phytochemistry.

## 1. Introduction

Most parts of the plants have some kind of medical use. Medicinal plants include a variety of secondary metabolites, many of which are helpful in the treatment of various ailments and are used in the production of drugs. Essential oil content varies based on the plant component, growth season, age of the plant, location, extraction methods, solvent, and time, among various factors [1]. Many plants have been shown to have numerous additional beneficial characteristics from the secondary metabolites or phytochemicals, such as antioxidant, anti-inflammatory, anti-insecticidal, anti-parasitic, antibiotic, and

anti-hemolytic capabilities, which have led to their widespread usage by indigenous peoples across the world [2]. About 80% of the world's population now relies on traditional medicine for their primary treatment, according to the World Health Organization. The creation of indigenous medicines and the usage of medicinal plants for the healing of a wide range of illnesses provides substantial economic benefits [3].

One of the greatest benefits of medicinal plants is their ability to improve the health of individuals and communities. There are a number of chemical active compounds in plants that have defined physiological effects on humans [4]. Phytochemicals provide the bioactivity in natural products and are often developed as a defensive mechanism for plants to ward off herbivory, pathogen assault, inter-plant competition, and abiotic stressors [5]. Some phytochemicals have been shown to inhibit carcinogens and function as antioxidants, while others have been used in therapies and preventative measures. Phytochemicals can work in the body in such ways that are complementary or overlap mechanism. For example, they can act as antioxidants, change the way enzymes work, boost the immune system, modify the hormonal response, stop bacteria and viruses from reproducing, and bind to cell walls to stop pathogens from sticking to them [6].

This review provides a comprehensive analysis of phytochemistry and biological studies on main six Kurdish medicinal plants (Table 1).

Table 1: Taxonomic Classification

Taxonomy	Tribulus Terrestris	Artemisia splendens Willd	Crataegus azarolus	Teucrium chamaedrys	Adiantum capillus-veneris	Matricaria chamomilla
Kingdom	Plantae	Plantae	Plantae	Plantae	Plantae	Plantae
Sub-kingdom	Tracheobionta	Tracheobionta	Tracheobionta	Tracheobionta	Tracheobionta	Tracheobionta
Division	Eudicots	Eudicots	Eudicots	Eudicots	Polypodiophyta	Eudicots
Class	Rosids	Asterids	Rosids	Asterids	Polypodiopsida	Asterids
Order	Zygophyllales	Asterales	Rosales	Lamiales	Polypodiales	Asterales
Family	Tribulaceae	Asteraceae	Rosaceae	Lamiaceae	Adiantaceae	Asteraceae
Genus	Tribulus	Artemisia L.	Crataegus	Teucrium	Adiantum L.	Matricaria

Species	T. terrestris	A. splendens Willd	C. azarolus	T. chamaedrys	A. capillus-veneris	M. chamomilla
Figure	Fig 1-A	Fig 1-B	Fig 1-C	Fig 1-D	Fig 1-E	Fig 1-F



Figure 1: Image of the Medicinal Plants; A) *Tribulus Terrestris*, B) *Artemisia splendens* Willd, C) *Crataegus azarolus*, D) *Teucrium chamaedrys*, E) *Adiantum capillus-veneris*, F) *Matricaria chamomilla*.

## 2. *Tribulus Terrestris*

*Tribulus terrestris* (TT) is one of the most important plants which is used commonly in various parts of the globe which can grow in many countries such as South Africa, Australia, India, and Europe, Iraq and Kurdistan region. This plant is rich contents of biologically active compounds and elements. These compounds are distributed in the leaves, flowers and fruits [7, 8].

### 2.1 Phytochemical Constituents

The chemistry of *Tribulus Terrestris* has been widely researched [9]. Among the numerous types of components, the most significant metabolites with varied bioactivities are steroidal saponins and flavonoids [10]. The saponins spirostanol and furostanol are thought to be the most distinctive chemicals in TT. These two steroidal saponins are thought to give TT its unique biological properties [11]. The flavonoids in TT are mostly quercetin, kaempferol, and isorhamnetin derivatives [12]. The foremost alkaloids isolated from the stems, leaves, and fruits of TT are tribulusamide C, tribulusterine, harmine, harman, N-transcoumaroyltyramine, N-transcafeoyltyramine, terretribisamide, (Fig. 2) [11].

