Fatma Tuğçe Gürağaç Dereli
Mert Ilhan
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# Novel Drug Targets With Traditional Herbal Medicines

## Scientific and Clinical Evidence

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# Preface

This book collects information on the most popular ethnomedicinal plants, which are common in Turkey and around the world. It presents the ethnopharmacological records, in vivo and in vitro studies, side effects, chemical compositions, and clinical studies of these medicinal plants. Its special focus is on the novel drug targets for disease and their possible mechanisms of action. It covers botanical descriptions, status of the plants, and food or drug interactions including precautions and warnings about the plants and the available market products. Also, the gap between the traditional practice and scientific/clinical evidence in the use of ethnomedicinal plants is mentioned. It is well known that traditional knowledge of the use of the medicinal plants in therapy is an important resource for the discovery of novel treatment options and drug targets. The main purpose of this book is to draw attention to ethnomedicinal plant species. Data on the therapeutic potentials of these medicinal plants can now be accessed from a single source. It provides an important resource for future research opportunities for harnessing the full potential of these plants. It is well known that traditional knowledge of medicinal plants in therapy is an important resource for discovering novel treatment options and drug targets. The main purpose of this book is to draw attention to ethnomedicinal plant species. Data on the therapeutic potentials of these medicinal plants can now be accessed from a single source. It provides an important resource for future research opportunities for harnessing the full potential of these plants.

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# Contents

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protocols, for which he has awarded by the prestigious ‘Governor award for Best Research’ by the Government of India, consequently for two years. His excellent research credentials are reflected by his four edited books, 125+ international research peer reviewed publications, and also editing journal special issues. His research work has been cited more than 3000 times. He has won several awards and also secured a China Postdoctoral Science Foundation research grant as Project Investigator. He is an active member of European Society of Sonochemistry and also an ‘Invited Speaker’ at several International Symposium/conferences. His research interest lies in the design and development of various bioprocess techniques (including cell culture techniques) for efficient utilization of natural resources. Further his research interests include scientific bases of traditional knowledge, nanotechnology, analytical systems, ultrasonic sonochemistry, design and development of scale-up bioprocess, and nutraceuticals for health use. For More: http://scholar.google.co.uk/citations?user=cuYvk0EAAAAJ&hl=en

# *Achillea biebersteinii* Afan.

1

Erkan Yılmaz

**Abstract**

*Achillea biebersteinii*, a flowering herbaceous perennial or semi-shrubby plant, is a member of the family Asteraceae represented by more than 100 species all over the world. The *Achillea* genus, which was named from the myth about Achilles using these plants to heal soldiers' wounds in Trojan War, have been known to be widely utilized in traditional medicine through ages by different cultures around the World. *Achillea biebersteinii*, known as yarrow commonly in English, appears with different vernacular names such as "Civan perçemi" in Turkey, Thafra'a in Saudi Arabia, and Bu:ma:dærʌn in Iran. Traditionally, it is frequently used for abdominal pain in stomachache, menstrual pain, and wound healing. Besides the essential oil of this species studied extensively by researchers, its extracts have been found to be rich in flavonoids, phenolic acids, ionone glucosides, sesquiterpene lactones, and terpenoids. The promising pharmacological activities such as antioxidant, antimicrobial, analgesic, antidiabetic, antiplatelet, antiulcer, antioxidant, insecticidal, antifungal, and anticancer have been reported by several researchers. In this present chapter, it is aimed that its traditional uses and phytochemistry and pharmacological properties of *Achillea biebersteinii* reported until date will be summarized and highlighted to explore gaps in this area and contribute future potential.

**Keywords**

*Achillea biebersteinii* · Asteraceae · Yarrow · Pharmacognosy · Phytoconstituents · Ethnopharmacology

## 1.1 Introduction

*Achillea biebersteinii* Afan. (family: Asteraceae, Section: Filipendulinae (D.C.) Boiss) (synonymous: *Achillea micrantha*) is a member of the *Achillea* genus which comprise approximately 110–140 species in the world (Ehrendorfer and Guo 2006). *Achillea* genus is represented with 56 taxa in Turkey and 28 of these are endemics (Arabacı 2006). *Achillea biebersteinii* which is known as the yarrow in English (Pirbalouti et al. 2013) has many vernacular names in different cultures. In Turkey, Eşek otu (Han and Bulut 2015), Erkurtaran (Demirci and Özhatay 2012; Güneş et al. 2017), Sarı çiçek (Sezik et al. 2001; Tuzlaci and Doğan 2010; Tetik et al. 2013), Çetuğçe (Sezik et al. 2001), Ayvadene (Kargioğlu et al. 2008), Ayvadana (Tuzlaci and Erol 1999),

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Ayvadanası (Tuzlaci and Erol 1999), Civan Perçemi (Özüdoğru et al. 2011; Ari et al. 2015; Mart and Türkmen 2018), Arı çiçeği (Tuzlaci and Doğan 2010), Pelikertik (Karakaya et al. 2019), Hırtkesen (Yeşil and Akalın 2009), Kılıç otu (Sezik et al. 1997; Karakaya et al. 2019), Sarılık otu (Sezik et al. 1997), Sarı civan perçemi (Karakaya et al. 2019), Kırk kilit (Karakaya et al. 2019), Pazıma (Özgen et al. 2012), Pazvanat (Özgen et al. 2012), Pazvana (Özgen et al. 2012), Paspanos (Özgen et al. 2012), Kulilkamaran (Arasan and Kaya 2015), Sancı çiçeği (Yeşilada et al. 1995), Pujdang (Demir 2020), Waşzerık (Polat et al. 2013), Vılıka çeker (Polat et al. 2013), Gihaye çexer (Polat et al. 2013), Wılazerd (Polat et al. 2013), Gihakêmara (Arasan and Kaya 2015) and Gihayêmaran (Arasan and Kaya 2015) were known by names like these. In addition, it is known as Thafra'a (Abulafatih 1987), Qaysoum (Hammad et al. 2013), Althufra (Al-Said et al. 2016), and Aldefera (Awadh Ali et al. 2017) in Arabic. In a study conducted in Uzbekistan, names such as Boymaderan, Boymadoran, Esxekgülü, and Sarıbash were encountered (Sezik et al. 2004). In Iran, there are many different names such as dæxi:le (Naghibi et al. 2014), Bu:ma:dærʌn (Mosaddegh et al. 2016), Sary-gul Boyboderan (Ghorbani 2005), Boomadaran (Mashayekhan et al. 2015), Bomadaran (Jafari Footami and Akbarlou 2017), Boomaro (Pirbalouti et al. 2013), Berenj daz (Pirbalouti et al. 2013), Gol Zard (Pirbalouti et al. 2013), and Boomadaran-e-Zard (Pirbalouti et al. 2013).

The general morphological properties of *Achillea biebersteinii* Afan. are as follows: plant height 10–100 cm. Perennial herb, thick or thin woody rhizome, rhizomes sometimes creeping. Stem erect, usually one or several, straight or slightly curved, unbranched or slightly branched upward with dense pubescent indumentum. Leaves homomorphic, cylindrical, 2–3-pinnatisect, rachilla is straight. Basal leaves linear to linear-lanceolate, leaves in the middle of stem oblong-linear to linear-lanceolate, leaves on upper the stem, small, sessile, and less segmented. Inflorescence is capitulum and corymbs 2–10 cm broad, peduncles 0′5–4 mm. Involucre oblong to broadly ovoid, 3–4 × 2–3 mm. Capitula 30–200 and more, corymbs 2–10 cm broad, peduncles 0.5–4 mm. Involucre oblong to broadly ovoid, 3–4 × 2–3 mm. Phyllaries ovate-triangular to oblong, ± obtuse, pale, pubescent, inner with scarious tip. Ligules 4–5, golden yellow, 1–2 mm; disc flowers 10–30 (Fig. 1.1). Flowering time usually between April and May. Steppe, forest gap, arid grasslands, rocky slopes, alpine or dry meadows, field edges. Growing altitudes 350–3450 m (Huber-Morath 1975; Arabacı 2006).

## 1.2 Distribution and Status of Species

*Achillea biebersteinii* seems to be widely distributed around the world. It grows wild in Eastern Europe, South Russia, Turkey, the Caucasus, the Middle East, Iran, Afghanistan, and Central Asia. *Achillea biebersteinii* is an Iranian-Turanian element, widely distributed in Turkey but more sparse west of Turkey (Fig. 1.2) (Arabacı 2006).

## 1.3 Comparison of Traditional/Ethnomedicinal/Local Uses

*Achillea biebersteinii* is widely distributed in Turkey but more sparsely in west Turkey (Arabacı 2006). Likewise, it can be seen that ethnobotanical data are generally found in studies conducted in the Eastern Anatolian region (Sezik et al. 1997; Yeşil and Akalın 2009; Tuzlaci and Doğan 2010; Polat et al. 2013; Karakaya et al. 2019, 2020; Demir 2020). Ethnobotanical uses regarding *Achillea biebersteinii* in Turkey and different cultures apart from Turkey with the geographic region where the plant is used, its medicinal uses, plant parts used, type of preparation, and utilization methods are summarized in Tables 1.1 and 1.2. These data gathered from ethnobotanical survey display that the most frequently traditional uses reported are against stomachache (Tuzlaci and Erol 1999; Sezik et al. 2001; Yeşil and Akalın 2009; Tuzlaci and Doğan 2010; Özgen et al. 2012; Güneş et al. 2017), abdominal pain (Yeşilada et al. 1995; Sezik et al. 2001;

**Fig. 1.1** General view photo of *A. biebersteinii* in its habitat. (Photo: Ömer Kılıç)

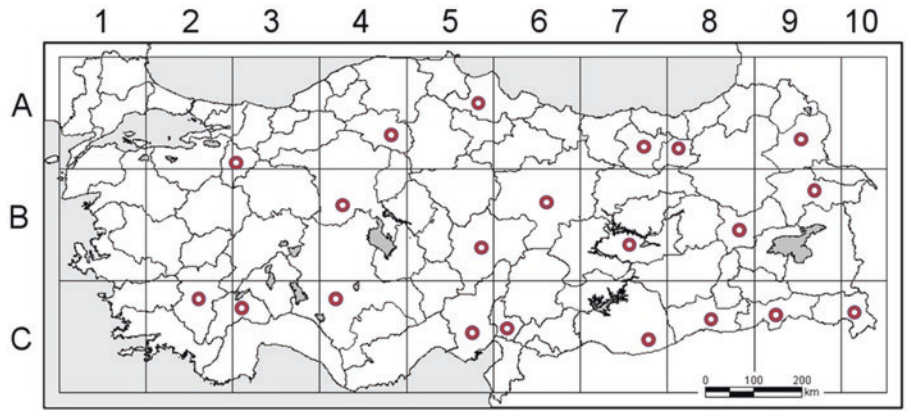


**Fig. 1.2** The distribution ( ) map of *A. biebersteinii* in Turkey (Huber-Morath 1975)

**Table 1.1** Ethnobotanical uses regarding *Achillea biebersteinii* in Turkey with geographic region, its medicinal uses, plant parts used, type of preparation, and utilization methods

| Geographic region | Medicinal uses | Plant part | Preparation/utilization method | References |
|---|---|---|---|---|
| Adana (Karaisalı), Turkey | Stomachache, hemorrhoids | Aerial parts | İnfusion/drinking one glass before a meal<br>Mash/compress | (Güneş et al. 2017) |
| Afyonkarahisar, Turkey | Pain relievers, stomachache, respiratory distress, shortness of breath | Flowers, leaves | Decoction/internal | (Ari et al. 2015) |
| Afyonkarahisar (South-western part), Turkey | Indigestion | Flowers | Infusion/internal | (Kargioğlu et al. 2008) |
| Amasya (Merzifon), Turkey | Insect repellent | Capitulum | Flowers are placed in different parts of the house | (Ezer and Mumcu Arisan 2006) |
| Bingöl (Solhan), Turkey | Anti-inflammation, rheumatism, hepatitis, sinusitis, toothache, menstrual pain | Flowers | Infusion/drinking one tea glass three times a day | (Polat et al. 2013) |
| Bitlis (Hizan), Turkey | Infertility | Aerial parts | Cooked/eaten | (Demir 2020) |
| Erzincan (Kemah), Turkey | Wound healing | Herb | Pounded/external | (Sezik et al. 1997) |
| Erzurum (Aziziye), Turkey | Wound healing, hemostatic<br>Hemostatic, eczema | Leaves<br>Aerial parts | Crushed/external<br>Boiled, paste/external | (Karakaya et al. 2020) |
| Erzurum (Ilıca District), Turkey | Hemorrhoids, stomachache<br>Dyspnea, gynecological diseases, urinary system infections | Flowers<br>Herb | Flower powder eaten with honey<br>Decoction | (Özgen et al. 2012) |
| Erzurum (South part), Turkey | Wound healing, hemostatic<br>Diuretic, menstrual pain | Leaves<br>Capitulum | Crushed/external<br>Crushed leaves are mixed with olive oil<br>Decoction/internal | (Karakaya et al. 2019) |
| Isparta (Eğirdir), Turkey | Ulcer<br>Stomachache<br>Stomachache<br>Stomachache<br>Stomachache<br>Stomachache<br>Stomachache<br>Ulcer, cold<br>Cold<br>Carminative for children | Aerial parts<br>Fruits<br>Fruits<br>Capitulum<br>Capitulum<br>Aerial parts<br>Aerial parts<br>Fruits<br>Fruits<br>Capitulum | Chewed<br>Infusion/internal<br>Chewed<br>Infusion/internal<br>Eaten<br>Infusion/internal<br>Boiled in water+flour/external<br>Chewed<br>Infusion/internal<br>Powdered+sugar/internal | (Tuzlaci and Erol 1999) |
| Kahramanmaraş (Andırın), Turkey | Abdominal pain, menstrual pain | Aerial parts | Infusion/internal | (Demirci and Özhatay 2012) |
| Kahramanmaraş, Turkey | Earache, abdominal pain | Flowers | Decoction/internal | (Yeşilada et al. 1995) |
| Kars, Turkey | Maturation of abscess | Herb | Pounded/external | (Sezik et al. 1997) |
| Kars (Arpaçay, Yalınçayır), Turkey | Jaundice | Herb | Boiled/internal | (Sezik et al. 1997) |
| Kayseri (Develi), Turkey | Abdominal pain, stomachache | Herb | Tea mixed with mint leaves | (Sezik et al. 2001) |
| Kayseri (Pınarbaşı), Turkey | Wound healing | Herb | Freshly pounded herb is applied over the wounds | (Sezik et al. 2001) |

(continued)

**Table 1.1** (continued)

| Geographic region | Medicinal uses | Plant part | Preparation/utilization method | References |
|---|---|---|---|---|
| Malatya, Turkey | Rheumatism, sinusitis, toothache | Flowers | Infusion/drinking one tea glass three times a day | (Tetik et al. 2013) |
| Malatya (Akçadağ), Turkey | Menstrual pain, stomachache<br>Women's sterility | Aerial parts | Infusion, decoction/internal<br>Decoction/internal | (Yeşil and Akalın 2009) |
| Mardin (Savur), Turkey | Women's illnesses<br>Abdominal pain | Flowers | Boiled/internal<br>Boiled/drinking before meal twice a day | (Arasan and Kaya 2015) |
| Osmaniye (Bahçe and Hasanbeyli), Turkey | Diuretic, menstruation | Aerial parts | Infusion | (Mart and Türkmen 2018) |
| Sivas (Ortaköy), Turkey | Menstrual pain | Whole plant | Infusion/internal | (Özüdoğru et al. 2011) |
| Tunceli (Ovacık), Turkey | Stomachache, carminative<br>Expectorant | Capitulum Flowers, leaves | Infusion/internal<br>Decoction/internal | (Tuzlaci and Doğan 2010) |
| Yozgat (Kadışehri), Turkey | Abdominal pain | Aerial parts | Decoction/internal | (Han and Bulut 2015) |

**Table 1.2** Ethnobotanical uses regarding *Achillea biebersteinii* in different cultures apart from Turkey with geographic region, medicinal uses, plant parts used, type of preparation and utilization methods

| Geographic region | Medicinal uses | Plant part | Preparation/utilization method | References |
|---|---|---|---|---|
| Hamedan province, Iran | Hypothermia<br>Carminative, stomachache<br>Fever, hypoglycemia<br>Infection, hypoglycemia<br>Food poisoning, carminative, inflammation | Flower, leaves, root<br>Flowers<br>Flowers<br>Leaves<br>Whole plant | Extraction/internal<br>Decoction/internal<br>Infusion/internal<br>Infusion/internal<br>Decoction/internal | (Naghibi et al. 2014) |
| Hamedan province, Iran | Fever, hypoglycemia, hypothermia, carminative, infection, stomachache | Flower, leaves, root, whole plant | Extraction, infusion, decoction/internal | (Mosaddegh et al. 2016) |
| Ilam province, Iran | Indigestion, rheumatism, sedative (toothache), antiseptic, hemagglutinate | Flowers, leaves | Internal, external | (Pirbalouti et al. 2013) |
| Mazandaran province, Iran | Flatulence, stomachache, wound healing | Flowering branches | Infusion/internal | (Jafari Footami and Akbarlou 2017) |
| North Khorasan province, Iran | Colds<br>Kidney disorder | Shoots<br>Flowers | Tea<br>Decoction | (Mashayekhan et al. 2015) |
| Turkmen Sahra region, Iran | Digestive disorders, cardiac failure, anthelmintic, burns, fever | Flowers | Infusion, decoction | (Ghorbani 2005) |
| Al-Baha region, Saudi Arabia | Leishmania<br>Insect repellent<br>Toothache | Aerial parts<br>Flowers<br>Flowers | Paste/topical<br>Topical<br>Chewing | (Awadh Ali et al. 2017) |
| South-western of Saudi Arabia | Itching<br>Toothache | Leaves<br>Leaves | Decoction<br>Chewing | (Abulafatih 1987) |
| Djizzax, and Samarqand provinces, Uzbekistan | Diarrhea<br>Headache<br>Pain in sub-umbilical area in children | Herb<br>Flowers<br>Flowers | Tea<br>Inhaled<br>Tea | (Sezik et al. 2004) |

Demirci and Özhatay 2012; Arasan and Kaya 2015; Han and Bulut 2015), menstrual pain (Yeşil and Akalın 2009; Özüdoğru et al. 2011; Demirci and Özhatay 2012; Polat et al. 2013; Karakaya et al. 2019), and wounds (Sezik et al. 1997, 2001; Karakaya et al. 2019, 2020). Based on these data, the mostly used plant parts of *Achillea biebersteinii* are the flowers (Yeşilada et al. 1995; Kargioğlu et al. 2008; Karakaya et al. 2019) and aerial parts (Tuzlaci and Erol 1999; Yeşil and Akalın 2009). Infusion and decoction are the most preferred ways to use the plant (Yeşilada et al. 1995; Tuzlaci and Erol 1999; Yeşil and Akalın 2009; Polat et al. 2013; Ari et al. 2015). Mashed (Güneş et al. 2017), pounded (Sezik et al. 1997), and crushed (Karakaya et al. 2019, 2020) forms are encountered if used topically. It has been seen that it is also used in other cultures (Sezik et al. 2004; Naghibi et al. 2014; Awadh Ali et al. 2017). In Iranian traditional medicine, it seems that the plant has been used for stomachache (Mosaddegh et al. 2016), rheumatism (Pirbalouti et al. 2013), wounds (Jafari Footami and Akbarlou 2017), and cold (Mashayekhan et al. 2015) as well as in Turkey (Sezik et al. 1997; Tuzlaci and Erol 1999; Polat et al. 2013; Güneş et al. 2017). Furthermore, in Saudi Arabia, it is used against leishmania (Awadh Ali et al. 2017), insects (Awadh Ali et al. 2017), toothache (Abulafatih 1987; Awadh Ali et al. 2017), and itching (Abulafatih 1987). In Uzbekistan, it is used for diarrhea, headache, and pain in sub-umbilical area in children (Sezik et al. 2004).

## 1.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques

Chemically, *Achillea biebersteinii* extracts were found to include sesquiterpene lactones (Badahdah and El-Orfy 2004; Abd-Alla et al. 2016), flavonoids (Valant-Vetschera and Wollenweber 1996; Hammad et al. 2013; Şabanoğlu et al. 2019), tannins (Strzępek-Gomółka et al. 2021), and phenolic acids (Salarbashi et al. 2014; Zengin et al. 2017; Şabanoğlu et al. 2019; Gaweł-Bęben et al. 2020). The main chemical compounds present in extracts obtained from different parts of *Achillea biebersteinii* are summarized in Table 1.3. Chlorogenic acid was reported as the predominant component in the three parts of the plant (Şabanoğlu et al. 2019). Some phenolic acids other than chlorogenic acids are caffeic acid (Zengin et al. 2017; Şabanoğlu et al. 2019), cynarin, quinic acid (Gaweł-Bęben et al. 2020), 3-caffeoylquinic acid, 4-caffeoylquinic acid (Zengin et al. 2017; Gaweł-Bęben et al. 2020; Strzępek-Gomółka et al. 2021), and ferulic acid (Hammad et al. 2013; Salarbashi et al. 2014). Moreover, analysis of the extracts revealed that some flavonoids including apigenin (Şabanoğlu et al. 2019), luteolin, rutin, quercetin (Hammad et al. 2013; Şabanoğlu et al. 2019), axillarin (Valant-Vetschera and Wollenweber 1996; Gaweł-Bęben et al. 2020), and jaceidin (Oskay and Yeşilada 1984; Badahdah and El-Orfy 2004) were present in the extracts. *Achillea biebersteinii* extracts also contain sesquiterpene lactones, in particular micranthin and sintenin (Abd-Alla et al. 2016). In researches, it has been also determined that monoterpenes such as ascaridole, diterpene such as strictic acid (Mahmoud and Al-Shihry 2006), sesquiterpenoid such as β-eudesmol (Akkol et al. 2011), fatty acids such as linoleic acid (Kordali et al. 2009), and phytosterol such as β-sitosterol (Badahdah and El-Orfy 2004) were found in extracts. In a study, total carotenoid amount (14.59 g vitamin A eq. $100^{-1}$), vitamin C (14.14 g 100 $g^{-1}$), vitamin E (24.29 g-Alfa tocopherol e g 100 $g^{-1}$), and proanthocyanidin (65.50%) were detected in flowers and leaves (Güneş et al. 2019). By development of alternative extraction techniques based on ultrasound-assisted extraction method, extraction yield and total phenolic and flavonoid contents were found to be high significantly, when compared with conventional methods (Salarbashi et al. 2014).

*Achillea biebersteinii* has been extensively studied in regard to its essential oil worldwide (Bader et al. 2003; Esmaeili et al. 2006; Tabanca et al. 2011; Mirahmadi et al. 2012; Polatoğlu

**Table 1.3** Main chemical compounds present in extracts obtained from different parts of *Achillea biebersteinii*

| Compound (s). | Solvent | Plant parts | References |
|---|---|---|---|
| Caffeic acid, chlorogenic acid, apigenin, luteolin, quercetin, rutin | Methanol | Flowers | (Şabanoğlu et al. 2019) |
| Caffeic acid, chlorogenic acid, luteolin, quercetin, rutin | Methanol | Leaves | (Şabanoğlu et al. 2019) |
| Caffeic acid, chlorogenic acid | Methanol | Roots | (Şabanoğlu et al. 2019) |
| 6-hydroxykaempferol 3,6-dimethyl ether, penduletin, axillarin, chrysosplenol-D, jaceidin, centaureidin, chrysosplenetin | Acetone | Aerial parts excluding inflorescence | (Valant-Vetschera and Wollenweber 1996) |
| Patuletin-7-O-β-D-glucoside, quercetin-7-O-β-D-glucoside | Methanol | Aerial parts | (Sevindik et al. 2015) |
| 2-Tricosanone, 1-hexacosanol, n-pentacosane, jaceidin, patulitrin, quercetagitrin, quercimeritrin | | Capitulum | (Oskay and Yeşilada 1984) |
| 3-Caffeoylquinic acid, 4-caffeoylquinic acid, 5-caffeoylquinic acid, caffeic acid, cynarin, quinic acid, kaempferol, jaceidin, axillarin, 3,8-dimethylherbacetin, coumaroyl-quinic acid isomers | Hydroglycolic | Aerial parts | (Gaweł-Bęben et al. 2020) |
| Ascaridole (43.22%), iso-ascaridole (37.87%), n-pentacosane (1.78%) | Methanol | Flowers | (Abbas et al. 2019) |
| Biebersteiniside, 6-epiroseoside, ascaridole, strictic acid, centipedic acid | Dichloromethane-methanol (1:1) | Aerial parts | (Mahmoud and Al-Shihry 2006) |
| Micranthin, sintenin, 4β,10α-dihydroxy-5β,7β,8βH-guaia-1,11(13)dien-12,8α-olide, santin, jaceidin, axillarin, 5,7 dihydroxy 3,3′,4′-trimethoxy flavone | Ethyl acetate | Aerial parts | (Abd-Alla et al. 2016) |
| Caffeic acid, 3-caffeoylquinic acid, 4-caffeoylquinic acid, 1,3-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, 4,5-dicaffeoylquinic acid, 3,4,5-tricaffeoylquinic acid, 1-feruloylquinic acid, protocatechuic acid | Water, ethyl acetate | Aerial parts | (Zengin et al. 2017) |
| Caffeic acid, 3-caffeoylquinic acid, 4-caffeoylquinic acid, 1,3-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, 4,5-dicaffeoylquinic acid, 3,4,5-tricaffeoylquinic acid, 1-feruloylquinic acid, 4-feruloylquinic acid, protocatechuic acid | Methanol | Aerial parts | (Zengin et al. 2017) |
| 3-Caffeoylquinic acid, 4-caffeoylquinic acid, 5-caffeoylquinic acid, achillin, apigenin, axillarin, caffeic acid, caffeoylglucoside isomers, citric acid and isocitric acid, coumaroyl quinic acid isomers, 1,3-dicaffeoylquinic acid, ellagic acid, ferulic acid, fraxetin-8-O-glucoside, gluconic acid, glutaric acid, gmelinin B, isovitexin, jaceidin, kaempferol, malic acid, protocatechuic acid glucoside, quercetin-O-glucopyranose, quinic acid, schaftoside or isoschaftoside, shikimic acid, succinic acid | Ethanol 75% | Aerial parts | (Strzępek-Gomółka et al. 2021) |
| β-Sitosterol, stigmasterol, jaceidin, 3,6-dimethoxy-5,7,4′-trihydroxyflavone | Petroleum ether-ether-methanol (1:1:1) | Whole plant | (Badahdah and El-Orfy 2004) |
| Caffeic acid, gallic acid, chlorogenic acid, ferulic acid, p-coumaric acid | Methanol 80% | Aerial parts | (Salarbashi et al. 2014) |
| Caffeic acid, ferulic acid, kaempferol, luteolin, rutin, myricetin, quercetin, quercetin 3-β-D-glucoside | Aqueous, ethanol 70% | Aerial parts | (Hammad et al. 2013) |
| β-Eudesmol (19.11%), piperitone (9.2%), cyclohexadecanolide (5.54%) | n-hexane | Aerial parts | (Akkol et al. 2011) |
| Camphor (17.97%), linoleic acid (16.40%), 1,8-cineole (15.12%) | n-hexane | Flowers | (Kordali et al. 2009) |

et al. 2013; Nenaah 2014a; Al-Said et al. 2016). The major components of *Achillea biebersteinii* essential oil in Turkey and different geographic regions in the world were summarized in Table 1.4. In Turkey, 1,8-cineole was usually detected as the major constituents of the essential oils researched, followed by camphor (Kordali et al. 2009; Toncer et al. 2010; Tabanca et al. 2011). It can be seen that some essential oils also differed by containing piperitone (Bariş et al. 2006), p-cymene (Tabanca et al. 2011), camphor (Yildirim et al. 2015), and ascaridol (Toncer et al. 2010) as major compounds in samples of Turkey origin. In a sample of Egypt origin, cis-ascaridol was determined as the dominant compound in essential oils (Nenaah 2014a). Significant differences were reported in the major constituents of the essential oils from different localities in Iran (Rustaiyan et al. 1998; Mirahmadi et al. 2012). According to the study which reported the compositions of essential oils obtained from 23 wild plants collected from different locations of Iran, 1,8-cineole was generally encountered as the major component in the vast majority of essential oil, followed by p-cymene. The remarkable point of the research was the existence of nepetalactone compounds especially encountered in the *Nepeta* species. Fourteen of 23 populations were found to contain at least one of these compounds of the three major components (Mirahmadi et al. 2012). In conclusion, the essential oil composition of *Achillea biebersteinii* growing in Turkey and other countries presents distinguishable quantitative and qualitative differences. The differences in the essential oil constituents may be influenced by numerous factors including environmental factors and genetic factors determining the chemotype, physiological age, seasonality, and developmental stage (Tabanca et al. 2011).

## 1.5 Scientific Evidences: Pharmacological Activities

### 1.5.1 Antioxidant Activity

Methanolic extracts of leaves exhibited high level of antioxidant activity than BHT according to three model systems including DPPH, β-carotene bleaching, and reducing power (Gharibi et al. 2015). In a different study investigating the methanolic extracts of different parts of the *Achillea biebersteinii* such as flowers, leaves, and roots, scavenging activity of leaf extracts was found to be remarkably higher than the others in both ABTS and DPPH tests (Şabanoğlu et al. 2019). In another study in which extracts were prepared by shaking and maceration methods, from different parts of a plant using ethanol and methanol as solvents, methanol extract of leaves was found to show the highest activity determined with DPPH, TBARS, and BCB assays (Varasteh-Kojourian et al. 2017). In another study, different extracts prepared with several solvents from aerial parts were investigated for their antioxidant activity. Among them, ethyl acetate extract was found to exhibit the best results with 67.7% DPPH radical scavenging activity, 97.4% ABTS cation radical scavenging activity, 83.1% superoxide anion radical scavenging activity, and 47.5% lipid peroxidation inhibition. Scavenging capacity of the extract and standard substances (α-tocopherol, trolox, gallic acid) was found to be close (Sevindik et al. 2015). In the other study, the different tests including free radical scavenging, metal chelating, reducing power, and total antioxidant capacity were assessed in ethyl acetate, methanol, and aqueous extract which were obtained from aerial parts. The highest total antioxidant capacity was seen in the ethyl acetate extract using the phosphomolybdenum assay. Methanolic extract with the best results for DPPH assay and water extract with higher values for TEAC assay were found. The highest result obtained in the FRAP assay and the most potent reducing capacity obtained in the CUPRAC assay were seen in the methanolic extract. The significant chelation activity against $Fe^{2+}$ was seen with the highest value in ethyl acetate extract (Zengin et al. 2017). In other research, the ethanol extract derived from aerial parts was found to exhibit high antioxidant activity, reducing power, and DPPH radical and metal chelating activities compared to different standards such as α-tocopherol and BHT. Total antioxidant activity of the ethanol extract was also tested in linoleic acid system by

**Table 1.4** Major components of essential oil of *Achillea biebersteinii* in Turkey and different regions in the world

| Geographic region | Plant parts | Major compounds | References |
|---|---|---|---|
| Turkey, Adana | Aerial parts | 1,8-cineole (34.6%), camphor (12.9%), terpinyl acetate (6.0%) | (Tosun and Kürkçüoğlu 2018) |
| Turkey, Ağrı | Aerial parts | 1,8-cineole (30.6%), piperitone (28.9%), camphor (11.7%) | (Polatoğlu et al. 2013) |
| Turkey, Ankara | Aerial parts | 1,8-cineol (36.0%), camphor (30.3%), borneol (6.7%) | (Tabanca et al. 2011) |
| Turkey, Ankara | Aerial parts | p-cymene (27.0%), camphor (24.5%),1,8-cineol (8.8%) | (Tabanca et al. 2011) |
| Turkey, Bingöl | Aerial parts | 1,8-cineol (15.04%), camphor (14.55%), d-piperitone (12.53%) | (Toncer et al. 2010) |
| Turkey, Elazığ | Aerial parts | 1,8-cineol (42.17%), camphor (15.92%), p-cymene (5.67%) | (Toncer et al. 2010) |
| Turkey, Elazığ | Aerial parts | 1,8-cineole(33.2%),camphor(11.4%),2-isopropyl-5-methyl-3-cyclohexen-1-one (10.4%) | (Akbaba et al. 2018) |
| Turkey, Erzurum | Aerial parts | 1,8-cineole (38.09%), camphor (23.56%), borneol (5.88%) | (Kordali et al. 2009) |
| Turkey, Erzurum | Herbal parts | Piperitone (31.06%), camphor (12.46%), 1,8-cineol (10.93%) | (Bariş et al. 2006) |
| Turkey, Isparta | Aerial parts | 1,8-cineol (34.3%), camphor (21.7%), p-cymene (13.4%) | (Tabanca et al. 2011) |
| Turkey, Konya | Aerial parts | 1,8-cineol (36.9%), camphor (15.6%), piperitone (10.9%) | (Tabanca et al. 2011) |
| Turkey, Konya | Aerial parts | 1,8-cineol (35.5%), camphor (21.7%), p-cymene (13.3%) | (Tabanca et al. 2011) |
| Turkey, Mardin | Aerial parts | 1,8-cineol (31.76%), camphor (27.46%), d-piperitone (11.97%) | (Toncer et al. 2010) |
| Turkey, Siirt | Aerial parts | Ascaridol (61.95%), p-cymene (15.61%), 1,8-cineol (5.05%) | (Toncer et al. 2010) |
| Turkey, Sivas | Aerial parts | 1,8-cineole (31.1%), camphor (14.4%), α-thujone (12.9%) | (Polatoğlu et al. 2013) |
| Turkey, Sivas | Aerial parts | Piperitone (34.9%), 1,8-cineole (13.0%), camphor (8.8%) | (Sökmen et al. 2004) |
| Turkey, Van | Aerial parts | Camphor (20.77%), 1,8-cineol (18.60%), artemisia ketone (14.69%) | (Yildirim et al. 2015) |
| Egypt | Aerial parts | Cis-ascaridol (33.8%), p-cymene (22.4%), camphor (8.6%) | (Nenaah 2014a) |
| Iran | Stem | Camphor (38.1%), borneol (22.6%), 1,8-cineole (13.5%) | (Esmaeili et al. 2006) |
| Iran | Leaves | Camphor (33.7%), borneol (20.8%), 1,8-cineole (9.6%) | (Esmaeili et al. 2006) |
| Iran | Flowers | Camphor (36.3%), 1,8-cineole (22.3%), borneol (7.3%) | (Esmaeili et al. 2006) |
| Iran | Leaves | Camphor (26.32%), germacrene-D (15.75%), spathulenol (12.54%) | (Gharibi et al. 2015) |
| Iran | Flowers | Piperitone (45.9%), 1,8-cineole (17.6%), limonene (5.6%) | (Jaimand and Rezaee 2001) |
| Iran | Aerial parts | 1,8-cineole (7.9%), camphor (6.5%), α-fenchene (5.7%) | (Morteza-Semnani et al. 2005) |
| Iran | Leaves and flowers | Ascaridole (37.0%), piperitone (17.0%), camphor (12.0%) | (Rustaiyan et al. 1998) |

(continued)

**Table 1.4** (continued)

| Geographic region | Plant parts | Major compounds | References |
|---|---|---|---|
| Iran | Aerial parts | 1,8-cineole (45.2%), p-cymene (20.8%), cis-chrysanthenyl acetate (20.4%) | (Mirahmadi and Norouzi 2017) |
| Iran | Aerial parts (21 plants from different areas) | 1,8-cineole (6.5–68.3%), p-cymene (1.4–38.6%), camphor (1.2–29.3%), cis-chrysanthenyl acetate (0.0–55.8%), 4aα-7α-7aβ.-nepetalactone (0.0–30.2%), 4aα-7β-7aα-nepetalactone (0.0–43.3%) | (Mirahmadi et al. 2012) |
| Jordan | Aerial parts | Cis-ascaridole (36.2%), p-cymene (31.6%), carvenone oxide (6.4%) | (Bader et al. 2003) |
| Jordan | Aerial flowering parts/ air-dried and fresh parts collected from different growth stages | α-Terpinene (8.04%-51.67%), ascaridol (5.66%-44.39%), p-cymene (7.7%–25.85%), iso-ascaridol (7.06%-25.39%) | (Al-Jaber et al. 2014) |
| Saudi Arabia | Aerial parts | α-Terpinene (29.2%), p-cymene (22.9%), terpinen-4-ol (4.7%) | (Al-Said et al. 2016) |
| Saudi Arabia | Aerial parts | α-Terpinene (23.7%), p-cymene (21.4%), camphor (7.3%) | (Almadiy 2020) |

using ferric thiocyanate and thiobarbituric acid methods. The ethanol extract was found to be comparable with α-tocopherol in terms of antioxidant activity (Bariş et al. 2011). In a different study, the DPPH radical scavenging activity (83%) of the extract prepared for infusion was found to be close to that of the BHT (86.5%) (Deliorman Orhan et al. 2012). In another study, the essential oil and the water-soluble subfraction of methanol extracts from aerial parts were evaluated for their antioxidant capacity in vitro. The extract was found to be more effective than ascorbic acid in inhibition of superoxide assay. Apart from that, both lipid peroxidation inhibition and hydroxyl radical scavenging activity of essential oil was were found to be better than curcumin. The main compounds of the essential oil such as piperitone, borneol, 1,8-cineole, terpinen-4-ol, camphor, α-pinene, β-pinene, and *p*-cymene were also individually evaluated in terms of antioxidant activities, and none of them were found to have a strong activity (Sökmen et al. 2004). In a different study, the antioxidant activity for aerial parts of *Achillea biebersteinii* extracted by ultrasound-assisted extraction method using methanol 80% as solvent was found to be improved when comparing to maceration (Salarbashi et al. 2014). In another study, infusion of flower heads was found to be effective on antioxidant enzyme systems including catalase, superoxide dismutase, and glutathione peroxidase and also protective on glutathione and lipid peroxide levels and erythrocytes and leucocytes against $H_2O_2$-induced oxidative damage (Konyalioglu and Karamenderes 2005). In a different study, the ethanol extract of aerial parts was found to efficiently prevent protein oxidation and lipid peroxidation in vitro and significantly inhibit DNA damage which was induced by reactive oxygen species (Kizil et al. 2010).

### 1.5.2 Antinociceptive and Analgesic Activity

Methanol extract of flower was found to possess analgesic activity. Thermal (hot plate test) and chemical model (formalin test) were used to reveal the activity. Reduced flinching behavior in both early and late phases of formalin test and increased latency time in hot plate test confirmed this activity (Abbas et al. 2019). Jaffal and Abbas (2019) used three pain models to reveal the analgesic effect of the methanolic flower extract. They found that 300 mg/kg extract inhibited acetic acid induced abdominal cramps; inhibition of the extract (77.6%) was better than that of 70 mg/kg indomethacin (59.4%) in writhing test. The extract was found to

increase latency at 30 min and be as potent as 100 mg/kg diclofenac sodium in tail-flick test. The extracts decreased licking time significantly in both early and late phases in formalin test. The researchers finally found that the antinociceptive action is mediated by cholinergic receptors.