The other components of TT are organic acids, amino acids, and other compounds. One of the organic acids extracted from TT is benzoic acid [10], vanillic acid, 2-methyl benzoic acid, ferulic acid [13], palmitic acid monoglyceride, succinic acid, docosanoic acid, and *Tribulus* acid [14]. Furthermore, the

primary amino acids are alanine and threonine. 4-ketopinoresinol, uracil nucleic acid, coumarin, emodin, and physcion are also found in TT [15].

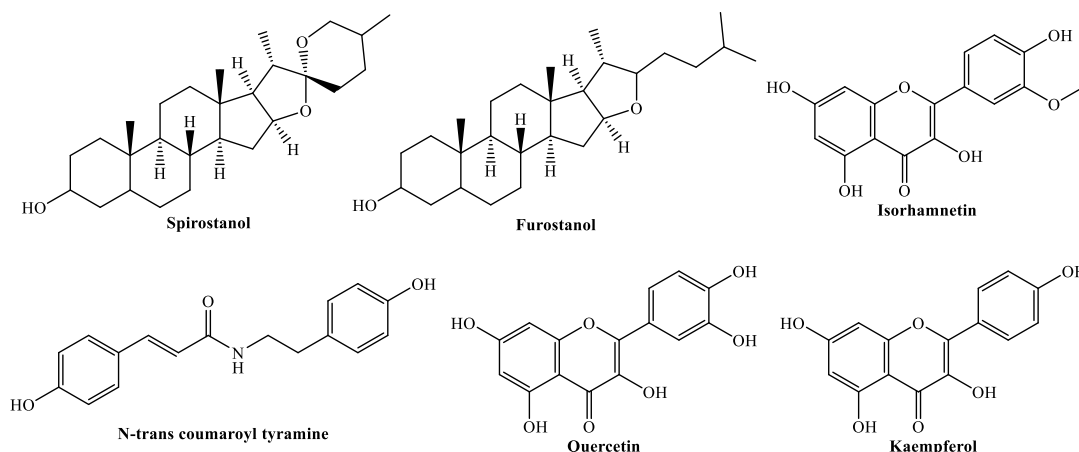


Figure 2: Structure of some chemical compounds found in Tribulus Terrestris

## 2.2 Biological activity of Tribulus Terrestris

Tribulus Terrestris extracts have yielded a diverse set of constituents with a variety of pharmacological activities and chemical structures. The most important constituents with various biological properties are steroidal saponins and flavonoids. The chemical composition of the extract depending on the extraction method and the plant parts studied [16].

The biological activities of Tribulus terrestris have been studied and shown to have Antibacterial activity [17], Antioxidant activity [18], Anticancer activity [19], Hepatoprotective activity [20].

Clinical research has shown that TT extracts can successfully treat infertility and menopausal symptoms in women [21].

## 2.3 Traditional uses of Tribulus Terrestris

The whole airborne plant (herb) of TT, including whole or clipped stems, leaves, flowers, and fruits, is utilized for therapeutic reasons. It has no distinct odor or taste [13].

The herb has been used to cure impotence, infertility, urinary issues, itchy skin, and purifying the blood in males and females. TT fruits are employed as a source of antiaging, cardiovascular, hepatic, and renal problems, besides its used as a treatment for antioxidative stress [22].

## 3. Artemisia splendens Willd

Artemisia splendens Willd, also known as Wormwood, is one of the most widely used herbs in traditional medicine and is typically used to treat conditions including cancer, hepatitis, malaria, and inflammation. A. splendens is found in mountains slopes at high or middle forest zones. It grows at inaccessible rock groves in dry or semi dry habitats. It is distributed in different parts of the world particularly in Europe, North America, Asia, and South Africa [23]. In Kurdistan of Iraq, it is existed in Gara mountain, Chamanke, Matin mountain, KaneMase. Common names: English: wormwood, sagewort, Kurdish: Giya band, Arabic: Sheeh

### 3.1 Phytochemical Constituents

The research into the phytochemical composition of *Artemisia* plants has revealed that the *Artemisia* species are rich of terpenoids and mostly made up of flavonoids, coumarins, caffeoylquinic acids, sterols, and acetylenes. A study indicated that the prevalent components of the oil of *A. splendens* among the 19 elements defined were 1,8-cineole (14.5%), germacrene D (14.3%),  $\alpha$ -pinene (11.3%), and bicyclogermacrene (11.3%), making up 93.3% of the total components found. Sesquiterpene hydrocarbons made up the majority (46.1%) of the oil, whereas oxygenated sesquiterpenes made up 9.8%. The proportions of monoterpene hydrocarbons were 18.1% while the oxygenated monoterpenes was 19.3% [24].