### 1.5.3 Wound Healing Activity

The wound healing activity of the extracts obtained by extracting the roots with different solvents were investigated on two different model including linear incision wound model and circular excision wound model which were tested on rats and mice. The n-hexane extract was found to perform better activity on wound models. The rats treated topically with n-hexane extract were found to exhibit a contraction value that was close to that of Madecassol used as the reference skin ointment on day 12. By application of n-hexane extract topically on incision wound model, a remarkable increase in wound tensile strength as compared to other extracts was observed on day 10. The remarkable wound healing activity was histopathologically supported as well (Akkol et al. 2011). Furthermore, in another study conducted on expression of some growth factors which is associated with wound healing activity, it was concluded that the pattern changes of growth factors such as decreased expression of TGFβ1 and increased expression of bFGF by hydroethanolic extract might have induced wound healing and reduce scar formation (Hormozi and Baharvand 2019).

### 1.5.4 Central Nervous System Activity

The effects of *Achillea biebersteinii* on anxiety, depression, and memory have also been investigated. In a study designed by giving essential oil to rats by inhalation to reveal these effects, anxiolytic and antidepressant effects and improved memory formation were seen in scopolamine-induced amnesic rats (Akbaba et al. 2018). In another study, methanol extract of flowers was found to possess anxiolytic but no antidepressant action (Abbas et al. 2019). In a study conducting the neuroprotective effect of *Achillea biebersteinii* on spinal motoneurons denegation after sciatic nerve compression in rats, the neuroprotection activity on spinal cord alpha motoneuron were detected after administration of alcoholic and aqueous extract of leaves intraperitoneally (Alikhanzade et al. 2014). In another study, copper nanoparticles synthesized using leaves of *Achillea biebersteinii* was assessed to possess cell death-suppressing effects on nerve cells, using high dose of methamphetamine which causes cell death in the PC12 cell line through induction of nitric oxide production and apoptosis. It significantly was found to increase cell viability and prevent nitric oxide production, suppress cell cytotoxicity, and inhibit caspase-3 activity and DNA fragmentation (Wang et al. 2020). In another study, Sevindik et al. (2015) recorded that the ethyl acetate extract at a dose of 200 μg/mL displayed the strongest inhibition to acetylcholinesterase (67.2%). Butyrylcholinesterase inhibitory activity was detected to be 50.3%. However, both inhibitory activities were found to be lower as compared with neostigmine (100%).

### 1.5.5 Anticancer Activity

The different extracts of aerial parts significantly were found to decrease the viability of HT-29 (colorectal adenocarcinoma) cells in a dose-dependent manner. It has been shown that at 200 and 1000 μg/mL, cell viability decreased from 72.1% to 23.1% for hexane, from 52.0% to 17.5% for chloroform, and from 44.1% to 12.0% for methanol extract, respectively. For 5-fluorouracil, these survival rates at 100 and 1000 μg/mL concentrations were 51.4% and 7.7%, respectively. Combined treatment of methanol, chloroform, and hexane extracts with 5-fluorouracil at IC50 doses decreased the cell viability to 14.9%, 19.1%, and 26.0%, respectively. Moreover, the extracts administered alone and in combination with 5-fluorouracil induced apoptosis; significantly downregulated Akt, mTOR, and Bcl-2

expression; upregulated p53, PTEN, Bax, and p38 MAPK expression; and exhibited anti-angiogenetic effects (Erdogan et al. 2020). In another study, the 80% ethanol extract of aerial part was tested for anticancer activity. It was found to exhibit cytotoxic activity against six cell lines, viz., MCF7 (human breast ductal carcinoma), AGS (human Caucasian gastric adenocarcinoma), SW742 (human colorectal adenocarcinoma), A375 (human melanoma cancer), PLC/PRF/5 (human liver hepatoma), and SKLC6 (human lung carcinoma) with IC50 values of 47.468 μg/mL, 32.773 μg/mL, 41.103 μg/mL, 36.178 μg/mL, 41.806 μg/mL, and 57.024 μg/mL, respectively (Ghavami et al. 2010). In another study conducted on the cytotoxic properties of the silver nanoparticles (Ag-NPs) synthesized using flower extract on the MCF-7 (human breast cancer) cell line, the Ag-NPs were found to decrease the viability of cell in a dose-dependent manner. DNA fragmentation in MCF-7 cells, inhibition of MCF-7 cell proliferation, occurrence of apoptosis on MCF-7 by suppressing specific cell cycle genes, and simulation of programmed cell dead genes were found to be the guiding mechanisms. Furthermore, caspase-3 and caspase-9 activities confirmed that the MCF-7 cell death was involved in a caspase-dependent intracellular pathway. Genes associated with apoptosis induced by the Ag-NPs were also confirmed by regulation of the Bax and Bcl-2 gene expression (Baharara et al. 2015). In a study investigating the potential melanoma-preventive effect of the hydroglycolic extracts from the flowering aerial parts of *Achillea biebersteinii* in topically applied formulations, in addition to displaying lower cytotoxicity against HaCaT cells – the non-cancerous human keratinocytes used as control cells – the hydroglycolic extracts were found to be cytotoxic against A375, the human malignant melanoma cell line (Gaweł-Bęben et al. 2020).

### 1.5.6 Insecticidal Activity

The essential oil obtained from aerial parts was found to be very effective against adult potato Colorado beetle (*Leptinotarsa decemlineata*) with high mortality percentages even at the lowest dose (Çakır et al. 2016). In another study in which essential oil was used, it was found that it may be used in the fight against *Hyphantria cunea* that cause severe damage in forests, agricultural fields, and fruit gardens (Gokturk et al. 2017). The essential oils of aerial parts from different locations in Turkey were found to exhibit high contact toxicity against *Sitophilus granarius*, but fumigant toxicity against this pest was low for this oil (Polatoğlu et al. 2013). In a study conducted by Nenaah (2014a), the powders or essential oils of *Achillea biebersteinii* were found to have significant toxicity against harmful pests (*Tribolium castaneum*, *Sitophilus oryzae*, *Rhyzopertha dominica*) of stored grains. In another study in which essential oil of aerial parts was used, it exhibited fumigant and contact toxicity as well as repellent activities against Khapra beetle (*Trogoderma granarium*) which harm stored cereal and their products worldwide (Nenaah 2014b). In the study in which the subject of another research was the red flour beetle (*Tribolium castaneum*) damaging stored grains, the essential oil was found to be exhibit fumigant and contact toxicity as well as growth inhibitory activities against this insect. Moreover, toxicity of the oil prepared as nano-emulsion was increased dramatically, when used as fumigant (Nenaah 2014c). As a last and important example, the essential oil and major fractions were observed to exhibit mosquitocidal activity considerably against *Aedes aegypti* known as the common vector of dengue fever (Almadiy 2020).

### 1.5.7 Antidiabetic Activity

The ethyl acetate extract was found to possess potent intestinal α-amylase inhibitory activity which causes reduced postprandial glycemic excursions induced by starch (Abd-Alla et al. 2016). In another study, the ethanolic extract of aerial parts exhibited potent antihyperglycemic effect in both diabetic model type I (streptozocin-induced diabetic rat model) and type II (high fat

diet streptozocin-induced diabetic rat model). The extract was found to decrease significantly fasting blood glucose levels, improve remarkably oral glucose tolerance, tend to raise serum insulin levels, and enhance β-cell regeneration. Moreover, it was found to be more effective than the reference standards, metformin and glibenclamide (Ahmad et al. 2017).

### 1.5.8 Antimicrobial, Antifungal, and Antiprotozoal Activity

Chloroform extract of *Achillea biebersteinii* was determined against some Gram-positive bacteria and Gram-negative bacteria and yeasts, *Candida albicans* and *Candida tropicalis* with disc diffusion method. The extract exhibited inhibition zones ranging from 5 to 27 to all bacteria tested except *Pseudomonas aeruginosa* and no anticandidal activity. The extract was found to possess better antibacterial activity against the Gram-positive bacteria than Gram-negative bacteria. The inhibition zones ranged from 25 to 27 mm with the largest inhibition zone values observed against *Bacillus cereus* and *Bacillus subtilis*, respectively. Among the Gram-negative bacteria, *Yersinia enterocolitica* (16 mm) and *Salmonella enteritidis* (18 mm) were the most sensitive bacteria to the extract (Doğan et al. 2010). In a different study, the extract prepared from decoction of inflorescence exhibited strong activity against both *Mycobacterium avium* and *Mycobacterium tuberculosis* (Deliorman Orhan et al. 2012). In a study investigating the effects of essential oil from dried flowering aerial parts on six bacteria, using disc diffusion method, the essential oil was found to display a low to moderate effect against all tested bacteria, including *Pseudomonas aeruginosa*, and it was found that its effects were rather weaker than antibiotics, ampicillin, and ofloxacin (Yildirim et al. 2015). In another study in which hydro-alcoholic and aqueous extracts were tested using disc diffusion method, the hydro-alcoholic extract was found to be susceptible to all Gram-positive bacteria including *Staphylococcus aureus* (22 mm), clinical strain methicillin-resistant *Staphylococcus aureus* (22 mm), *Bacillus cereus* (22 mm), and *Streptococcus pneumoniae* (30 mm) except *Enterococcus faecalis*. On the other hand, researchers did not observe significant activity on Gram-negative bacteria and *Candida* species. Determination of the MIC and MBC values showed that the hydro-alcoholic extract possessed bactericidal activity against *Enterococcus faecalis*, *Streptococcus pneumoniae*, *Bacillus cereus*, and *Klebsiella pneumoniae* rather than inhibitory effect (Hammad et al. 2013). Zengin et al. (2017) detected good antibacterial potential against some pathogens such as Gram-negative bacteria (*Salmonella typhimurium*, *Escherichia coli*, *Listeria monocytogenes*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*) and Gram-positive bacteria (*Staphylococcus aureus*, *Micrococcus flavus*, *Bacillus cereus*) in a study in which they tested extracts prepared with different solvents. While all extracts showed higher antibacterial effect than ampicillin, ethyl acetate extract was found to show the highest antibacterial effect, followed by methanol and water extract, respectively. They also found good antifungal activity against *Aspergillus ochraceus*, *Aspergillus versicolor*, *Aspergillus fumigatus*, *Aspergillus niger*, *Penicillium verrucosum*, *Penicillium ochrochloron*, *Penicillium funiculosum*, and *Trichoderma viride*. In antifungal tests, methanol and water extract were found to possess the highest and lowest effect, respectively. Ketoconazole and bifanazole displayed same or less activity than the extracts, but the exception for bifonazole was observed; their fungicidal activity was higher than extracts. In a different study, methanolic extract obtained from flowers and leaves showed promising antibacterial effects on *Staphylococcus aureus* and *Klebsiella pneumoniae*, but no antimicrobial activity on *Salmonella enteritidis*, *Escherichia coli*, and *Pseudomonas aeruginosa* was detected (Kılıc et al. 2018). In another study in which methanolic extract and essential oil of herbal parts were tested against 35 bacterial strains, 19 fungi, and 1 yeast, the extract did not exert any antimicrobial activity, but the essential oil of plant was found to be effective on only six bacteria. The activity was weaker than the antibiotics. However, essential

oil exhibited strong antifungal activities against fungi strains such as *Fusarium acuminatum*, *Sclorotinia sclerotiorum*, *Sclorotinia minor*, *Rhizoctonia solani*, and *Trichophyton mentagrophytes* (Bariş et al. 2006). In a study conducted on the essential oil, its fractions and two fractions of methanol extracts from aerial parts, although the water fraction of methanol extract did not show any antimicrobial activity, chloroform fraction was found to possess moderate activity against *Clostridium perfringens*, *Bacillus cereus*, and *Candida albicans*. As for the essential oil, it showed stronger and broader activity, compared to the methanolic extracts, against microorganisms, *Candida albicans* in particular, followed by *Clostridium perfringens*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, and *Mycobacterium smegmatis*, in that order. *Pseudomonas aeruginosa* was the only microorganism that was resistant to both the oil and the extracts. As a result of the investigation of antimicrobial activity of essential oil fractions, the fractions generally showed same or higher activity than crude one. Especially, the fractions containing camphor and 1,8-cineole were found to be more effective, followed by piperitone and borneol (Sökmen et al. 2004). In a different study conducted on essential oil, it is found to show good activity against all tested bacteria with MIC value ranging from 0.125 to 1 mg/mL. Non-biofilm-forming strains *Staphylococcus epidermidis* and *Pseudomonas aeruginosa* were the most susceptible and resistant, respectively. The essential oil was effective against methicillin-resistant *Staphylococcus aureus* at sub-inhibitory concentrations. In addition to antibacterial effect, it has been determined to be an antibiofilm agent causing cellular death by impairing permeability of the cell membrane. Minimum biofilm inhibitory concentrations were found to be in the range of 0.125–4 mg/mL (Al-Shuneigat et al. 2020). In addition to the antimicrobial effects of essential oil, its synergistic effect with amikacin can be given as an example of lowering the dose of antibiotics by creating a synergistic effect with antibiotics (Mahboubi and Feizabadi 2016). In another study, the essential oil of aerial parts was found to possess potent antifungal activities against five phytopathogenic fungal species including *Rhizoctonia solani*, *Aspergillus flavus*, *Sclerotini aclerotiorum*, *Bipolaris oryzae*, and *Fusarium verticillioides* (Mirahmadi and Norouzi 2017). In another study monitoring different extraction techniques on antibacterial activity, it was found that ultrasound-assisted extraction of *Achillea biebersteinii* significantly increased the antimicrobial effects of the extracts compared to macerates. Remarkable effects on methicillin-resistant *Staphylococcus aureus*, biofilm-producing *Staphylococcus epidermidis*, and resistant hospital strains of *Staphylococcus aureus* were observed. For example, as a result of testing different extraction techniques on resistant hospital strains of *Staphylococcus aureus*, MIC value was found to decrease from 10 mg/ml in maceration technique to 0.08 mg/ml in ultrasound-assisted extraction with 100% high intensity (Salarbashi et al. 2014). In a similar study, methanol extracts of the aerial parts using classical maceration and high-intensity ultrasound-assisted extraction methods at three different pH values were prepared to investigate the antimicrobial effects. Extracts, especially those prepared by ultrasound methods, were active against all of the tested microorganisms, namely, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Salmonella typhi*, *Bacillus cereus*, and *Candida albicans*. The MIC values were eight times on *Escherichia coli*, two times on *Pseudomonas aeruginosa*, and approximately ten times lower on *Candida albicans* in high-intensity ultrasound-assisted extraction methods (Salarbashi et al. 2012). In a different study, essential oil and major fractions from aerial parts and nano-emulsions prepared from both essential oil and major fractions by high pressure homogenization technique were assessed against Gram-negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella enteritidis*) and Gram-positive bacteria (*Listeria monocytogenes*, *Staphylococcus aureus*). As a result, essential oils tested were found to be more effective on the Gram-positive bacteria. The most resistant bacteria was found to be *Pseudomonas aeruginosa*. The crude oil was found to be more active than its

major components. When nano-emulsions were tested, it was found that the activity of essential oil and fractions increased significantly. To give an example, diameter of inhibition zones reached from 21.5 to 34.5 mm, and MIC was found to reach from 60.0 to 15.0 mg/ml with nano-emulsions against *Staphylococcus aureus* (Almadiy et al. 2016). In a study conducted on the 13 plant extracts including *Achillea biebersteinii*, all plants were tested against promastigote and amastigote forms of *Leishmania amazonensis*, and also cytotoxic activity on normal macrophages from normal mice was assessed. The most promising plant was found to be *Achillea biebersteinii* (Al-Sokari et al. 2015). In a different study, by testing various fractions of the aerial parts on *Trypanosoma cruzi*, which was the parasitic agent of Chagas disease in vitro, it was found that especially the diethyl ether fraction of aerial parts was more effective, but it was observed that the effect was reduced in the water and methanol fraction (Gohari and Saeidnia 2005).

### 1.5.9 Protective of the Liver and Kidney

Administration of aqueous extract to guinea pigs whose liver was damaged by dimethoate pesticide was found to display hepatoprotective activity. The treatment with extract remarkably was detected to reduce serum levels of hepatic enzymes such as AST, ALT, and ALP. This finding also was supported by histopathological examination of the liver (Al-Awthan et al. 2017). In another study, researchers investigated the effect of oral administration of essential oil on $CCl_4$-induced hepatoxicity in rats. They found that the elevation of the enzymes (GPT, GGT, GOT, and ALP) and bilirubin concentrations as well as the level of malondialdehyde, nonprotein sulfhydryl, and total protein contents in liver tissues were significantly restored toward normalization by pretreatment with essential oil. Central vein and normal hepatocytes were also confirmed by histopathological examination in the rats treated with essential oil (Al-Said et al. 2016).

### 1.5.10 Other Activities

In a study evaluating therapeutic and protective effects of ethyl acetate extract against gastric ulcer induced by ethanol in rats, it was found that treatment with extract resulted in therapeutic and protective effects against gastric ulcer by improving in gastric volume, total acidity, lesion counts, and oxidative stress markers: malondialdehyde, glutathione, and superoxide dismutase. The results were confirmed by histopathological changes seen in gastric mucosa. Therapeutic effects of the plant extract were found to be higher than its protective effect (Abd-Alla et al. 2016).

The silver nanoparticles using *Achillea biebersteinii* extracts were found to display significant effect on the angiogenesis process in different studies using angiogenesis of chick chorioallantoic membrane model (Zamani-Esmati et al. 2018) and rat aortic ring model (Baharara et al. 2014).

The high serum total cholesterol, triglyceride, LDL levels, and hepatic total cholesterol and triglycerides were found to decrease by oral administration of the ethanolic extract of the aerial part at a dose of 400 mg/kg for 20 days in hyperlipidemic hamsters caused by hypercholesterolemic diet, with no significant effect on HDL cholesterol (Mais et al. 2016).

Demirel et al. (2014) investigated the effects of plant extracts prepared from different polarity solvents on the treatment of endometriosis. After treatment with the extracts, they found that volumes of endometrial foci significantly decreased, and no adhesion was detected. The decrease of TNF-α, VEGF, and IL-6 levels was also observed.

In one of two similar studies based on the measurement of antiplatelet activity on human whole blood in vitro, the hydroalcoholic extract of the plant was tested. Although the hydroalcoholic extract did not show any inhibition of platelet aggregation induced by both collagen and ADP at lower concentration, the platelet aggregation induced by ADP was seen with increasing dose of the extract given. Platelet aggregation induced by collagen less effectively was found to increase (Hammad et al. 2013). In the second similar study conducted on essential oil, strong inhibition of the platelet aggregation induced by ADP and collagen was found by Al-Jaber et al. (2014).

The hydroglycolic extracts from the flowering aerial parts showed significant tyrosinase inhibitory in the study evaluating potential cosmetic application of extract (Gaweł-Bęben et al. 2020). In other research, many extracts and their active fraction from flowering aerial parts extracted with a different extraction procedure using ethanol (75%) were assessed on mushroom and murine tyrosinase inhibitory assays and melanin release assay. The dicaffeoylquinic acid derivatives and caffeoylquinic acid derivatives were found to be more likely responsible for inhibition of mushroom tyrosinase in extracts and fractions. In murine tyrosinase inhibitor assay, ferulic acid was seen as the most active compound. Apart from that, melanin release from B16F10 murine melanoma cells was reduced by ferulic acid (Strzępek-Gomółka et al. 2021).

## 1.6 Clinical Studies

No information available.