But according to [25], 1,8-cineol (4.7%), caryophyllene oxide (3.8%), valencene (3.5%), and terpinyl acetate (3.4%) were the primary volatile components of *A. splendens*, (Fig. 3).

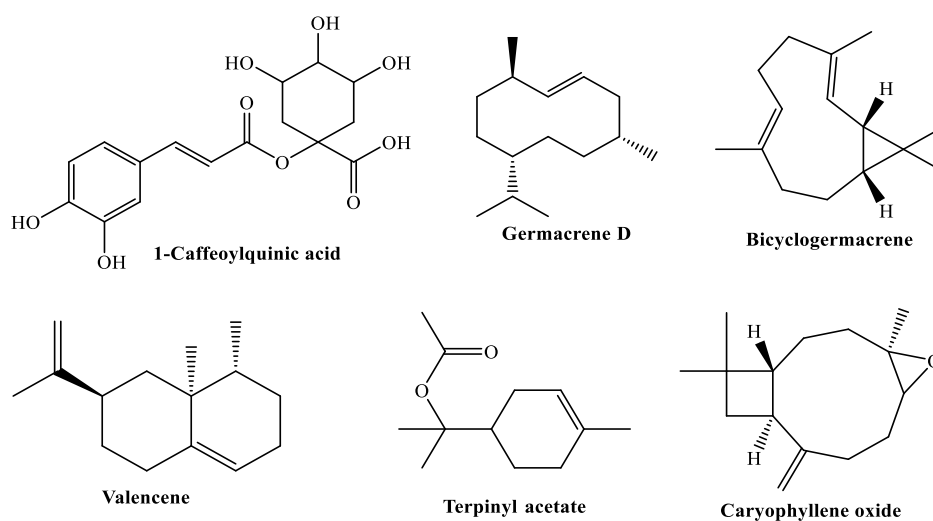


Figure 3: Structure of some chemical compounds found in *Artemisia splendens*

### 3.2 Biological activity of *Artemisia Splendens* Willd

Some studies have suggested that *Artemisia* species exhibit several pharmacological properties, including antiulcer, anticancer, antimalarial, hepatoprotective, antidiabetic, antioxidant, and antibacterial properties. *Artemisia*'s phenolic components (coumaric acid, gallic acid, chlorogenic salicylic acid, syringic acid, and vanillic acid) and flavonoids (quercetin and rutin) [26].

The inhibition of inflammatory regulators like bradykinins, histamine, prostaglandins, and serotonin are mediated by the plant's secondary metabolites, which include flavonoids and sesquiterpene-type compounds [27].

### 3.3 Traditional Uses of *Artemisia Splendens* Willd

*Artemisia* has been used for medicinal purpose for centuries. The traditional uses include: an antispasmodic, antidiabetic, anticoagulant, stomachic, heart stimulant, anthelmintic remedy for memory loss, hypertension treatment, liver inflammation, and sluggish mental performance [28]. Headaches, coughs, colds, dyspepsia, colic, malaria, diabetes, bladder and renal diseases, and as a purgative medicine are some conditions for which it has been used as a remedy [29]. In Chinese tradition, it has been used for remedy of different types of inflammatory diseases and fevers including

malaria [30]. In eastern and Egyptian medicine, Artemisia has been employed to treat cancer, inflammation, infections, digestive issues, and ulcerogenic illnesses [31, 32].

#### 4. Crataegus Azarolus

*Crataegus azarolus* L. is a rocky mountainside tree with a small round crown that grows to about 6 meters in height [33]. Commonly it is known as hawthorn, has been utilized for decades in alternative medicine and dietary supplements. It is a widespread plant in the Mediterranean Basin, occurring in similar habitats as the European common hawthorn. In Arab nations, it is the most popular hawthorn species. In Kurdistan region of Iraq, this herb is very common in Sulaimany governorate especially in Zalan and Qaradagh [34].

The used parts of this plant are flowers, leaves and fruits. Each part has an important role in treatment of different diseases.