## 1.7 Toxicological Studies

The acute toxicity of the essential oil was studied at various dose concentrations, and no pathological symptoms or mortality were observed even at the maximum dose of 0.5 ml/kg, p.o. on mice (Al-Said et al. 2016).

## 1.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies

No information available.

## 1.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

*Achillea biebersteinii* has been a valuable plant for people that suffered from many diseases in terms of ethnobotanical for a long time (Yeşilada et al. 1995; Sezik et al. 1997). Its extracts and essential oils were found to exhibit powerful biological activities such as potent antioxidant (Sökmen et al. 2004; Deliorman Orhan et al. 2012), insecticidal (Almadiy 2020), antimicrobial (Salarbashi et al. 2012; Zengin et al. 2017), anti-ulcerogenic (Abd-Alla et al. 2016), antiplatelet (Hammad et al. 2013), anxiolytic (Akbaba et al. 2018), antidiabetic (Ahmad et al. 2017), anti-nociceptive (Jaffal and Abbas 2019), and antitumoral (Baharara et al. 2015). Apparently, there is a close relationship between ethnobotanical usage and pharmacological data. However, some reported information from ethnobotanical survey of *Achillea biebersteinii* have not been supported by pharmacological studies, e.g., eczema, respiratory problems, diuretic, expectorant, and indigestion. Since many studies are lacking in terms of active compounds and their mechanisms of action pathways, more studies must be designed to find out their potential biological activities of responsible components. Although acute toxicity of essential oil was not observed even at highest dose on mice (Al-Said et al. 2016), toxicity studies and safety testing should be performed because flowers and aerial parts are especially widely preferred by local people for curing themselves against health complaints. On the other hand, even though in humans clinical effectiveness of *Achillea millefolium* and *Achillea wilhelmsii* (Salehi et al. 2020), which share the same genus with *Achillea biebersteinii*, have been proved, there are no clinical trials on *Achillea biebersteinii*.

## 1.10 Challenges and Future Recommendations as Potential Drug Candidate

The phytochemistry and bioactivity results conducted on *Achillea biebersteinii* are very promising. In addition to the discovery of new pharmacologically active compounds, the use of essential oils and extracts seems possible in the near future, especially for the food and cosmetic industries. It appears to be an alternative to artificial additives in terms of food technologies due to its potent antioxidant, antimicrobial, and antifungal effects on plant and food pathogens. At the same time, an ecofriendly solution is waiting at our door against insects, which cause serious product losses and are vectors of dangerous disease for many people. However, the scarcity of toxicity studies on these areas should be resolved as soon as possible and effective use in these areas will be provided. Unfortunately, this plant, on which there are no clinical studies, but whose valuable effects have been discovered, will provide valuable contributions in the field of treatment by revealing the effects of this plant with clinical studies.

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# *Aesculus hippocastanum* L.

2

Sefa Gözcü

**Abstract**

Medicinal plants have been used in the treatment of various diseases since ancient times. *Aesculus hippocastanum* (horse chestnut) is a popular herb recognized worldwide and used in treatment. The seed extract of the plant contains phytocompounds such as flavonoids, hydroxycoumarins, proanthocyanidins, sterols, tannins, amino acids, and triterpenoid saponin glycosides. Studies have confirmed that *Hippocastani semen* extracts and pure substance have various activities, including anti-inflammatory, antibacterial, antifungal, antiviral, antiangiogenic (vascular protection), anti-obesity, antioxidative, antidiabetic, antidiabetic neuropathy, hepatoprotective, anticoagulant, antihematoma, antigenotoxic, anti-infertility, and cytotoxic properties. Due to the activity of *A. hippocastanum* extracts and their bioactive compounds, this herb may be useful as an alternative therapy for a variety of ailments.

**Keywords**

*Aesculus hippocastanum* · Horse chestnut · Folk medicine · Bioactive compound · Aescin · Pharmacological properties

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## 2.1 Introduction

### 2.1.1 Description of *Aesculus hippocastanum* L.

*Aesculus hippocastanum* L. (Hippocastanaceae) is a perennial plant. It is a plant in the form of a tree with a height of 30–35 m and a body circumference of 2 m. Leaves are 20 cm long and 10 cm wide, mucronate, with petiole of 15–20 cm long and oblong leaf blade. Most of the flowers, which are usually white-red, are male and have 5–7 petals. There are yellow-red spots on the petals and sepals are campanulate. Stamens have red anthers, the ovary is 3-valved. The fruit capsules have 1–3 large seeds (PDR 2000; Bombardelli et al. 1996).

### 2.1.2 Synonyms

*asplenifolia* Loudon
*castanea* Gilib.
*hippocastanum* var. beaumanii C.K.Schneid.
*hippocastanum* f. beaumanii (C.K.Schneid.) Dole
*memmingeri* K.Koch
*procera* Salisb
*septenata* Stokes
*Hippocastanum vulgare* Gaertn.
*Pawia hippocastanum* (L.) Kuntze
*Castanea equina* Bauh.



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### 2.1.3 Local Names

At kestanesi tohumu (Turkey); horse chestnut, buckeye (England); Castaño de Indias (Spain); Marronier, Marronier d'Inde, Marronnier d'Inde (France); Ronskii kashtan (Russia); Castanha-da-India (Portugal); Jírovec (Czech); Rosskastanie (German); Ippocastano (Italy); Paardekastanje (Netherlands); Kasztan bialy (Poland); Divji kostanj (Slovenia); Haestkastanj (Sweden) (Blaschek et al. 2013; WHO 2002).

### 2.1.4 Occurrence/Habitat

Naturally, *A. hippocastanum* grows in sunny, moist, and windless areas at altitudes of 1300 and 1000 m. It also easily thrives in almost any soil including clay, chalk, sand, and acidic/alkaline. Although the plant copes with harsh climatic conditions, it can be negatively affected by salty soil, drought of upper soil layers, and water logging (Brune 2016).

### 2.1.5 Registered Pharmacopoeias and Monographs

German pharmacopoeia, European pharmacopoeia, French pharmacopoeia, English pharmacopoeia, Spanish pharmacopoeia, Martindale, EMA monographs, ESCOP monographs, Commission E monographs, PDR for herbal medicine, WHO monographs, FFD monographs.

### 2.1.6 Importance

*A. hippocastanum* L. is a well-known medicinal plant widely utilized in phytotherapy. The drug of *A. hippocastanum* is found in many countries' pharmacopoeias and monographs. It is a plant used in cosmetics and phytotherapeutic, especially in peripheral vascular diseases (Gastaldo et al. 1994).

### 2.1.7 Objective of This Chapter

The objective of this chapter reviews the medicinal and pharmacological properties along with botanical properties and chemical composition of *A. hippocastanum* plant.

## 2.2 Distribution and Status of Species

It is a tree that spreads naturally in West Asia and is cultivated in parks, waysides, and yards in America and Europe. It is widely grown in Eastern European countries, especially in Bulgaria, Greece, Albania, Turkey, the Caucasus, north of Iran, and the Himalayas. In addition to these, the plant is also cultivated in Northern Europe (Blumenthal 2000; PDR 2000; Bombardelli et al. 1996).

## 2.3 Comparison of Traditional/Ethnomedicinal/Local Uses: In Turkey and Throughout the World (Asia and Europe)

It is known that the tea prepared by crushing the seeds of horse chestnut is used for kidney and stomach pain in Turkey. In addition, it has been reported that the extract obtained from the seeds is consumed to eliminate the symptoms of hemorrhoids (Küçükkurt et al. 2010). It is stated that the extract obtained from horse chestnut fruits and leaves is used in cases of venous insufficiency, sinusitis, and sprains and for kidney stone reduction (Sarı et al. 2010). In Europe, the seeds of the plant are used internally as strengthening, narcotic, and antipyretic in folk medicine and externally as wound healing (Grieve 1971; Edwards et al. 2015). It also is reported that horse chestnut seeds and shells are used in venous insufficiency in Europe (EMA 2009; ESCOP 2003). In folk medicine, it is known that seeds and shells of horse chestnut are used for hemorrhoids and uterine bleeding. It is also known that

oral over-consumption of horse chestnut seeds in children causes poisoning (Fluck 1988). In China, it has been used as a spasmolytic in the treatment of distention and as analgesic in the chest and heart disease (WHO 2002).

## 2.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques (Classification and Structures of Few Representatives)

The major therapeutically effective compound is aescin in its seeds. Aescin, which has a triterpene saponin structure, is available in three different forms. These are $\alpha$-aescin, $\beta$-aescin, and cryptoaescin. In addition, there are flavonoids (rutin, quercitrin, isoquercitrin, quercetin kaempferol, and glycosides of aglycones), hydroxycoumarins (aesculin, fraxin, scopolin), tannins, proanthocyanidins, sterols (stigmasterol, $\alpha$-spinasterol, $\beta$-sitosterol), and amino acids (Yoshikawa et al. 1994; Blumenthal 2000; PDR 2000; WHO 2002; Morimoto et al. 1987; ESCOP 2003; Barnes et al. 2003; Zhang et al. 2010; Idris et al. 2020). The extract produced from *Hippocastani semen* is standardized to 16–20% aescin content (PDR 2000).

## 2.5 Scientific Evidences: Pharmacological Activities (All Major Therapeutic Activity with In Vitro and In Vivo Studies, Mechanism of Action)

### 2.5.1 In Vitro Assays

#### Anti-inflammatory Activity

In a completed study, the anti-inflammatory effect of aescin in a synoviocyte model for osteoarthritis was investigated. Comparing the anti-inflammatory effect of aescin, dexamethasone, and ibuprofen on the protein expression of Cox-2, IL-1$\beta$, IL-$_{18}$, TNF-α, and INOS in lipopolysaccharide (LPS) derived bovine fibroblast-like synoviocyte, aescin reduced the productions of COX-2 (30%), IL-1$\beta$ (29%), IL-$_{18}$ (28%), TNF-$\alpha$ (32%), and INOS (28%). It was observed that ibuprofen and dexamethasone, which are positive controls, decreased all parameters by 25–29%. It was emphasized that aescin mimics the pharmacological effects of dexamethasone and ibuprofen and can replace synthetic drugs (Maghsoudi et al. 2018).

#### Antioxidant Activity

Superoxide-anion and hydroxyl radical scavenging effect of *A. hippocastanum* seeds extract was investigated. It was observed that the extract ($IC_{50:}$ 0.24 μM) scavenged a high percentage of superoxide-anion when compared with ascorbic acid ($IC_{50:}$ 4.10 μM). In addition, considering the hydroxyl radical scavenging effect, the extract ($IC_{50:}$ 7.39 μM) showed a close effect to ascorbic acid ($IC_{50:}$ 3.30 μM) (Wilkinson and Brown 1999). In another study, in vitro antioxidant properties of ethanol extracts of *A. hippocastanum* seeds (0.2–1 mg/ml) were investigated. The scavenging ratio (80.25%) of the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical of the ethanolic extract (1 mg/ml) showed values close to the control group ascorbic acid (97.5%) (Selamoglu et al. 2017). In vitro antioxidant properties of methanol extract prepared from *A. hippocastanum* seeds and aescin compound obtained from this extract were investigated. In general, the activity of the methanol extract against superoxide radicals did not exceed 15% at pH 7.4, with the highest inhibition (46.11%) noted against hydroxyl radicals at a concentration of 100 μg/ml; however, no significant activity against other radicals was observed. Aescin (50%) showed a better ability to counteract nitric oxide oxidation products, nitrites (50 μg/ml). However, as the concentration increased, the efficiency of both the extract and aescin completely disappeared (Vašková et al. 2015).

#### Antibacterial Activity

In study on *Hippocastani semen*, using the extract obtained from the seed of the plant, ZnO nanoparticles were made, and the antimicrobial activity

of this formulation and extract was measured. At the end of the study, it was reported that both the formulation (100 µg/ml) prepared with the extract and the extract (150 µg/ml) had a bactericidal effect against *Bacillus thuringiensis* (Colak et al. 2017). In another study, the antimicrobial activity of ethanol extracts of folia, semen, and capsule of *A. hippocastanum* were investigated. All of the extracts (1 mg/ml) were evaluated by the disk diffusion method using seven strains (*Bacillus cereus*, *Staphylococcus epidermidis*, *Proteus vulgaris*, *Streptococcus pneumonia*, *Listeria monocytogenes*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*) of bacteria. The ethanolic extract of horse chestnut capsule (12.0 mm) showed higher bactericidal effect on *P. vulgaris* bacteria compared to cefazoline (7.0 mm) as positive control group (Ertürk 2017). In a similar study, the antimicrobial activity of methanol extract of flower of *A. hippocastanum* was investigated. The extract was evaluated by means of the microbroth dilution method using ten strains (*Listeria ivanovi*, *Serratia rubidaea*, *Listeria innocua*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus raffinosus*, *Lactobacillus rhamnosus*, *Staphylococcus epidermis*, *Brochothrix thermosphacta*, and *Paenibacillus larvae*) of bacteria. The methanolic extract of horse chestnut flower ($MIC_{50}$:383.65) showed higher bactericidal effect on *L. ivanovi* bacteria (Vatľák et al. 2021).

## Antifungal Activity

In a study, the antifungal activity of ethanol extracts of folia, semen, and capsule of *A. hippocastanum* were investigated. *A. hippocastanum* extracts (1 mg/ml) were evaluated by the disk diffusion method using one fungus strain (*Aspergillus niger*). The ethanolic extracts of folia of *A. hippocastanum* (7.0 mm) and semen of *A. hippocastanum* (7.0 mm) showed weak antifungal effect compared to nystatin (15.3 mm) as positive control (Ertürk 2017).

## Antiviral Activity

In a study, the antiviral activity of horse chestnut seed (HCE) extract and its main component, *β*-aescin, was investigated. *β*-aescin and extract were tested between 100 and 0.1 µg/ml dosages on human epidermoid cancer cell line (HEp-2) and human lung carcinoma cell line (A-549) infected with respiratory syncytial virus. *β*-aescin showed high antiviral effect on both HEp-2 cell line ($EC_{50}$:1.6 µg/ml) and A-549 ($EC_{50}$:2.4 µg/ml) (Salinas et al. 2019). In a similar study, the antiviral activity of HCE and its main component, *β*-aescin, on herpes simplex virus (HSV-1) was investigated. *β*-aescin and extract were tested on human corneal-limbal epithelial (HCLE) cells and normal human conjunctival epithelial cell line (NHC) infected with HSV-1. *β*-aescin showed high antiviral effect on both HCLE cell line ($EC_{50}$:1.5 µg/ml) and NHC ($EC_{50}$:2.4 µg/ml) (Michelini et al. 2018). In another study, the antiviral activity of aescin on SARS virus was investigated. *β*-aescin was tested on Vero E6 cells infected with SARS virus. *β*-aescin ($EC_{50}$:6.0 µM) showed high antiviral effect on SARS virus (Wu et al. 2004). In another study, the porcine epidemic diarrhea virus (PEDV) inhibitory effects of aescin (10–40 µM) was investigated on vero cell. Aescin ($EC_{50}$:20 µM) showed higher antiviral effect on PEDV compared to 6-azauridine ($EC_{50}$:40 µM) as positive control group (Kim et al. 2017).

## Cytotoxic Activity

It has been reported that aescin ($IC_{50}$:30 µM) provides a cytotoxic effect by providing TNF-*α* mediated apoptosis on Cellosaurus cell line (KBM-5) and the human T lymphocyte cell line (Jurkat). It has been determined that aescin exerts this effect by inhibiting the activation of the NF-*k*B signaling pathway (Harikumar et al. 2010). Aescin ($IC_{50}$:35 µM) has been tested on 786-O human kidney cancer cell line, and it has been observed that a high proportion of cancer cells have apoptosis. In addition, aescin does this by activating caspase-9 which is the caspase initiating and caspase-3 which is the effector caspase (Yuan et al. 2017). The antiproliferative and apoptotic effects of the extract standardized on aescin (18–22%) were investigated on breast cancer cell line (MCF-7), Jurkat, human epithelial carcinoma cell line (HeLa), and human leukemic lymphoblasts (CEM) cancer cell lines. At the end

of the study, it was observed that apoptosis was induced in all cell lines given the extract (incubation of MCF-7, Jurkat, HeLa, and CEM cancer cell lines with HCE at 125 μg/mL for 72 h caused 40.3%, 93.7%, 20.4%, and 32.3% reduction in cell survival, respectively) (Mojžišová et al. 2013). In a similar study, the cytotoxic effects of ethanolic extract from horse chestnut bark (0.01–0.5 mg/mL) were examined on MCF-7. Cell viability was reduced to 30% upon the addition of 0.5 mg/mL bark extract for MCF-7 cell line (Celep et al. 2012). In another study, the cytotoxic effects of aescin purified from HCE in C6 glioma and A549 lung adenocarcinoma cell lines were investigated using MTT. The results indicated that aescin has potent antiproliferative effects against C6 glioma ($IC_{50}$:16.3 μg/mL) and A549 cells ($IC_{50}$:11.3 μg/mL) (Çiftçi et al. 2015). Aescin, isolated from *A. hippocastanum*, has examined anti-tumor effects on four osteosarcoma cell lines MNNG/HOS, Saos-2, MG-63, and U2-OS. The $IC_{50}$ values of MNNG/HOS, Saos-2, MG-63, and U2-OS osteosarcoma cell lines after a 24 hour incubation with aescin were determined as 30.44 μM, 29.93 μM, 25.51 μM, and 32.40 μM respectively (Zhu et al. 2017).

#### Vasoactive Effects

The vasoactive effect of standardized horse chestnut seed extracts (16% aescin) and aescin on cow vein endothelium and human vascular endothelium was investigated. It was observed in standardized extract at a dose of 0.2 mg/ml and pure aescin at a dose of 0.1 mg/ml, vasoconstricted for 3 hours (ESCOP 2003). In a similar study, in the dose range of 5–10 mg/ml, aescin has been reported to cause vasoconstriction in veins isolated from humans and portal veins isolated from rabbit (Edwards et al. 2015). In another study conducted in the same direction, aescin was tested on an isolated rat aorta. According to this, aescin (100–400 mg/kg) exerted a protective effect by increasing nitric oxide formation in the aorta and caused contractions in the vascular endothelium depending on the dose (Guillaume and Padioleau 1994). In a study to investigate the mechanism of action of horse chestnut standardized extract with aescin (16–22%) on vascular contraction, it has been observed that the standardized extract (1 mg/ml) causes contraction in cow mesenteric veins ($K^+$ 100%) and arteries ($K^+$ 60%) depending on the dose. This contraction has been found to be mediated by 5-$HT_{2A}$ receptors (Felixsson et al. 2010).

### 2.5.2 In Vivo Assays

#### Anti-Obesity Activity

In a completed study, the anti-obesity effect of the aescin compound was investigated in mice fed with a high-fat diet for 5 weeks. In the control group animals, leptin (2.86 μg/L), $T_3$ (1.19 pg/ml), $T_4$ (0.62 ng/ml), and HDL (62.95 mg/ml) parameters increased compared to the aescin group in the parameters of leptin (5.33 μg/L), $T_3$ (1.21 pg/ml), $T_4$ (0.32 ng/ml), and HDL (92.71 mg/ml). However, there was no change in LDL concentration (Avci et al. 2010).