Due to well-studied phytochemical makeup, bioactive components, and health advantages of hawthorn, it's considered classic natural products for cardiovascular health. For additional naturally health-promoting ingredients have separated, identified, and described, the majority of these investigations have focused on polyphenolic chemicals discovered in various hawthorn anatomical sections and extracts. Environmental factors, especially air, temperature and water availability, have a significant impact on plant distribution [35] There is a lot of evidence to suggest that this plant is beneficial to health, and it is clear that its medicinal potential is significant.

Common names: English (Hawthorn); Kurdish (Gohyshka zar, Gewzhi zard); Arabic (Zaaror) [36].

##### 4.1 Phytochemical Constituents

Plants create secondary metabolites such as vitamins, terpenoids, phenolic acids, flavonoids, quinines, and coumarins, which all have antioxidant characteristics [37]. Various investigations were conducted to explore the antioxidant activity and phenolic content of the flowers extract [38]. The (70% ethanol) extract showed the strongest diphenyl-1-picrylhydrazyl (DPPH) scavenging activity. Six chemicals belonging to triterpenes and phenolics were isolated from chloroform and n-butanol fractions. These chemicals are Ursolic acid, 3-O-acetyl ursolic acid, ellagic acid, quercetin 3-O-methyl ether, rutin, and apigenin 7-O-rutinoside [39]. The extract of ethyl acetate of *C. azarolus* yielded azarolic acid, a new ursane type triterpene acid, and eight other compounds. The other constituents were acids, sugars and sugar alcohols, minerals, vitamins, and amino acid composition, (Fig. 4) [40].

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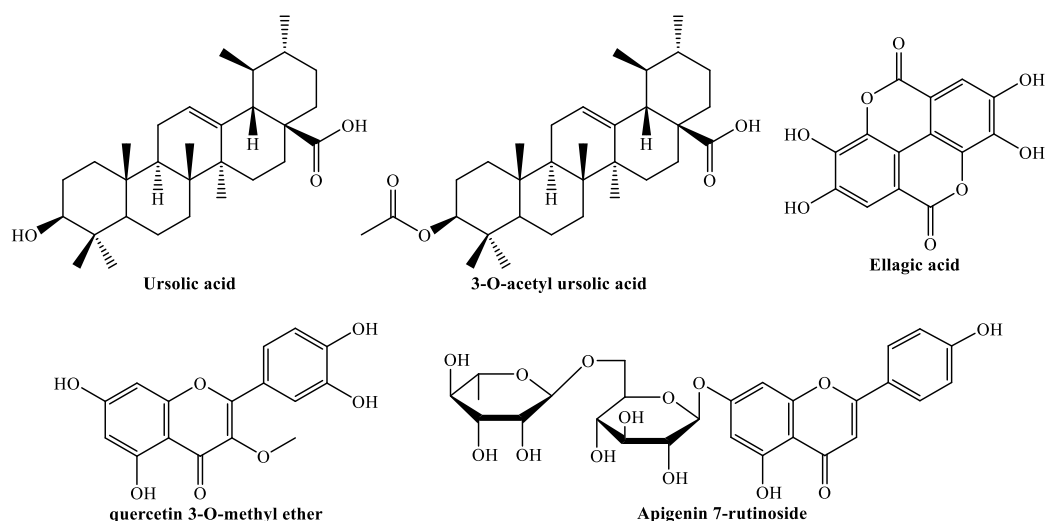


Figure 4: Structure of some chemical compounds found in *Crataegus Azarolus*

## 4.2 Biological Activity Of *Crataegus Azarolus*

The biological activities of *Crataegus azarolus* leaves and flowers have been studied and shown to have the following biological activities:

### 4.2.1 Anticancer Properties

The leaves and flowers of hawthorn prevent melanoma and other tumor cells from proliferation [41, 42].

### 4.2.2 Antioxidant Activity

*C. azarolus* can be used as a source of natural antioxidant compounds in which the extracts of ethanol, methanol and water shows to have significant action as antioxidant [43].

The total phenolic content TPC of crude extract of methanol and its fractions (ethyl acetate, diethyl ether, and chloroform) produced from Algerian *C. azarolus* revealed that aerial parts extracts are good natural sources of antioxidants [40].

### 4.2.3 Anti-inflammatory Activity

*C. azarolus* var. *eu-azarolus* Maire leaves ethanolic extract shown antibacterial effect against *E. coli*, *P. aeruginosa*, *S. aureus*, and *Candida albicans* [39].

### 4.2.4 The other biological activities are antihyperglycemia activity [44], and cardiotoxic activity [45]

## 4.3 Traditional Uses Of *Crataegus Azarolus*

In traditional medicine, the genus *Crataegus* is used to treat a number of disorders affecting the central nervous, reproductive, circulatory, and immunological systems [46].

In local treatment, the leaves is used to treat diabetes and removing kidney stones. The fruits, flowers and leaves are used as antihypertensive and to treat irregular heartbeat (cardiotonic).

## 5. Teucrium Chamaedrys

Wall germander is a creeping perennial plant that stays green all year and grows to a height of 6–18 inches. It has glossy, dark green leaves that are between 0.5 and 1.5 inches long and have scalloped edges. In late summer, whorls of tubular flowers grow from the leaf axils.

*Teucrium chamaedrys* (Wall germander) is a pretty plant that is native to the area around the Mediterranean Sea in Europe, North Africa, the Middle East, and Iran. In Kurdistan region of Iraq, *Teucrium chamaedrys* is found in Baradost, Mosul, Duhok, Gara, Sirsang,

Sharanish, Zawita, Khantur, Atrush, Suwara Tuka, Ser Amadiyah, Qara Dagh [47].

It was once used as a herb to treat gout.

Common names: English (Wall germander), Kurdish (Qesel Mahmid) , Arabic (Balut al arth)

### 5.1 Phytochemical Constituents

There are many phytochemicals identified in *Teucrium chamaedrys* plant. The identified components vary in different countries. These components include terpenoids, flavonoids, Steroids, iridoids, clerodanes, Phenolic Compounds, (Fig. 5). [47].

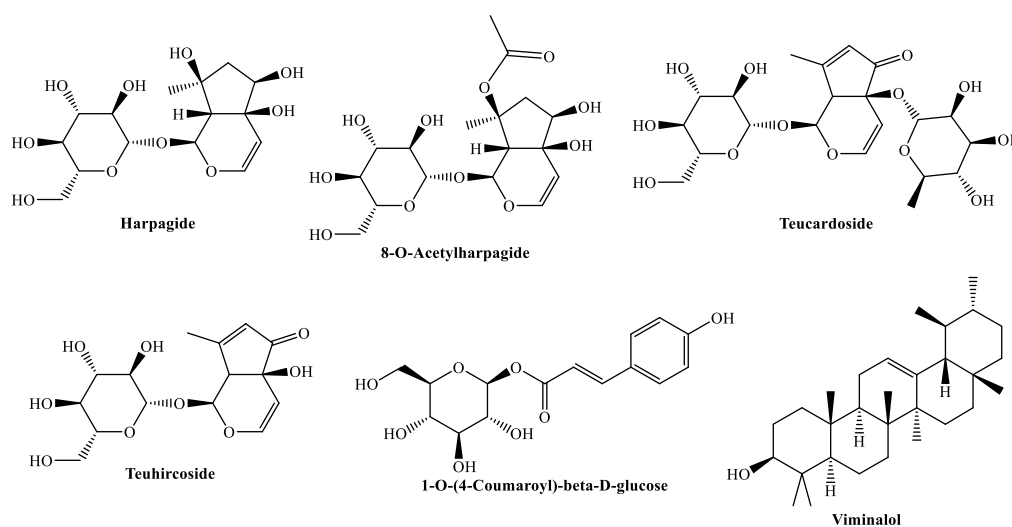


Figure 5: Structure of some chemical compounds found in *Teucrium Chamaedrys*

### 5.2 Biological Activity Of *Teucrium Chamaedrys*

The ethanolic extracts of *Teucrium chamaedrys* exhibited high antioxidant activity and high antimicrobial activity according to the study of Laurian Vlase et al. The radical scavenging activity of *T. chamaedrys* was very high comparing to other plants with  $IC_{50} = 26.70 \pm 0.96 \mu\text{g/mL}$ . *T. chamaedrys* extract had a high antioxidant activity, as measured by the DPPH bleaching technique, the TEAC test, and an EPR spectroscopy method, and this was connected to the polyphenolic total content. The antimicrobial activity of *Teucrium chamaedrys* was tested by disk-diffusion method and the results showed severe activity against the fungal strains [48].