#### Antioxidant Activity

Ethanol extract of horse chestnut seeds was tested in mice induced by oxidative damage by feeding a high-fat diet for 5 weeks. When the blood taken from mice was examined at the end of the study, the MDA parameter was found to be lower in the mice given the extract (3.48 nmol/dl) compared to the control group (4.55 nmol/dl) (Küçükkurt et al. 2010). A completed study investigated the efficiency of aescin against cyclophosphamide (CPM)-induced cardiac damage. Catalase (CAT) and superoxide dismutase (SOD) enzymes were measured in blood samples, and it was stated that the CAT (32.78 mg/protein) and SOD (21.8 U/mg) enzyme activities of the aescin (10 mg/kg) group compared to the control group were very close to the CAT (30.2 mg/protein) and SOD (21.7 U/mg) enzyme activities (Gür et al. 2021). In another study, the effect of aescin was evaluated on acute lung injury induced by lipopolysaccharide (LPS) in mice. At the end of the study, SOD, GSH, and MDA parameters were measured in lung tissues extracted from mice. While SOD was measured as 80 U/mg protein in the aescin (3.6 mg/kg) group, it was observed that SOD was 72 U/mg protein in the control group. While GSH

and MDA values of the group given aescin were determined as 0.016 mg/kg protein and 24 nmol/mg protein, respectively, these parameters were found as 0.014 mg/kg protein and 22 nmol/mg protein, respectively, in the control group (Xin et al. 2011a).

### Anti-inflammatory Activity

In the study designed to investigate the anti-inflammatory effects of aescin against histamine-induced capillary permeability and carrageenan-induced paw edema in rats by applying topical gel, the carrageenan-induced paw edema animal model received 0.02 and 0.04 g/kg of aescin, with the inhibition rates being 33.7% and 37.2% at 1 h and 32.9% and 36.1% at 4 h, respectively. Dexamethasone (references drug) pretreatment demonstrated greater inhibition on paw edema at both times with the inhibition rates of 41.3% and 38%, respectively. In histamine-induced capillary permeability animal model, the effect of aescin on vascular permeability in this study was expressed as optical density at 610 nm ($OD_{610}$) aescin exhibited a dose-dependent decrease in $OD_{610}$, and the effects at the doses of 0.02 and 0.04 g/kg were significant, showing 23.8% and 27.3% inhibition, respectively, compared to that of dexamethasone as the positive control (30.5%) (ZHAO et al. 2018). In another study, the anti-inflammatory effect of aescin on a carrageenan-induced rat model was investigated. A dose of 50–200 mg/kg of aescin is sufficient to inhibit the increase of vascular permeability, while a dose of 200 mg/kg of aescins reduced the hind paw edema induced by carrageenin in rats (Matsuda et al. 1997). In another similar study, the anti-inflammatory activity of aescin was investigated in rats with paw edema with carrageenan induction. While the reference molecule corticosterone (1 mg/kg) edema inhibition was 0.69%, edema inhibition of aescin (2 mg/kg) was 7.91% (Xin et al. 2011b). In a similar study, the anti-inflammatory effect of aescin on carrageenan-induced paw edema and acetic acid-induced capillary permeability model was investigated. Aescin (1.8 mg/kg) inhibited paw edema that developed from 4 hours to 24 hours. Similarly, the positive control dexamethasone (4 mg/kg) inhibited paw edema from 4 hours to 12 hours. Diclofenac (6 mg/kg) given to the other positive control group could only inhibit paw edema from 2 hours to 6 hours ($p < 0.05$). When looking at the other animal model, aescin (3.6 mg/kg) was observed to inhibit acetic acid-induced capillary permeability from 8 hours to 24 hours, while diclofenac (3.6 mg/kg) inhibited from 10 minutes to 8 hours (Wang et al. 2013). In another completed study, the effect of aescin on omethoate-induced cerebral edema in rats was investigated. Seven hours after omethoate intoxication, the brain water content in the cerebrum was 78.1% in the group given with 0.9 mg/kg aescin and 77.6% in the healthy group ($p < 0.01$). While the effect of aescin on the amount of Evans blue in the cerebrum was 50.1 μg/g brain tissue, the amount of Evans blue in the cerebrum was measured as 49.9 μg/g brain tissue in the healthy group ($p < 0.01$) (Wang et al. 2011).

### Antidiabetic Activity

Saponins of aescin Ia, Ib, IIa, IIb, and IIIa purified from ethanolic extract of horse chestnut seeds were tested in an oral glucose tolerance test at a dosage of 100 mg/kg. Two hours after the start of OGTT, the closest result to the control group (87.9 mg/ml) was observed in the secondary substance aescin IIa (92.9 mg/dl). The results showed that more detailed studies are needed (Yoshikawa et al. 1994).

### Antidiabetic Neuropathy Activity

Venotrex tablets containing extract of *A. hippocastanum* were tested on 21 male rats with diabetic neuropathy. At the end of the 4 weeks, while the levels of fibronectin (117%), MDA (123.6 nM), TGF-$\alpha$ (18.9 pg/mL), creatinine (0.6 mg/dL), and urine proteinuria (1.71 mg/mL) decreased in the extract group, in the control group, fibronectin (147%), MDA (314.9 nM), TGF-a (29.3 pg/mL), creatinine (1.06 mg/dL), and urine proteinuria (3.1 mg/mL) did not reach the desired levels. Thus, it was reported that the side effects of stz-induced diabetic neuropathy disappeared in rats given

with Venotrex tablets containing extract (Elmas et al. 2016).

### Hepatoprotective Activity

Aescin was tested in rats with liver damage induced by $CCl_4$. When the aspartate aminotransferase (AST) (64.68 IU/L), alanine aminotransferase (ALT) (68.95 IU/L), alkaline phosphatase (ALP) (108.20 IU/L), and glutathione (GSH) (0.01 μmol/mg protein) parameters of the rats in the silymarin (50 mg/kg, po) group were compared with the AST (71.39 IU/L), ALT (71.7 IU/L), ALP (121.20 IU/L), and GSH (0.095 μmol/mg protein) values of the rats in the aescin (3.6 mg/kg.) group, it was found that silymarin was as effective in the aescin group (Singh et al. 2017). In a similar study, aescin (0.9 mg/kg, 1.8 mg/kg or 3.6 mg/kg) was tested in 56 male Swiss mice with liver damage induced by endotoxin. The AST (79 IU/L), ALT (39 IU/L), TNF-$\alpha$ (620 ng/L), and IL-1$\beta$ (0.275 ng/L) parameters of the mice in the control group were compared with the AST (82 IU/L), ALT (57 IU/L), TNF-$\alpha$ (630 ng/L), and IL-1$\beta$ (0.275 ng/L) values of the rats in the aescin (3.6 mg/kg.) groups. According to these results, it was emphasized that aescin has high hepatoprotective activity (Jiang et al. 2011).

### Anticancer Activity

Aescin (3 mg/kg) was tested in a xenograft animal model of human bladder cancer. Tumor size decreased (from 125 $mm^3$ to 75 $mm^3$) in cancer mice treated with aescin (3 mg/kg) for 25 days, while tumor size increased (from 125 $mm^3$ to 275 $mm^3$) in the control group (Cheng et al. 2018). In another study, aescin Ia (0.7, 1.4, 2.8 or 5.6 mg/kg) was tested in an animal model of lung cancer. Tumor size decreased (from 105 $mm^3$ to 65 $mm^3$) in cancer mice treated with aescin (2.8 mg/kg) for 10 days (Yang et al. 2004). In a similar study, $\beta$-aescin (500 ppm) was tested for inhibition of lung adenoma and adenocarcinoma induced by the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in female A/J mice. $\beta$-Aescin was observed to inhibit NNK-induced lung adenocarcinoma formation by 65% ($P < 0.001$) at 20 weeks and by 53% ($P < 0.0001$) at 37 weeks (Patlolla et al. 2013).

## 2.6 Clinical Studies (Ongoing, Proposed, and Completed Studies)

### 2.6.1 Anti-inflammatory Activity

In an 8-week study conducted to evaluate the safety and tolerability of *A. hippocastanum* seeds in the treatment of chronic venous insufficiency (CVI), patients were given 100 mg of extract. Ninety-one adverse events were reported in 87 patients with CVI complaints between the ages of 18 and 75. At the end of the 8-week study, it was reported that 81% of the patients in the study had clinical improvement in leg and ankle pain ($p < 0.001$) (Suter et al. 2006). Standardized extract (aescin: 100 mg) was tested in a double-blind study involving 240 patients with venous edema due to CVI. In the measurements made with the hydroplethysmometer, it was observed that the average leg volume, which was 1565 ml before the treatment, decreased to 1481 ml in the patients who were given the extract ($p < 0.001$) (Diehm et al. 1996). In a published review, *A. hippocastanum* seed extract was tested in patients with CVI for 2–16 weeks. In six of the seven randomized, controlled studies in the review, it has been reported that patients with CVI who use extracts compared to placebo have a significant reduction in their pain ($p < 0.005$). Similar improvement was observed in symptoms such as edema, leg circumference volume, and pruritus (Pittler and Ernst 2012). In a study involving 39 patients with chronic venous insufficiency, 19 patients received standardized horse chestnut extract (aescin 100 mg) and 20 patients placebo for 4 weeks. There was a significant decrease in foot and lower leg volumes in the extract group (after 14 days $p < 0.01$, after 28 days $p < 0.01$). In the same study, there was no significant difference in venous capacity or venous drainage when the legs were raised between the two groups (ESCOP 2003). In a double-blind study in which

23 healthy young individuals were given 150 mg of horse chestnut seed extract orally and another group of 14 people were given placebo, vascular tone and capillary capacity were measured. In the measurements made with plethysmometer before the extract was applied and 2 hours after the extract was applied, it was observed that the vascular tone significantly increased and the capillary capacity decreased in the standardized extract group (ESCOP 2003). In a double-blind study involving 137 postmenopausal women with chronic venous insufficiency, 51 patients were orally administered with 600 mg of standardized horse chestnut seed extract for 12 weeks; 1000 mg of standardized oxerutin mix was administered orally to 51 patients for 12 weeks; and placebo was administered to 35 patients. After 12 weeks of treatment, it was observed that patients who received standardized horse chestnut seed extract had a 100 ml reduction in leg volume (ESCOP 2003).

### 2.6.2 Anticoagulant Activity

Blood flow rate and coagulation were investigated in 30 patients with CVI who were given with 1800 mg/kg horse chestnut seed extract for 12 days. At the end of the study, while 30% increase was observed in the venous blood flow of the patients using aescin, it was revealed that blood viscosity decreased. In addition, it was reported that in 73% of the cases, their complaints disappeared (ESCOP 2003).

### 2.6.3 Anticancer Activity

In a clinical study conducted on 120 patients with thyroid cancer, the efficient and tolerability of aescin was investigated. After 9 days of 0.6 mg/kg aescin (IV) treatment, when the first and last measurements were compared, thyroid-stimulating hormone (TSH) level decreased to 0.77 IU/L, thyroglobulin antibodies (TgAb) level 10.13 IU/mL, thyroxine binding globulin (TBG) level 24.09 μg/L, and calcitonin level 74.01 ng/L. In addition to these data, the group treated with aescin increased both median PFS (progression-free survival) and median OS (overall survival). The median PFS (progression-free survival) was 2.44 years in the aescin group and 1.04 years in the placebo group. The median OS (overall survival) was also 7.6 years in aescin group and 3.73 years in the placebo group (Mei et al. 2017).

### 2.6.4 Antihematoma Activity

In a completed clinical trial, the efficacy of 2% aescin gel applied topically in 70 healthy volunteers with induced hematoma was investigated. It was determined that a significant decrease in hematoma pressure was observed between 1 and 9 hours following topical application ($p < 0.001$) (Calabrese and Preston 1993).

### 2.6.5 Anti-Infertility Activity

In a completed clinical trial, the effectiveness of aescin in improving sperm quality was investigated in male patients with infertility due to varicocele. In this study conducted on 219 patients, the patients were divided into three groups, namely, the group receiving standard drug therapy (control group), the group that underwent surgery, and the group receiving aescin (300 mg daily) in addition to the standard drug. After 2 months of treatment, the increase in sperm density was determined as 38.5%, 68.8%, and 57.5% in the control group, surgery group, and aescin group, respectively (Fang et al. 2010).

### 2.6.6 Gastroprotective Effect

In a clinical study, the gastric protective effect of aescin (5–25 mg) on 72 postoperative colorectal patients was investigated. Time to recovery of passage of gas (TRPG), time to recovery of gastrointestinal sounds (TRGS), and time to recovery of bowel movements (TRBM) were recorded to evaluate the efficacy of aescin. While TRPG was 65.50 + 26.70 h in the group given with

25 mg of aescin, it was determined as 82.81 + 14.85 h in the placebo group ($p = 0.022$). TRGS was 40.33 ± 14.09 h in the group given with 25 mg aescin and 49.61 ± 15.10 h in the placebo group ($p = 0.065$). When the TRBM of the 25 mg aescin (84.44 ± 19.74 h) group was compared with the placebo group (108.28 ± 35.78 h), again, TRBM was significantly shortened ($p = 0.019$) (Xie et al. 2009).

## 2.7 Toxicological Studies (Dose and Safety Profile, Acute, Chronic, and Mutagenicity Studies to Demonstrate Broad Spectrum Safety, GARS Status)

### 2.7.1 Dose and Safety Profile

#### Internal Usage

It is used in the treatment of varicose veins, phlebitis, and hemorrhoids occurring due to CVI (Barnes et al. 2003; Blumenthal 2000; ESCOP 2003; EMA 2009; WHO 2002; Demirezer et al. 2019). It is stated that it is used in flatulence, pain relief, and coronary heart diseases in China (Idris et al. 2020; WHO 2002). It is not used as food (Barnes et al. 2003; Blumenthal 2000; EMA 2009; ESCOP 2003; WHO 2002).

#### External Usage

It is registered to use in the form of compresses to eliminate the symptoms that occur in venous insufficiency, sprains, and crushes. In addition, it is also used in hematomas that occur after surgery and trauma (Blumenthal 2000; WHO 2002; Idris et al. 2020; Demirezer et al. 2019).

#### Mode of Administration and Dosage

The usage and doses of horse chestnut seeds and bark are given in Table 2.1 (EMA 2009; ESCOP 2003; Blumenthal 2000; Küçükkurt et al. 2010; PDR 2000; WHO 2002).

#### Side Effects

Case studies have shown that it can cause gastrointestinal system complaints such as nausea, vomiting, reflux, and allergic symptoms such as itching, rash, and contact dermatitis (Blumenthal 2000; ESCOP 2003; WHO 2002). It has also been stated that oral consumption of aescin causes delay of gastric emptying time and can cause hemolysis in red blood cells when administered IV (Küçükkurt and Fidan 2008; Blumenthal 2003).

#### Contraindications

It is not recommended in children under 12 years of age and during pregnancy/lactation, as there is not enough study (Edwards et al. 2015). It is contraindicated in patients with allergies to the Hippocastanaceae family, in patients with gall bladder disease and chronic renal failure, and externally to ulcerative skin (Mills and Bone 2004; Blumenthal 2000; WHO 2002).

#### Pregnancy and Lactation

It is not recommended to be used during pregnancy and breastfeeding unless prescribed by the physician (Mills and Bone 2004). In the clinical study conducted on pregnant women in the third trimester, it was stated that no side effects were observed (WHO 2002; Blumenthal 2003; ESCOP 2003). No side effects were detected in the oral use of standardized seeds of *A. hippocastanum* extract at a dose of 600 mg/daily (100 mg aescin/daily) for 2–4 weeks to support venous performance in pregnant women (Mills and Bone 2004).

**Table 2.1** The usage and doses of horse chestnut seeds and bark

| Mode of administration | Seeds | Bark |
|---|---|---|
| Dried powder drug | 1–2 g/daily | 3 × 275 mg/daily |
| Liquid extract of horse chestnut (1:2) | 2–5 ml/daily | |
| 5 mg aescin ampule | 5–20 mg daily | |
| 2% aescin gel | 2 × 1 daily | |
| Tincture of seeds of *A. hippocastanum* (1:5) with 75% ethanol | 5–15 ml/daily | |
| Standardized extract (100 mg/gr aescin) | 1–2 g/daily | |

### Warnings

It should be used with caution in patients with gall bladder disease and cardiac/renal failure and those using anticoagulants (Blumenthal 2003; WHO 2002; Mills and Bone 2004; PDR 2000).

### Drug Interactions and Other Interactions

It has been reported that it develops nephropathy due to the aescin in horse chestnut seed extract, so it should not be used with nephrotoxic drugs such as gentamicin (WHO 2002). It has been stated that due to the aesculetin in horse chestnut shell extract, when used together with agents such as acetyl salicylic acid and warfarin, the blood coagulation time will be prolonged (Blumenthal 2003; PDR 2000). In a study on rats, aescin has been observed to increase CYP1A2 enzyme activity while inhibiting CYP2C9 and CYP3A4 enzymes. Thus, it has been reported that it should be used carefully with drugs that are metabolized through these pathways (Huang et al. 2014).

## 2.7.2 Acute, Chronic, and Mutagenicity Studies to Demonstrate Broad Spectrum Safety

### Acute Toxicity

As a result of acute toxicity studies of horse chestnut seed extract on animals, $LD_{50}$ values are given in Table 2.2 (ESCOP 2003; WHO 2002).

**Table 2.2** $LD_{50}$ values of horse chestnut seed extract on animals

| | Mode of administration | | |
|---|---|---|---|
| Animal | Oral | IP | IV |
| Rabbit | 1530 mg/kg | – | 180 mg/kg |
| Rat | 2150 mg/kg | – | 165 mg/kg |
| Mouse | 990 mg/kg | 342 mg/kg | 138 mg/kg |
| Hamster | 10.7 g/kg | – | – |

### Subacute Toxicity

*Hippocastani semen* extract was given intravenously at a dose range of 9–90 mg/kg for 8 weeks in rats. At the end of the study, it was reported that 8 of 30 rats receiving horse chestnut extract (90 mg/kg) died (ESCOP 2003; WHO 2002).

### Chronic Toxicity

*Hippocastani semen* extract was orally administered to dogs at a dose range of 20–80 mg/kg per day for 34 weeks. It was reported that no toxic effects and organ damage were encountered at the end of 34 weeks. In another study, *Hippocastani semen* extract was administered orally to rats at a dose range of 100–400 mg/kg daily for 34 weeks. At the end of the study, no toxic effects and organ damage were observed in the rats. In addition, it has been reported that the oral daily therapeutic dose used for humans is eight times the highest oral dose administered to dogs (ESCOP 2003; WHO 2002).

### Mutagenicity and Teratogenicity

Mutagenicity of *Hippocastani semen* extract (0–10 mg/ml) was investigated on *Salmonella typhimurium* TA97a, TA98, TA100, TA102, and *E. coli* DH10B and CC104 strains by using Kado test. The extract ($8.8 \times 10^{-8}$) has been reported to have a weak mutagenic effect compared to methylene blue ($6.9 \times 10^{-9}$), which is a positive control against frameshift mutations in *E. coli* CC104 strain (Felipe et al. 2013). *Hippocastani semen* extract was administered intragastrically to rats (100–300 mg/kg) and rabbits (100 mg/kg), and no teratogenic effects were observed. However, a decrease in birth weight has been reported when pregnant rabbits are administered the extract at a dose of 300 mg/kg (WHO 2002).

### 2.7.3 GRAS Status

In the United States, no phlebotonic drug is approved by the US Food and Drug Administration (FDA) for treatment of CVI (Nitin Garg 2013).

## 2.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies (with Special Focus on Bioavailability and Metabolism of Active Constituents)

### 2.8.1 Commercial Formulations/Products

**Turkey**
Prepagel gel, Reparil gel N, Jelgo gel, horse chestnut complex lambert tablet, Venoxen tablet, Venomed tablet, Venotrex tablet, horse chestnut capsule.

**Europe**
Venostasin retard, Escin gel, Aescorin forte tablet, Prepagel gel, Noricave retard tablet, Venalot depot.

**USA**
Nature's Way Standardized Horse Chestnut, GNC Herbal Plus Horse Chestnut Extract, Best Naturals Horse Chestnut extract 300 mg.