### 5.3 Traditional Uses Of *Teucrium Chamaedrys*

Germander is derived from the aerial parts of a perennial fragrant mint plant (*Teucrium* Lamiaceae) that has been used for decades in Europe to treat inflammatory and digestive disorders. Since more than 2000 years ago, *Teucrium* species have been utilized as medicinal plants, and some of them are being employed in folk medicine today as antispasmodics, tonics, antipyretics, and antiseptics [49]. It was used to treat hemorrhoids, stomach pain, heart disorders, intestinal colic, renal ailments, chapped, and fissured finger tips [50]. The plant germander was supposed to aid in the treatment of inflammatory conditions such as fever, arthritis, gout, and digestive problems. Germander extracts were developed and promoted in Europe as a weight reduction and cholesterol-lowering medication as capsules [51].

Although *T. chamaedrys* and the *lydium* subspecies of this genus are most commonly used to cure hemorrhoids, they have also been shown to be effective in treating mouth ulcers, kidney infections, heart disease, malaria, and a number of other conditions. The ritual usage of this object is also well documented besides the discomfort in the stomach.

Rheumatism and gout are two conditions that have been treated using *T. Chameadrys*. The eyes can be soothed with a decoction of leaves and stems [52].

However, multiple reports of hepatotoxicity from some species of *Teucrium* L. in pill and tea form led to its ban as a herbal treatment in several countries for their responsibility to liver damage [53].

### 6. *Adiantum Capillus-Veneris*

*Adiantum capillus – veneris*, is a clumping, deciduous fern that reaches heights of 30 to 45 cm and spreads slowly by short, creeping rhizomes. The true maidenhair fern thrives in limestone-based, rocky, and moist environments. It is commonly found in ponds, shaded alkaline, damp cliffs, and self-sown on the brick foundation of greenhouses. It favors calcareous soils and may also be found on sandstone [54].

Common names: English (Maidenhair Fern, Venus hair, Avenka); Kurdish(Gia Zava, Gya qeiteran); Arabic(Shaar ul- jibal, Krafis al-bir) [55].

#### 6.1 Phytochemical Constituents

The phytochemical analysis of *Adiantum capillus-veneris* reveals the presence of flavonoids, triterpenoids, oleananes, phenylpropanoids, carotenoids, and alicyclics compounds [56].

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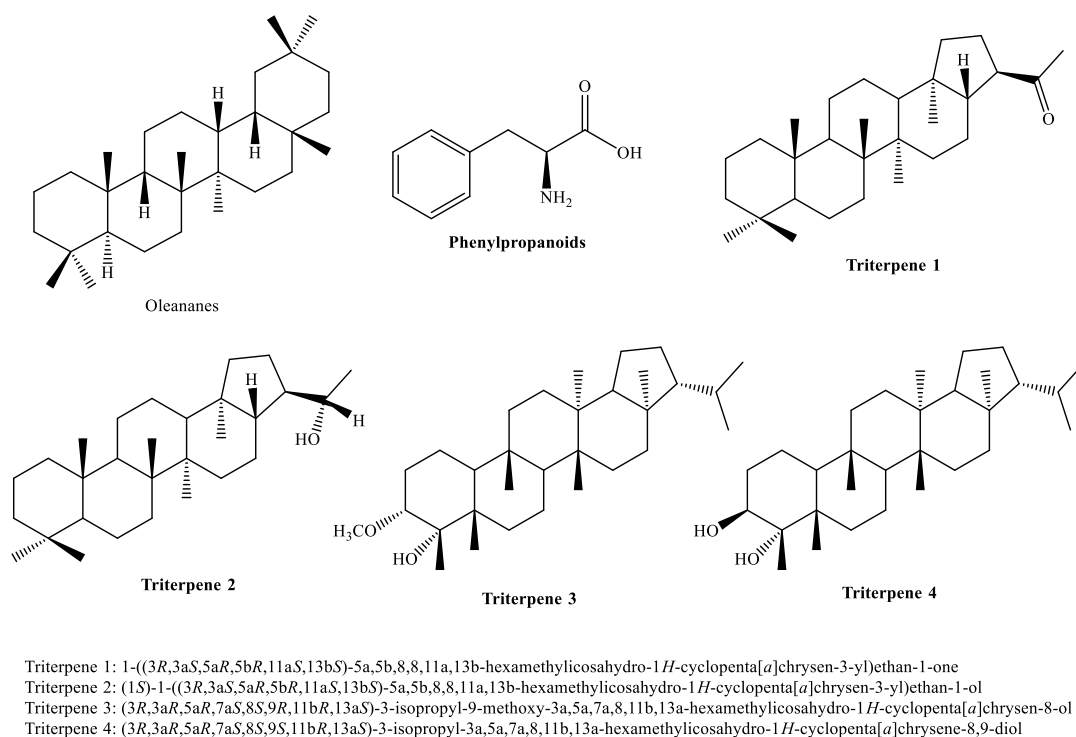


Figure 6: Structure of some chemical compounds found in *Adiantum capillus-veneris*

## 6.2 Biological Activity Of *Adiantum Capillus-Veneris*

The studies reveal many biological activities of *Adiantum veneris* plant which is used by ancient physicians and scientists for curing various diseases. The plant components were found to have anti-inflammatory, antioxidant, analgesic, antibacterial, antifungal, antidiarrheal, antispasmodic, anticonvulsant, hypoglycemic, hypocholesterolemia, anti-obesity, goitrogenic, anti-thyroidal, anti-asthmatic, anti-androgenic alopecia, diuretic, antilithiatic, and detoxifying activities [57]. As a result of its biological activities, *A. capillus-veneris* was discovered to be a natural source in the manufacture of natural pharmacological drugs [58].

## 6.3. Traditional Uses Of *Adiantum Capillus-Veneris*

The species of *Adiantum* were used traditionally as expectorants, lactation aids, renal function aids, antiparasitic, and dandruff treatments, in addition to treating chest ailments, coughs, and colds. The fresh or dried leafy fronds were used as an antitussive, antidandruff, demulcent, astringent, emetic, depurative, emollient, febrifuge, mild expectorant, galactagogues, laxatives, stimulants, pectoral, tonic, diuretic and refrigerant [59].

## 7. *Matricaria Chamomilla*

The Asteraceae family has many useful medical plants, but the chamomile (*Matricaria chamomilla* L.) is one of the most valuable plants in the family. Now more than ever, it is widely regarded as a vital component of both modern and traditional medicine. Years of traditional and scientific use and research have confirmed its multitherapeutic and nutritional properties. *Matricaria chamomilla* L. spreads in southern and eastern Europe. It is cultivated in Brazil, Germany, Hungary, France, Russia, and Yugoslavia. North Africa, Asia, North and South America, Australia, and New Zealand are among the places where the plants may be found [60].

The primary components of flowers and flower heads are used in the manufacturing of essential oil. The majority of plant biomass is produced in Hungary. It also thrives on Hungary's poor soils and provides a source of income for the area's underprivileged residents. For the purpose of distilling the oil, flowers are bulk transported to Germany. Given that chamomile is a rich source of natural products and information on the chemical elements of essential oil and plant parts are provided [61]. Common names: English (German chamomile, crown mayweed); Kurdish (Baybin); Arabic (Babonaj)

### 7.1 Phytochemical Constituents

The production parameters, such as climate, soil, harvest date, storage period, variety, and cultivar variables, have a significant impact on the chemical components of essential oils of *M. chamomilla* [62].

As secondary metabolites, more than 120 chemical compounds of phytochemicals in *M. chamomilla* flower have been found. The extracts were found to contain phenolic acids, flavonoids, coumarin, and amino acids after a chemical analysis. Furthermore, sterols, triterpenes, saponins, tannins, and alkaloids are found in the extract [63].

To separate the essential oil air-dried parts of chamomile plant material were hydro-distilled for six hours in a Clevenger device. Over anhydrous sodium sulphate, the extracted essential oils were dehydrated. After filtering, the samples were placed in dark glass vials and kept at 4 °C for further analysis [64].

As assessed by GC/MS in a study of chamomile cultivars, the following were the main components of the essential oil isolated from the capitula flowers: (E)- $\beta$ -farnesene (4.9-8.1%), terpene alcohol (farnesol), chamazulene (2.3-10.9%),  $\alpha$ -bisabolol (4.8-11.3%), and  $\alpha$ -bisabolol oxides A (25.5-28.7%) and  $\alpha$ -bisabolol oxides B (12.2-30.9%). Chamomile flower oil is mostly composed of sesquiterpene derivatives (75-90%) with just minor amounts of monoterpenes [65].