### 2.8.2 Pharmacokinetic Studies

In a study carried out through IV administration of 5 mg aescin (rate of infusion 718 μg/min), the elimination half-life was determined at $t_{0.5}\alpha$ 6.6 min, $t_{0.5}\beta$ 1.74 hours, and $t_{0.5}\gamma$ 14.36 hours. Distribution volume under constant conditions was determined as 100.9 L and renal clearance as 1.7 ml/min. In addition, the bioavailability of aescin was determined to be 1.5% (ESCOP 2003). In another pharmacokinetic study, rats were given with daily IV 0.5 mg/kg doses of aescin and isoaescin, and $t_{1/2}$, MRT, CL, $V_d$, AUC, and F parameters were measured in blood samples taken at certain times. Absorption of aescin and isoaescin was very low with F values <0.25%. $t_{1/2,}$ MRT, CL, $V_d$, and AUC parameters of aescin were 6.09 ± 1.13 h, 5.23 ± 1.42 h, 0.880 ± 0.405 ml/min, 0.437 ± 0.116 l, and 10,720 ± 3990 ng h/ml respectively. $t_{1/2}$ and AUC parameters of isoaescin also were 7.33 ± 1.62 h and 9000 ± 4420 ng h/ml, respectively (Wu et al. 2012). In transdermal absorption study, aescin was applied to the ventral skin of pigs, and the concentration of total activity, non-volatile activity on blood, urine, various organs, and tissues of these pigs was evaluated. Very high concentrations of aescin have been detected in the skin and muscle tissues in the area where aescin was administered. It has been determined that the concentration of aescin in internal organs, blood, urine, skin, and muscles outside the application area is very low. In addition, the non-volatile activity concentration is 50–600 times higher in the subcutis than in the blood. Twenty-four hours after the application, only 0.5–1% is excreted in urine. The calculated total elimination is 1–2.5% of the initial dose of aescin. Half of the aescin applied to the tissue is excreted as is, while the remainder is excreted by converting it into different metabolites (Lang 1977). In another completed study, Wistar rats were treated with either an intravenous (IV) dose (0.5 mg/kg) of mixed aescin Ib and isoaescin Ib, IV dose (0.5 mg/kg) of pure aescin Ib, IV dose (0.5 mg/kg) of pure isoaescin Ib, oral dose (4 mg/kg) of pure aescin Ib, or oral dose (4 mg/kg) of pure isoaescin Ib. Aescin Ib and isoaescin Ib concentrations in rat plasma were determined by LC-MS/MS at different time periods following administration of drugs. It was observed that the $C_{max}$ (2672 ± 750 ng/ml) value and AUC (5791 ± 3690 ngh/ml) of IV pure isoaescin Ib were higher than the $C_{max}$ (76.4 ± 21.9 ng/ml) value and AUC (5791 ± 3690 ngh/ml) of IV pure aescin Ib. In same direction it was observed that the $C_{max}$

(56.8 ± 26.2 ng/ml) value and AUC (711 ± 317 ngh/ml) of oral pure isoaescin Ib were higher than the $C_{max}$ (0.676 ± 0.309 ng/ml) value and AUC (11.5 ± 7.6 ngh/ml) of oral pure aescin Ib. The values of IV application of the mixture of aesin Ib and isoaescin Ib were observed close to the values of IV application of single isomers (Wu et al. 2014).

### 2.8.3 Clinical Safety

In a controlled study conducted in patients with CVI complaints, it was emphasized that the rate of side effects such as dizziness, headache, and itching, which occur due to the use of horse chestnut extract, ranged from 0.9 to 3.0%. It also was stated that only 0.6% of the patients using horse chestnut extract and aescin had side effects which were very well tolerated in this study (Oschmann et al. 1996). In a similar completed study, one case of nausea and vomiting and two cases of urticaria were observed in 1262 surgical cases treated with aescin (IV) for postoperative edema. In addition, a small number of burning or heat sensations were observed after aescin (IV) application (Sirtori 2001). In Spain, urticaria and shortness of breath have been observed after topical aescin preparation. It has been reported that this case was successfully treated with IM chloropheniramine and hydrocortisone (Escribano et al. 1997).

## 2.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

*A. hippocastanum* is a herbal source used both in folk medicine and registered in Pharmacopeias. Traditionally the standardized extract of *Hippocastani semen* or the aescin compound derived from *Hippocastani semen*, its use in chronic venous insufficiency, hemorrhoids, and edema has been proven by in vitro, in vivo, and clinical studies.

## 2.10 Challenges and Future Recommendations as a Potential Drug Candidate

It is known that plants have been used in the treatment of many diseases since the formation of civilizations. Today, these plants are seen as an important source for drug active ingredient production. The use of *A. hippocastanum* in the treatment of various diseases is due to the presence of aescin in its content. Preparations that will be prepared by loading the extract or aescin obtained from this plant into new delivery systems in the future will increase the life quality of the patients.

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# *Berberis crataegina* DC.

3

Ayşe Baldemir Kılıç and Sadi Yusufbeyoğlu

**Abstract**

Berberidaceae, which grows in the northern hemisphere's temperate regions, is a family of perennial herbaceous plants and shrubs. Some members of the *Berberis* species only grow naturally in certain areas. *Berberis crataegina* DC., one of these species, is used locally in Turkey, Iran, and Turkmenistan as a food and in the treatment of various diseases. While the fruits of *B. crataegina* are used as food, diuretic, and expectorant, its root, bark, and branches have an ethnobotanical uses such as antipyretic, anthelmintic, anti-inflammatory, and antidiabetic. Especially in Turkish folk medicine, it has been used against jaundice, hemorrhoids, and dysuria and as fever reducer, tonic, and appetizer in fever cases. Considering all this information, it is thought that *B. crataegina* should be evaluated in terms of phytotherapeutic, pharmacological, and toxicologic potential. Therefore, it is compiled to studies on *B. crataegina* extracts in the literature, and one of the major components of *B. crataegina*, berberine, was also examined. Hence, this study analyzes and presents the current research in the therapeutic use, content analysis, in vivo and/or pharmacological and toxicological studies of *B. crataegina* and offers suggestions for future reference.

**Keywords**

*Berberis crataegina* · *Berberine* · Alkaloid · Medicinal and therapeutic values · Ethnobotany

## 3.1 Introduction

The Berberidaceae family (order Ranunculales), a member of the flowering plants, is called the barberry family (Atici et al. 2018). It contains 15–17 genera of flowering plants and is monophyletic. It is common in Europe, Asia, and Africa. These species are distributed in South and North America (Srivastava et al. 2015; Yeşilada and Küpeli 2002). Taxonomically the *Berberis* genus is quite difficult and complex. Climatic and geographic variability, interspecific crosses, polyploidy, spontaneous mutations, and ontogenetic variations create

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complex synonyms, creating difficulties in properly distinguishing species. *Berberis* members are mostly diploid (2n = 2x = 28) but some members have triploid. Bottini et al. (2007) reported that tetraploid *Berberis* was grown in areas with low rainfall, while diploids were limited to regions with high rainfall (Sodagar et al. 2011). Similarly, all berberises studied in Khorasan provinces with dry and semi-dry climates are tetraploids. This shows that tetraploid seems to be an advantage over the drought situation in *Berberis* (Bottini et al. 2007; Furness 2008).

There are 12 genera and about 200 species that contain the "berberine" substance, which gives the woody parts a yellow color. Most of these species are found in the temperate regions of the northern hemisphere (Kaya et al. 2018; Davis 1970). The four *Berberis* L. species grow naturally in Turkey, namely, *Berberis vulgaris* L., *Berberis integerrima* Bunge, *Berberis cretica* L., and *Berberis crataegina* DC. (Davis 1970). *B. crataegina* is a 2-m-tall shrub. It has a distribution of 800–1500 m, especially in mature rocky slopes and grooves. Leaves are yellow small oval-shaped and flowers bloom in late summer. In the fall, its fruit turns into black color from dark purple. It is one of the most important shrub species and widespread vegetation of Turkey's lake district (Küpeli et al. 2002; Fontaine et al. 2007). *Berberis crataegina* fruits are called by different names in Turkish such as Karamuk, Karamuk dikeni, Diken üzümü, Şam püremi, and Kadın tuzluğu (Baytop 1994; Erarslan and Kültür 2019).

The purpose of this section is to reveal the spread of *B. crataegina* species in the World and Turkey, various usages among the public and its important pharmacological effects, chemical contents, and toxicological effects based on the literature.

## 3.2 Distribution and Status of Species

The Berberidaceae family is generally distributed in the temperate regions of the northern hemisphere. The *Berberis* genus, which is the major plant of the Berberidaceae family, includes approximately 450–500 species (Sodagar et al. 2011; Alamzeb 2013; Salehi et al. 2019). There are two important places in the distribution of the breeds; approximately 300 species are found in Eurasia and 200 species are found in South America (Ahrendt 1961; Sodagar et al. 2011). These species, which are in the form of a bush, grow naturally in Asia and Europe. On the other hand, Ahrendt (1961) identified approximately 500 *Berberis* types. The genus has two significant centers of variety, corresponding to Eurasia with 300 types and South America with ca. 200 types. However, according to Landrum (1999), this number could be less, as Ahrendt (1961) cited 60 types in Chile and contiguous Southern Argentina, whereas Landrum accepted just 20 types (Bottini et al. 2007) (Fig. 3.1).

*B. crataegina* shows natural distrubution in Turkey, İran and Turkmenistan (Fig. 3.2) (Web-2). It grows naturally in Turkey and has a wide dispersion. Besides, *B. crataegina* grows in Asia and European regions (Baytop 1994; Yeşilada and Küpeli 2002).

*B. crataegina* is one of the most important and common shrub vegetation types in Turkey's lake (Eroğlu et al. 2020, Gulsoy et al. 2011). It is distributed in North, South, Middle, and East Anatolian regions (Fig. 3.3) (Web-2).

## 3.3 Traditional/Ethnomedical/ Local Uses

*B. crataegina* is a species mainly used in parasitic diseases. Especially infusion of roots is traditionally regarded as efficient in the treatment of

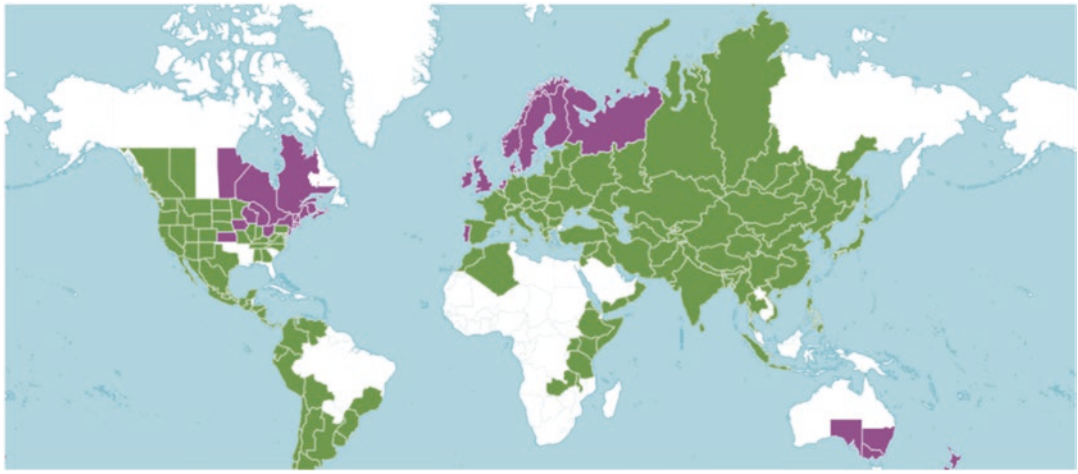

**Fig. 3.1** Distribution of *Berberis* species in the world. Green area is native, purple area is introduced (Web-1)

**Fig. 3.2** Distribution of *B. crataegina* in the world (Web-1)

worms, cough, gastrointestinal parasites, and fasciolosis. Erarslan and Kültür (2019) stated in their review article about plants used in ethnoveterinary medicine that *B. crataegina* has been used as an anthelmintic (roots as a decoction) [Fujita et al. 1995] and antiparasitic (roots as a decoction) [Yeşil and Akalın 2009] for dysuria (root, decoction) [Yeşilada et al. 1995]; respiratory diseases, reproductive diseases (fructus and leaf) [Yipel et al. 2017]; endoparasites, liver pain, mastitis [Arı et al. 2018]; cough, gastrointestinal parasites (root as an infusion) [Sinmez and Yaşar 2017]; fasciolosis, gastrointestinal parasites of ruminants (root as an infusion) [Yaşar et al. 2015]; and deworming (root as an infusion, external) [Yeşil and Akalın 2009]. *B. crataegina* was recorded that its root substances are antipyretic and effective against boils, prevent the growth of bacteria, and drain bile (Bayhan 1968). Moreover, the leaves and fruits of *B. crataegina* have been used as a medicinal herb in the traditional medicine of many cultures as well as in food additives. Its roots and shells, fresh or dried, were used as dyestuffs. Fruits of *B. crataegina* are commonly used as a diuretic and expectorant and also consumed. In Turkey, the radix and bark of *B. cratae-*

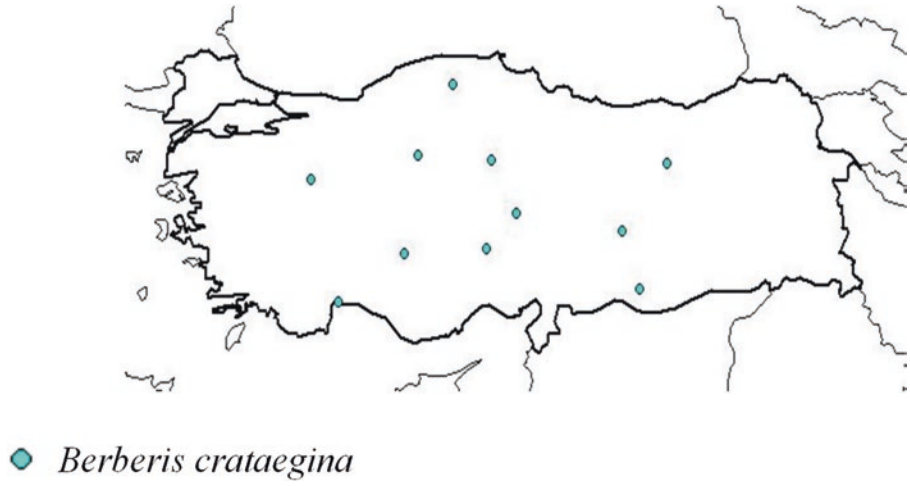


**Fig. 3.3** Distribution of *B. crataegina* in Turkey (Web-2)

*gina* are used traditionally for icterus, hemorrhoids, and dysuria and as an antipyretic, a tonic, and an appetizer (Sezik et al. 1997; Küpeli et al. 2002). The dried fruits of *B. crataegina* are mostly used as a daily snack of Anatolian people and as natural juices, marmalades, and jellies (Işıklı and Yılmaz 2011).

## 3.4 Bioactive Composition

*Berberis* species have been determined to be effective due to their phenolic compounds and anthocyanin and alkaloid content (Yeşilada et al. 1995; Yildiz et al. 2014).

### 3.4.1 Phenolics, Organic Acid, and Mineral Components

The fruits and leaves of *B. crataegina* have been identified with the highest concentrations of phenolics (chlorogenic acid and rutin) and organic acids (malic acid and citric acid), respectively. The phenolic contents of leaves and fruits extracted with acetone-methanol-acetic acid (50:49.5:0.5) were determined by high-pressure liquid chromatography (HPLC). In addition, mineral elements are found in both leaves and fruits wherein there is an abundance of calcium and potassium, respectively. Calcium in leaves and potassium in fruits are significantly higher. In a study investigating the phenolic contents of *B. crataegina*, leaves and fruits were evaluated separately. According to the results of this study, the amounts of chlorogenic acid (70.24 ± 1.54), quamaric acid (1.10 ± 0.01), apigenin 7-o glucoside (20.08 ± 3.71), epicatechin (1.60 ± 0.00), catechin (8.41 ± 0.08), and rutin (27.09 ± 0.97) in fruits were calculated (mg/kg dry extract). In the leaves, the amounts of luteolin (0.24 ± 0.02), vitexin (0.029 ± 0.02), and rutin (170.87 ± 2.99) were also reported (mg/kg dry extract). Also, in this study, the elemental compositions of leaves and fruits from *B. crataegina* DC. have been determined (Gulsoy et al. 2011) (Table 3.1).

In another view, the fruits and leaves of *B. crataegina* have been established with the highest concentrations of phenolics, such as chlorogenic acid and rutin, and organic acids such as malic acid and citric. Furthermore, it was calculated as 73.48 mu g GAE/mg KM total phenolic content in fruit of *B. crataegina*, and chlorogenic acid is the major phenolic component followed by sinapic, syringic, and gallic acid. The mineral composition of *B. crataegina* is as follows: potassium with the highest concentration of 10981.14941 ppm followed by P (2138.54285 ppm), Mg (979.50355 ppm), Ca (547.5389 ppm), Na

**Table 3.1** Elemental compositions of *B. crataegina* leaves and fruits extract (Gulsoy et al. 2011)

| | The amount of ug/g in the dry sample | |
|---|---|---|
| Element | Leaves | Fruits |
| Zn | 14.00 ± 1.00 | 25.00 ± 1.00 |
| Cu | 0.00 ± 0.00 | 3.00 ± 1.00 |
| Fe | 95.00 ± 1.00 | 44.00 ± 1.00 |
| Mg | 1777.00 ± 10.00 | 711.00 ± 10.00 |
| Mn | 41.00 ± 10.00 | 14.00 ± 2.00 |
| Cd | 2.00 ± 1.00 | 3.00 ± 1.00 |
| B | 38.00 ± 10.00 | 11.00 ± 0.00 |
| P | 4.00 ± 1.00 | 10.00 ± 0.00 |
| As | 3.00 ± 1.00 | 2.00 ± 1.00 |
| Ba | 17.00 ± 1.00 | 3.00 ± 0.00 |
| Na | 116.00 ± 10. 00 | 86.00 ± 10.00 |
| K | 7857.00 ± 10.00 | 11210.00 ± 10.00 |
| Ca | 11130.00 ± 10.00 | 2389.00 ± 10.00 |

(119.28465 ppm), Zn (84.97637 ppm), Al (38.86034 ppm), Mn (25.65597 ppm), Fe (23.26839 ppm), Cu (15.40609 ppm), Ni (8.31635 ppm), Cd (7.19416 ppm), Rb (7.00841 ppm), Sr (5.46809 ppm), Ba (2.33907 ppm), Pb (1.51456 ppm), V (0.21657 ppm), Co (0.20514 ppm), and Cr (0.05224 ppm) (Çakır and Karabulut 2020).

### 3.4.2 Alkaloid Content of *B. crataegina*

In the *Berberis* species, the dispensation of berberine and other alkaloids is usually in the radix, accompanied by the stem shell and the stem itself. Additionally, its existence in trace values has been detected from leaves and fruits (Bhardwaj and Kaushik 2012). Bayhan (1968) showed that there are alkaloids called berberine, palmatine, jatrorrhizine, and magnoflorine in the roots of the plant. Koşar (1999) studied the quantitative analysis of alkaloids found in the roots, shells, and stems of Turkish *Berberis* species by high-pressure liquid chromatography (HPLC) techniques. Major alkaloids of *B. crataegina* were determined (yield %) in roots, berberine (1.16%), berbamine (0.7%), palmatine (0.17%), and magnoflorine (0.59%); in shells, berberine (0.06%), berbamine (0.02%), palmatine (0.02%), and magnoflorine (0.56%); and in stems, berberine (0.19%), berbamine (0.17%), palmatine (0.18%), and magnoflorine (0.55%).