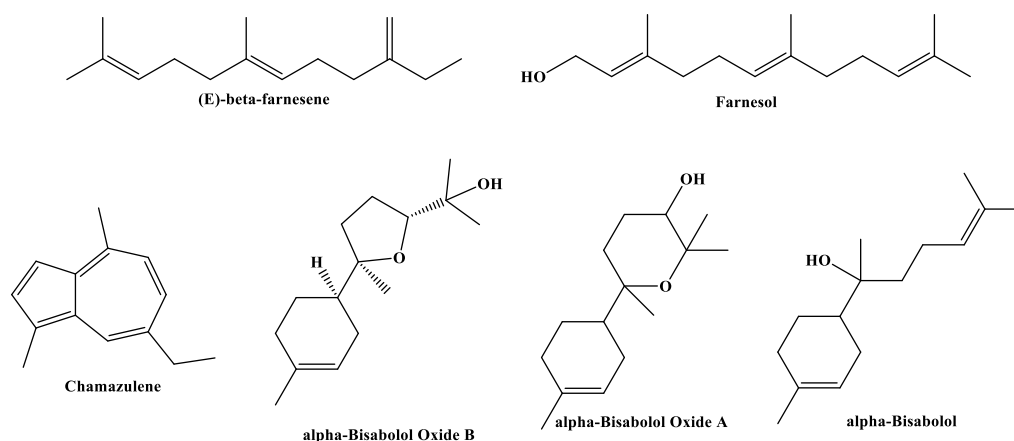


Figure 7: Structure of some chemical compounds found in *Matricaria chamomilla*

### 7.2 Biological Activity Of *Matricaria Chamomilla*

There are several classes of compounds present in *Matricaria chamomilla*, many of which have potential as therapeutics. The most vital components of chamomile medicine are sesquiterpenes, flavonoids, coumarins, and polyacetylenes [66].

Chamomile flower essential oil is widely utilized in medicinal and cosmetic preparations due to its antibacterial, antifungal, antioxidant, and anti-inflammatory antiseptic activities [67].

*Matricaria chamomilla* is reported to have the following biological activities: [60].

Analgesic, Antiallergic, Anticancer, Antihyperglycemic, Anti-inflammatory, Antimicrobial, Antipruritic, Antisolar, Antispasmodic, Antistress, Antiulcer, Anxiolytic, Arcaricadal property, Gastrointestinal disorders, Hepatoprotective, Immunomodulatory, Inhibition of poliovirus replication, Intracanal irrigant, Lousicidal, ovicidal, repellent, Prevent osteoporosis, Sedative, Treatment of infant botulism, Treatment of oral mucositis, Uterotonic, Virucidal agent, Wound healing property.

The antibacterial activity of chamomile is represented by the presence of  $\alpha$ -bisabolol and cyclic ethers [68]. whereas the antifungal and antiseptic activities is due to the presence of Chamazulene and  $\alpha$ -bisabolol [69].

### 7.3 Traditional Uses Of *Matricaria Chamomilla*

In traditional medicine, *M. chamomile* has a wide range of uses depending on the portions of the plant, the preparation techniques and the country. The infusion of *M. chamomile* is used to treat diabetes, nervous system disorders, colic spasm, cold, diarrhea, angina, sore throat, infections, kidney stones, painful menstruation and as a sedative [70]. In addition, the herbal plant can be used as a sedative, antiseptic, antiemetic against nausea, and anti-inflammatory against gastric and intestinal disorders [71]. Moreover, the *M. chamomile* is used externally to treat irritations and inflammation of the skin [72].

## 8. Conclusion

This review focuses on the components and uses of some plants existing in different places of Kurdistan Region, Iraq and the world. On the global market, these medicinal plants are in high demand due to their broad therapeutic worth and faultless pharmacological capabilities. Furthermore, there has been a growth in the usage of natural substances as opposed to synthetic chemicals because many herbal medications are free of adverse effects, easily accessible, seen as healthful, and generate revenue.

It is recommended to cultivate these medicinal plants in order to better regulate the quality of the desired bioactive components. This method also permits the creation of homogenous plant material in the needed quantities at specified times. There has been a growth in the use of natural substances as opposed to synthetic chemicals since many herbal medications have no adverse effects, are simple to get, are seen as healthful, and generate money and antibacterial activity, which are seldom evaluated.

However, it is crucial and vital to do more study into the discovery of plant-derived medications for the treatment of many ailments.

## 9. Author's Contribution

We confirm that the manuscript has been read and approved by all named authors. We also confirm that each author has the same contribution to the paper. We further confirm that the order of authors listed in the manuscript has been approved by all authors.

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## 10. Conflict of Interest

There is no conflict of interest for this paper.

## 11. Acknowledgement

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