## 3.5 Pharmacological Activities

*Berberis* is an important wild plant genus with numerous uses in the pharmacology and food industry. These types are abundant sources of important natural compounds, namely, vitamins, minerals, alkaloids, and antioxidants that can be used in a wide variety of pharmaceutical and nutraceutical products (Alimirzaee et al. 2009; Salehi et al. 2019; Gulsoy et al. 2011).

Medicinal properties have been reported for all parts of *Berberis* species, and its leaves, fruits, and roots have been used with liver and gastrointestinal disorders as well as enteritis and diarrhea (Ye et al. 1993) and as an antimicrobial (Gulsoy et al. 2011; Alimirzaee et al. 2009), an antihistamine, an anticholinergic (Shamsa et al. 1999), an anti-inflammatory (Yeşilada and Küpeli 2002; Ivanovska and Philipov 1996), and a vasodilator (Gulsoy et al. 2011; Sezik et al. 1997).

### 3.5.1 Anti-Inflammatory, Analgesic, and Antipyretic Activities

An experimental study indicated that *B. crataegina* roots have anti-inflammatory, antinociceptive, antirheumatic activity and antipyretic activities owing to berberine, berbamine, and palmatine, which are the main alkaloids (Küpeli 2000; Küpeli et al. 2002). The anti-inflammatory, analgesic, and antipyretic effects of roots were studied in a different study, and findings supporting traditional use were achieved (Yeşilada and Küpeli 2002). Moreover, the methanolic extract of fruits and aerial parts exhibited significant antioxidant activity in diverse studies (Souri et al. 2004).

*B. crataegina* and its hybrids are generally consumed as food. *Berberis* species have been used in traditional medicines worldwide, especially against inflammatory diseases (Küpeli 2000; Küpeli et al. 2002); besides, Fukuda et al. (1999) showed that berberine inhibited cyclooxy-

genase-2 (COX-2) transcriptional activity in a dose-dependent manner in colon cancer cells.

Yeşilada and Küpeli (2002) investigated the anti-inflammatory efficacy of *B. crataegina* root extract using an in vivo (mice and rat) model of gangrene-induced paw edema. They observed the water extract significant anti-inflammatory effect at 75 and 150 mg/kg doses. In addition, the extracts/ fractions to determine the effect of antipyretic, the body temperature difference between treated and un treated back paws were monitored using a digital thermometer every 2 days in rats induced by FCA (Freund's Complete Adjuvant). Extracts and fractions were also found to have potent antipyretic, anti-arthritis and anti-inflammatory activities. The active compound, berberine, also demonstrated strong dose-dependent analgesic activity against acetic acid-induced writhing reflex in mice.

### 3.5.2 Antioxidant Activity

The methanol extract (80%) of the *B. crataegina* fruit is investigated with antioxidant capacity according to three methods [β-carotene (90.50 ± 0.42%), DPPH (2,2-diphenyl-1-picrylhydrazyl) $IC_{50}$ mg/ml (6.30 ± 0.28), and CUPRAC (cupric reducing antioxidant capacity) 1.07 ± 0.04 mmol TR/g-smp] (Çakır and Karabulut 2020).

The free radical scavenging ability of *B. crataegina* fruit extract (80% MeOH) was evaluated with DPPH, superoxide radical scavenging, and β-carotene bleaching assay tests (% in 1 mg/mL extract or reference compound) by Charehsaz et al. (2015). Antioxidant values of *B. crataegina* are shown as comparatively with butylated hydroxytoluene (BHT) in Table 3.2.

### 3.5.3 Antimicrobial Activity

In one study, the antimicrobial activity of water extracts of *Berberis* fruits was tested against food-borne pathogens, and three extracts showed antimicrobial activity against three pathogenic bacteria. It has been reported that *B. crataegina* fruit extracts are effective against *Salmonella typhimurium*, *Yersinia enterocolitica*, and *Staphylococcus aureus* bacteria (Eroğlu et al. 2020).

Ertürk (1994) investigated the antimicrobial activity of berberine, alkaloid fraction, and aqueous extract obtained from *B. crataegina* roots. Berberine was ineffective only against *Aspergillus niger* and *Candida albicans*, while it was strong against *Epidermophyton floccosum*, *Microsporum canis*, *Pleurotus ostreatus*, and *Allescheria boydii*. The aqueous extract is strong against *E. floccosum* and *A. boydii*. It has been found to be moderately effective against *P. ostreatus*, *N. oryzae*, *C. lunata*, and *D. rostrata*. According to antibacterial activity results, Berberine was effective against *S. aureus* and *C. diphtheriae* (Ertürk 1994).

### 3.5.4 Use of Diabetes Treatment

Sarıoğlu (1978) examined the effect of the extract obtained from *B. crataegina* roots by decoction method on blood sugar and its antidiabetic activity in dogs. According to the results, it was determined that decoction did not have an acute effect on hunger and elevated blood sugar. However, the extracts prepared from the plant are used orally and chronically among the public. Therefore, it can be thought that the substances contained in the plant are metabolized in the digestive system and the main effect may be caused by these metabolites or due to the accumulating effects of active substances, causing a decrease in blood sugar.

Hypoglycemic and antidiabetic activity experiments were carried out by Ertürk (1994) with the alkaloid fraction and aqueous extract obtained from *B. crataegina* roots. The hypoglycemic activity of the aqueous extract and the alkaloid fraction was investigated by experiments on rats. As a result of these experiments, it was determined that both samples did not have hypoglycemic activities. The antidiabetic activity test was performed with the isolated berberine. As a result of this experiment on rats, it was found that berberine has an antidiabetic potential, albeit temporarily.

**Table 3.2** Antioxidant activities of *B. crataegina* fruit (Charehsaz et al. 2015)

| | DPPH radical scavenging activity (IC50 value µg/mL) | FRAP (reducingantioxidant power of 1 g) | β-carotenebleaching assay (1 mg/mL) |
|---|---|---|---|
| *B. crataegina* fruit extract | 405 ± 11.6 | 0.76 ± 0.03 | 77 ± 2.2 |
| BHT | 133 ± 6.4 | 3.02 ± 0.07 | 96 ± 2.6 |

## 3.6 Toxicological Studies

Despite the widespread custom use of barberries, there is no overall examination categorizing the toxic substance of barberry studies in animal models and its implementation on humans. It has been reported that the berberine contents can increase bilirubin levels and cause genetic damage to the fetus. Therefore, it should not be used by pregnant women. Individuals with high bilirubin levels or other liver diseases should also avoid herbs containing berberine. Its safety in young children and nursing mothers has also not been established (Shamsa et al. 1999).

It is noted that berberine is well tolerated up to 500 mg (per os). However, drowsiness, nosebleeds, shortness of breath, skin and eye irritation, kidney irritation, and nephritis have been described inadvertently through high doses of berberine (ESCOP 2003).

### 3.6.1 In Vitro, Genotoxicity, and Cytotoxicity

The genotoxic capacity of the extract of *B. crataegina* fruit (BCFE) in HeLa cells was assessed at concentrations lower than its IC50 value. The results achieved in Neutral Red Uptake (NRU) cytotoxicity tests were used to identify the IC50 value of the BCFE in HeLa cells. Subsequently, the quantified IC50 values of BCFE and SDS (sodium dodecyl sulphate: positive control) were 4.98 mg/mL and 0.055 mg/mL. The genotoxic effect of BCFE has worked out also in human peripheral blood lymphocytes. The DNA damage led to show at 2 mg/mL with a remarkably extended ($p < 0.05$) mean tail % intensity value (Charehsaz et al. 2015).

### 3.6.2 Acute Toxicity

In the acute toxicity test, berberine from *B. crataegina* produced a dose-dependent stomach injury and caused lethality at high doses (418 mg/kg) (Yeşilada and Küpeli 2002).

In another study, the acute toxicity of berberine hydrochloride in mice showed the following LD50 values: 9.0386 mg/kg (IV) and 57.6103 mg/kg (IP). The safe dose for oral administration of berberine in mice is 20.8 g / kg, whereas in humans it will be 2.97 g / kg, which is 100 times the recommended dose in clinical trials (Kheir et al. 2010).

### 3.6.3 Sub-Acute Toxicity

The root extract of *B. crataegina* was clear to rats for 21 days without any toxicity and death, individually. Nevertheless, liver and kidney growth were prepared with ethanol extract (21.3% and 9.7%), butanol fraction (14.6% and 4.2%), and $CHCl_3$-ethanol fraction (7.2% and 2.8%), subsequently. Bodyweight was raised to 30% with $H_2O$-I fraction, 27% with butanol fraction, 17.8% with ethanol extract, and 11.3% with $CHCl_3$-ethanol fraction (Yeşilada and Küpeli 2002). Also, intraperitoneal injection of berberine (10 and 20 mg/kg/day for 1 week) has been stated to decrease bilirubin connective in adult rats. It should not be forgotten that clinically, this subject may increase the risk of kernicterus in risky patients (Ho et al. 2014).

### 3.6.4 Sub-Chronic Toxicity

For subacute toxicity assessment, rats treated with active extract/fractions for 14 successive

days for those induced by Freund's complete adjuvant (FCA) were assessed for arthritis. No death or other signs of toxicity were noted during the 21-day experience period. The animals reached up to 30% weight after 21 days. During the autopsy, no signs of toxicity were detected (Yeşilada and Küpeli 2002).

### 3.6.5 Chronic Toxicity

Some studies on the chronic toxicity of berberine have been found in the literature. The phototoxic effect of berberine on mosquito larvae (*Aedes atropalpus*) in combination with UVA radiation was evaluated. Larvae were conducted with 10 ppm berberine by exposure to 0.4 W/m2 UV for 24 hours, then turned over to clean jars, and investigations were carried out into adult stages over 4 weeks of development. Berberine demonstrated chronic toxicity and a noticeable rise in aggregate mortality. The mechanism controlling berberine can be joined to single $O_2$ production by DNA-bound berberine (Philogene et al. 1984). Treatment of rats with 50 mg/kg of berberine showed that berberine had no significant toxic effects on the kidney and liver (Jiang et al. 2012). In line with these results, another research indicated that berberine at concentrations >50, 100, and 150 mg/kg after 16 weeks caused liver tissue deterioration in diabetic rats but not healthy rats (Zhou et al. 2008). Li et al. (2009) showed that chronic treatment with berberine (5 mg/kg/day, IP for 15 weeks) led to atherosclerosis in apoE – / – mice.

### 3.6.6 Clinical Toxicity

According to the research, the effect of berberine was likewise examined in clinical toxicity studies. In a survey, 34.5% of patients with type 2 diabetes was treated with berberine (500 mg three times daily) for 13 weeks, with transient GI side effects such as diarrhea, constipation, swelling, and abdominal troubles. However, no significant changes in liver enzymes and creatinine were recognized (Yin et al. 2008). In refractory cardiac patients ($n$ = 12), infusion of 0.2 mg/kg/min berberine for 30 minutes enhanced cardiac performance due to defeat, probably peripheral vasodilator and inotropic effects. However, in four patients, berberine occurred 1–20 hours after infusion of ventricular tachycardia with torsade de pointes (Marin-Neto et al. 1988).

## 3.7 Pharmacokinetic Studies

Pharmacokinetic studies on berberine, which is the major component of *B. crataegina* extracts, were conducted. Despite the fact that berberine is a cationic alkaloid, its structure is by no means optimized for rapid absorption from the intestine. It is poorly soluble in water, which indicates that it has poor intestinal absorption and / or bioavailability (Habtemariam 2020). The pharmacokinetic information is shown in Fig. 3.4. Berberine, however, can be absorbed by the gastrointestinal (GI) tract; its oral bioavailability and plasma level are too low. It should be recognized that berberine transforms into ionized form under physiological conditions and collects itself in low pH conditions. Self-assembly reduces GI trace viability and resolution. Other obstacles are the oral bioavailability of berberine, P-glycoprotein mediated efflux in the intestine, hepatobiliary re-extraction, and metabolization by CYP2D6 and CYP3A4 (Liu et al. 2016). A berberine derivative, dihydroberberine, is formed by the higher intestinal flora. Compared to berberine, its absorbability rate in the intestine is higher (Feng et al. 2015).

Berberine is distributed in the liver, kidneys, muscle, lungs, brain, heart, pancreas, and fat. Dramatically, the tissue concentration of berberine and its metabolites is higher than the plasma concentration (Tan et al. 2013). Berberine is metabolized by oxidative demethylation in the liver and has the forms of berberrubine, thalifendine glucuronidation, demethyleneberberine, and jatrorrhizine and glucuronide. Also, metabolites of berberine are excreted in the feces, urine, and bile. It is significant to note that some of these are co-administered pharmacokinetic interactions such as metformin, ketoconazole, digoxin, and cyclosporine A (Imenshahidi and Hosseinzadeh 2016).

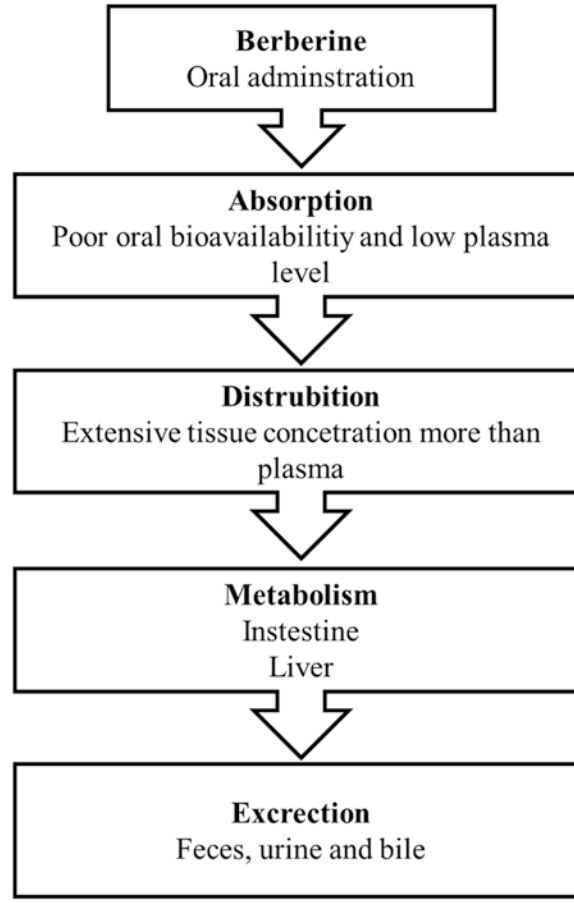


**Fig. 3.4** Pharmacokinetic information of Berberine (Rad et al. 2017)

## 3.8 Conclusion

*B. crataegina* has significant potential for the food industry and other technological purposes as antioxidant compounds. Its fruits can be used in the prevention and treatment of many diseases and health problems, thanks to their important components such as vitamin C and malic acid. Because the potassium content *B. crataegina* is high, it can be considered as a food with high medicinal value and a source of potassium. These fruits, which are currently used by the local people for medicinal purposes, can be processed and transformed into different products and evaluated in preventive alternative medicine practices and food supplements. Studies have demonstrated that extracts and fractions from *B. crataegina* roots have anti-inflammatory properties, and a dose-dependent analgesic activity was determined using a model based on antipyretic activity on body temperature. A review of the scientific literature revealed that extracts, which are alkaloids isolated from *Berberis* species, including berberine and its derivatives, show promising effects in studies of diabetes and other metabolic diseases. Compared to other synthetic drugs, the relatively low cost of the berberine or berberine-containing supplements or extracts will provide an advantage for patients living in developing countries and with poor socioeconomic status. For this purpose, standardization studies of *B. crataegina* fruit extract, which has a high potential, should be carried out to ensure its use as herbal medicine.

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# *Calendula officinalis* L.

4

Derya Egeli

**Abstract**

*Calendula officinalis*, commonly known as "marigold," is a plant with yellow-orange flowers belonging to the Asteraceae family. The plant, which has been used since ancient times, is widely used in both traditional and homeopathic medicine for the treatment of various diseases. This chapter firstly summarized the description, distribution, and chemical composition of the plant. In vivo, in vitro, and clinical studies on the plant have been shown in detail. In addition, toxicity and mutagenicity studies have been reported.

**Keywords**

*Calendula officinalis* L. · Chemical composition · Traditional use · Biological activities

## 4.1 Introduction

*Calendula officinalis* is a cultivated plant with bright yellow-orange flowers, 20–50 cm tall, grown in many regions of our country, especially in parks and gardens due to its beautiful appearance. It is grown and cultured in a wide range of places including Central, Southern, and Eastern Europe, West Asia, Germany, and America (Council 2005; Fleming 2000).

*Calendula officinalis* is one of the medicinal plants in use since ancient times. *Calendula officinalis* L. is a plant belonging to the Asteraceae (Compositae) family, *Calendula* L. genus (Table 4.1). Since the plant appears to bloom continuously, its name is derived from the word "Calendar," which means "Calendar" in English, derived from the Latin word *Kalendae*. The word "calend" is also used to mean the first day of each month (Dinda and Craker 1998). In ancient Roman times, it was associated with this word because the plant blooms on the first day of each month (Çolak 2018).

In Turkey, the *Calendula officinalis* plant is known as "Aynısafa," "Öküzgözü," "Altıncık," "Portakal nergisi," "Ölüçiçeği," "Tıbbi nergis," "Nerkiz," and "Kadife çiçeği" (Çolak 2018). It is called Marigold, Pot Marigold, English Marigold, Garden Marigold, African Marigold, Field Marigold, Gold Bloom, Holligold, Maravilla, Marybud, Bride of the Sun, Bull Flower, Butterwort, Poet's Marigold, Rudders (English), Butterblume (German), Galbinele (Romanian), Zergul (Hindi), and Chin Chan Ts'ao (Chinese) in the world (Jan et al. 2017).

The flowers of *C. officinalis* are wound healing, granulation-enhancing, and anti-inflammatory in Commission E monographs; PDR also increases granulation and is antimicro-

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**Table 4.1** Taxonomic classification for *Calendula officinalis* L. (Ashwlayan et al. 2018)

| Kingdom | Plantae |
|---|---|
| Subkingdom | Tracheobionta |
| Division | Magnoliophyta |
| Class | Magnoliopsida |
| Subclass | Asteridae |
| Order | Asterales |
| Family | Asteraceae (=Compositae) |
| Genus | *Calendula* |
| Species | *Calendula officinalis L.* |

bial and antiviral; in ESCOP, antimicrobial, antiviral, immunomodulator, antioxidant, and angiogenic activities are recorded (Blumenthal 1998; ESCOP 2003; Fleming 2000). In addition, the granulation-enhancing and astringent activity of the aboveground parts of the plant is also mentioned in PDR (Fleming 2000).

*Calendula officinalis* is an annual or perennial plant. It is a plant that is wooded only at the base. The trunk is upright, broad or creeping, highly branched, leaf at the top. Leaves are oblanceolate, narrow ovate or spatulate, very short acute or obtuse, flat-edged or toothed, scattered slightly hairy glandular pubescent, ciliate hairy on the edges, leaves at the bottom are narrowed as a long stem, the tip is short pointed. The branches bearing the capitulum are of different length, stand upright, and firm in the fruit period, and the capitulum is 4–7 cm wide. Involucrum is cup-shaped, bracteas lanceolate, lash-like hairy. Tongue flowers are usually 2 cm, two times longer than involucrum. Tongue flowers are occasionally blade-shaped orange or yolky color, dry bright; tubular flowers 15–20 mm, usually monochrome and sometimes brown. Akenes are 2–2.5 cm, short beak, and hard (Demirezer et al. 2017).

## 4.2 Distribution and Status of Species

The genus *Calendula* L. belonging to the *Calendulae* tribus of the Asteroideae, which is a subfamily of the Asteraceae family, contains both 1-year and perennial plants specific to the Mediterranean Basin (Faustino et al. 2018). It is represented worldwide with 10–27 species. There are three species belonging to the *Calendula* genus registered in the Turkish Plants List. These are *Calendula arvensis* L., *Calendula suffruticosa* Vahl., and *Calendula officinalis* L. (Güner et al. 2012). Current literature reveals the pharmacological effects of these three species.

*Calendula stellata* Cav., *Calendula alata* Rech., *Calendula tripterocarpa* Rupr. are some of the *Calendula* species not seen in Turkey (Baciu et al. 2010).

*C. officinalis* occurs naturally in Central, Eastern, and Southern Europe. It is cultured in North America, the Balkans, Eastern Europe, Germany, and Turkey (WHO 2002). *Calendula arvensis* and *Calendula suffruticosa* species are also grown in Turkey. While *C. suffruticosa* spreads in Istanbul, Hatay, and Sinop, *C. arvensis* spreads in Adana, Şırnak, Amasya, Antalya, Balıkesir, Bilecik, Çanakkale, Denizli, İzmir, Kocaeli, Sinop, and Şanlıurfa (Çolak 2018).

## 4.3 Comparison of Traditional/Ethnomedicinal/Local Uses

First attributions to the medicinal use of *Calendula officinalis* is found in a fourteenth-century medical manuscript book. The use of *C. officinalis* is widely known even in the thirteenth century (Patrick et al. 1996). It was first used to heal wounds. These ancient manuscript books clearly describe *C. officinalis* because of its wound healing properties (Scheffer 1979). At the same time, it is known that *C. officinalis*, cultured by Egyptians, Greeks, Hindus, and Arabs, was cultivated in European gardens and used medicinally (Krag 1976).

*C. officinalis* is an important medicinal plant widely used in traditional medicine and homeopathic medicine for the treatment of various diseases. It has been traditionally used as an anti-inflammatory, analgesic, and antiseptic and a diaphoretic and in the treatment of jaundice (Chakraborthy 2008). Tincture is preferred in homeopathy for the treatment of mental tension and insomnia (Arora et al. 2013). It is used in

both traditional and homeopathic medicine to treat wounds and burns, conjunctivitis and vision impairment, menstrual irregularities, varicose veins, internal and external inflammation conditions, gastric and duodenal ulcers, and hemorrhoids (Bezbradica et al. 2005; Preethi et al. 2006). However, it is also known to be used in Ayurveda for fever and cancer treatment (Krag 1976).

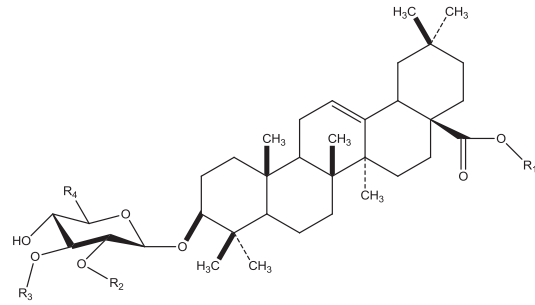
The leaves of *C. officinalis* are used as a solvent and diaphoretic in Europe, and its flowers are used as a stimulant and an antispasmodic and emmenagogue. Decoction of plant flowers is used as a medicine in the treatment of measles and smallpox in England, and the juice of the plant to stop jaundice, constipation, and menstrual discharge (Muley et al. 2009). *Calendula* genus is used in the treatment of skin diseases in North Africa and Asia due to its anti-inflammatory properties (Abdel-Aziem et al. 2014; Jiménez-Medina et al. 2006). In Turkey, flowering branches are used as constipation and wound healing, and seeds are used as urine enhancer (Baytop 1984). In the past, preparations prepared from *C. officinalis* flowers were used for fabric dye, food, and cosmetics in Indian, Arab, Greek, and Roman civilizations (Efstratiou et al. 2012).

*C. officinalis* is one of the widely used species clinically around the world. The plant is included in German Commission E, European Scientific Cooperative on Phytotherapy (ESCOP), British Herbal Pharmacopoeia, World Health Organization (WHO) monographs, and Turkish Pharmacopoeia (Demirezer et al. 2017; Özkan et al. 2016).

## 4.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques

The most used and studied parts of the *Calendula officinalis* plant are its flowers. However, there are various studies on all plants and leaves. As a result of the studies, it was seen that the triterpenoid composition was abundant in the plant. In addition to triterpene saponins, triterpenic esters, flavonoids, essential oils, sesquiterpenes, and polysaccharides have also been identified in the plant (Ukiya et al. 2006; Yoshikawa et al. 2001).

### 4.4.1 Triterpene Saponosides

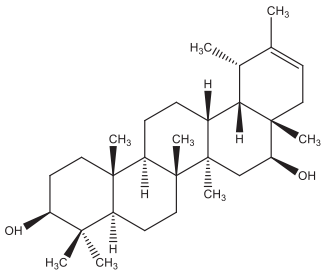



In *Calendula officinalis*, triterpene saponosides are found at a rate of 2–10% (Fleming 2000). Some of these are in the form of heteroside of oleanolic acid (EMA 2018).

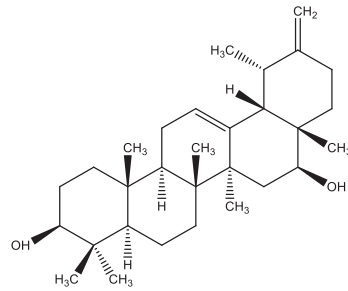
Six saponosides (calendulaglucoside A–D, D2 and F), whose basic chemical structure is oleanolic acid-3-O-6-D glucuronide, have been isolated from the plants with the studies conducted to determine the triterpene composition of *C. officinalis* flowers. When the components were respectively examined, it has determined that galactose and glucose in calendulaglucoside A and B were bound to glucuronic acid at positions 3 and 2 (Vidal-Ollivier et al. 1989). In addition, calendulocyte D, averoroside A, and four new triterpene saponins calendasaponin A, B, C, and D have been isolated with subsequent studies (Yoshikawa et al. 2001). With recent studies, calendulaglucoside A 6′-butylester, calendulaglycoside B 6′-butylester, calendulaglucoside C 6′-methylester, calendulaglucoside C 6′-butylester, calenduloside F 6′-butylester, and calenduloside F6'-methylester saponosides have been also isolated from *C. officinalis* flowers (Ukiya et al. 2006) (Table 4.2).

### 4.4.2 Triterpene Alcohol and Esters

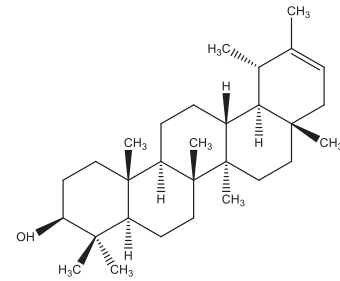
*Calendula officinalis* plant contains the pentacyclic mono-, di-, and trihydroxy triterpenes in free



**Faradiol**



**Arnidiol**



**Calenduladiol**

**Table 4.2** Oleanolic acid derivative triterpene glycosides found in *Calendula officinalis* flowers (Ukiya et al. 2006; Yoshikawa et al. 2001)

| Saponosides | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| Calendulaglucoside A | Glucose | Glucose | Galactose | COOH |
| Calendulaglucoside B | H | Glucose | Galactose | COOH |
| Calendulaglucoside C | Glucose | H | Galactose | COOH |
| Calendulaglucoside D | H | H | Galactose | COOH |
| Calendulaglucoside $D_2$ | Galactose | H | H | COOH |
| Calendulaglucoside F | H | H | H | COOH |
| Calenduloside D | Glucose | Glucose | Galactose | $CH_2OH$ |
| Averoroside A | H | H | Galactose | $CH_2OH$ |
| Calendulaglucoside A-6′-methylester | Glucose | Glucose | Galactose | $COOCH_3$ |
| Calendulaglucoside A-6′-butylester | Glucose | Glucose | Galactose | $COOC_4H_{12}$ |
| Calendulaglucoside B-6′-butylester | H | Glucose | Galactose | $COOC_4H_{12}$ |
| Calendulaglucoside C-6′-methylester | Glucose | H | Galactose | $COOCH_3$ |
| Calendulaglucoside C-6′-butylester | Glucose | H | Galactose | $COOC_4H_{12}$ |
| Calenduloside F-6′-butylester | Glucose | H | H | $COOC_4H_{12}$ |
| Calenduloside F-6′-methylester | H | H | Galactose | $COOCH_3$ |

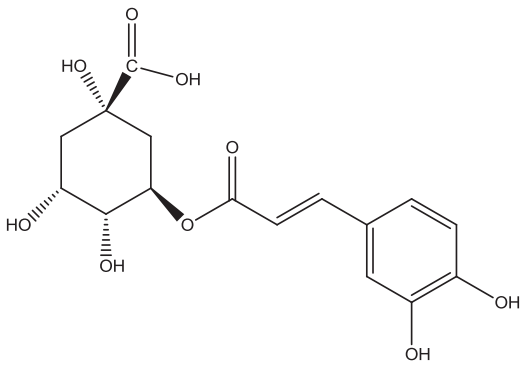
or ester form [triterpene monols (0.8%), triterpendiols (4%), and triterpene triols] (Fleming 2000). Dichloromethane extract contains, faradiol-3-O-palmitate, faradiol-3-O-myristate, faradiol-3-O-laurate, arnidiol-3-O-palmitate, arnidiol-3-O-myristate, arnidiol-3-O-laurate, calenduladiol-3-O-palmitate, calenduladiol-3-O-myristate and very small amounts of calenduladiol-3-O-laurate (Neukirch et al. 2004). The main triterpendiol esters in lipophilic extracts are faradiol laurate, faradiol myristate, and faradiol palmitate (Wilen et al. 2004). The main components responsible for its anti-inflammatory activity are thought to be faradiol-3-monoesters of lauric, myristic, and palmitic acids (Della Loggia et al. 1994). For this reason, different methods have been tried by different researchers for the analysis of these components. First, the components have been isolated by using column chromatography and HPLC. Later, the structure illumination of these three esters and psi-taraxasterol was carried out by using MS, $^{1}$H-NMR, $^{13}$CNMR, and $^{2}$D-NMR (Zitterl-Eglseer et al. 1997). These esters, which are thought to have anti-inflammatory activity, have been tried for the efficient isolation from the flower heads of the plant of the plant supercritical fluid extraction, normal phase, and reverse phase column chromatography. The amount of each ingredient has been determined as 96% to 98% purity (Hamburger et al. 2003).

In a study conducted with *C. officinalis* flowers, the amount of faradiol monoesters in the flowers dried at different temperatures and brought to constant weight was determined by reverse-phase HPLC, and it was observed that there was no significant loss even at temperatures above 115 °C (Zitterl-Eglseer et al. 2000). In a study made by

Zitter-Eglseer et al., the variation of faradiol-3-monoesters of 36 different *C. officinalis* plants in populations with commercial content in different regions in Austria and Germany was investigated. It has been determined that the place where it is grown has no significant effect on the amount of faradiol esters. Faradiol-3-monoesters were found in high amount in tongue flowers and low amount in tubular flowers, seeds, and involucral bracts. In addition, it was observed that the receptaculum did not contain esters in many samples (Zitterl-Eglseer et al. 1996; Zitterl-Eglseer et al. 2001).

### 4.4.3 Phenolic Components

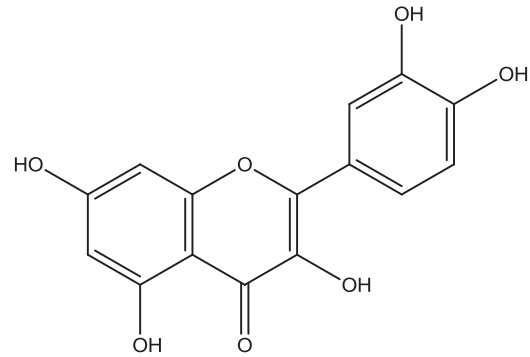
Heptane, ethyl acetate, and methanol extracts of *Calendula officinalis* flowers have been examined by using HPLC and HPTLC methods, and it has been determined that the main phenolic acids were p-coumaric, caffeic, syringic, chlorogenic, vanillic, protocatechuic, and ferulic acids (Matysik et al. 2005; Wojciak-Kosior et al. 2003). Chlorogenic acid, which the plant contains as a phenolic compound, is an important intermediate product of lignin biosynthesis (Soto-Hernandez et al. 2014). At the same time, chlorogenic acid is an antioxidant and antitumor effective. It contributes to the treatment of atherosclerosis and ischemia-perfusion diseases (Soto-Hernandez et al. 2014).




**Chlorogenic acid**

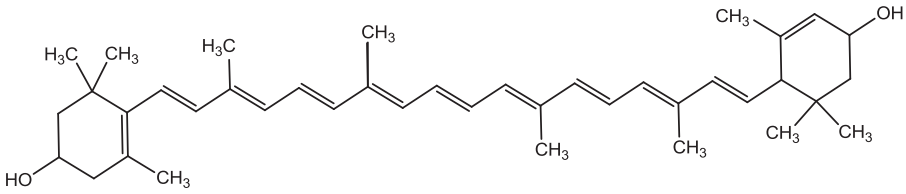
With the HPLC-UV/VIS method, chlorogenic acid, epicatechin, gallic acid, coumaric acid, gallocatechin gallate, caffeic acid, epigallocatechin gallate, rutin, sinapic acid, vanillin, ellagic acid, rosmarinic acid, and resveratrol have been identified (Mekinić et al. 2013). As a result of the determination with high-performance liquid chromatography-diode array detection-mass spectrometry detection (HPLC-DAD-MS), vanillic acid, caftaric acid, p-hydroxybenzoic acid, syringic acid, and ferulic acid have been found as phenolic acid. Then catechin, epicatechin gallate, quercetin-3-O-galactoside, quercetin-3-O-rhamnosite, calendoflavoside, calendoflaside, and calendoflavobioside have been found as flavonoid (Hernández-Saavedra et al. 2016).

The flavonoids in the *C. officinalis* plant are 0.3–0.8%, the most well-known of these are the 3-mono and oligosaccharides of isoramnetol and kersetol (Fleming 2000). However, hesperidin and quercetin were determined as the main components of *C. officinalis* infusion as a result of the analysis performed by using high-performance liquid chromatography-ultraviolet/visible light absorption spectroscopy (HPLC-UV/VIS) method. Quercetin is one of the main flavonoids of the ethanolic extract (Hernández-Saavedra et al. 2016).




**Quercetin**

Anthocyanins were first identified in *C. officinalis* flowers in a study conducted in 2013. Anthocyanins (0.79–3.12 mg/g) were found in four varieties in the study. As a result of the analysis performed by using high-performance liquid chromatography (HPLC), the 3-O-glycopyranoside ester of cyanidin, delphinidin, malvidin, peonidin, pelargonidin, petunidin; 3,5-di-O-glucopyranoside ester of cyanidin and pelargonidin; and cyanidin-3-O-rutinoside ester have been found. The main compound has been




**Lutein**

reported as cyanidin-3-O-glucopyranoside (Olennikov and Kashchenko 2013).

### 4.4.4 Carotenoids

The methanolic extract of the pollen, petals, and leaves of *Calendula officinalis* flowers contains a variety of carotenoids. Carotenoids are substances in tetraterpenoid structure. The carotenoids found in *C. officinalis* plant are flavoxanthin, luteoxanthin, lutein, and zeaxanthin (Bakó et al. 2002; Fleming 2000). The total amount of carotenoids in the petals of the plant is higher than in pollen (Bakó et al. 2002). The main ingredient is lutein (Crabas et al. 2003).

Bakó et al. have investigated the carotenoid composition in flowers, leaves, and stems of *C. officinalis* grown in Hungary. They had determined that the main carotenoids in flowers are flavoxanthin, luteoxanthin, and auroxanthin. In addition, the leaves and stem are rich in terms of lutein and β-carotene (Bakó et al. 2002).

Various studies have shown that carotenoids have a beneficial effect on the epithelialization process by affecting the cell cycle progression of fibroblasts. However, they have reported that carotenoids act as photoprotective agents; it can reduce the risk of sunburn, photoallergy, and skin cancer types; and it has antioxidant activity (Pintea 2003).

### 4.4.5 Volatile Components

The essential oil composition of *Calendula officinalis* shows different patterns in different phases of the vegetative cycle. The highest essential oil ratio has been detected in the flower heads during the flowering period (Crabas et al. 2003). Many monoterpenes and sesquiterpenes have been reported in essential oil. The essential oil obtained from its flowers contains 70 different components (Crabas et al. 2003). Some of those are α-tuyene, α-pinene, sabinene, β-pinene, limonene, 1,8-cineole, p-cymene, trans-β-ocimene, γ-terpinene, δ-3-karene, nonanal, terpene-4-ol, 3-cyclohexene-1-ol, α-fellandrene, α-terpineol, geraniol, carvacrol, bornyl acetate, sabinyl acetate, α-kubeben, α-kopaene, α-bourbonene, β-cubeben, α-gurjunene, aromadendren, β-caryophyllene, α-ylangen, α-humulene, epibicyclosesquiphellandrene, germacrene D, alloaromadendrene, β-salien, calarene, murolene, δ-cadene, cadina-1,4-diene, α-cadene, nerolidol, palustron, endoburbonene, oplopenone, α-cadinol, and T-muurolol (Gruenwald et al. 2007; Muley et al. 2009; Okoh et al. 2007).

### 4.4.6 Other Components

Studies have shown that the ethanolic extract of the plant contains 15 different amino acids in free form. These amino acids which are detected in leaves, stems, and flowers are alanine, arginine, aspartic acid, asparagine, valine, histidine, glutamic acid, leucine, lysine, proline, serine, tyrosine, threonine, methionine, and phenylalanine. Amino acid content has been found to be about 5% in leaves, 3.5% in stem, and 4.5% in flowers (Abasova et al. 1994).

The ethanolic extract of the flowers of the plant also contains polysaccharides (Varljen et al. 1989). Polysaccharides in the plant have showed immunostimulant and antitumor activity (Muley et al. 2009).

Lipophilic extract obtained from *Calendula officinalis* flowers has been analyzed by using TLC. As a result of the analysis, glycolipids (25.50%), triterpenol (23.10%), hydrocarbon (9.24%), phthalate esters, triacylglycerides, free fatty acids, sterols, chlorophyll, phospholipids, triterpenol, and fatty acid esters of sterols have been detected (Khidoyatova et al. 2016). The plant infusion also has been found as phytosterols, sitosterol, β-campesterol, Δ5-avenasterol, Δ7-stigmasterol, and Δ7-avenasterol, and as alkaloids, vinblastine, vindoline, catharanthine, and vinleurocin (Khidoyatova et al. 2016). The essential fatty acid in seeds is calendic acid (Qiu et al. 2001).

## 4.5 Scientific Evidences

### 4.5.1 In Vivo and In Vitro Studies

*Calendula officinalis* is commonly used clinically. *C. officinalis* plant has many pharmacological activities. These are antioxidant, anti-inflammatory, antibacterial, antifungal, antiviral, immunostimulant, analgesic, antiseptic, anti-edematous, antihemorrhagic, astringent, antisuppurative, antiphlogistic, diuretic, antispasmodic, and anthelmintic effects. It has also been reported that the plant has antitumoral and cytotoxic effects (Chandran and Kuttan 2008; Duran et al. 2005; Gopinathan et al. 2006; Preethi et al. 2006).

The pharmacological effects of *C. officinalis* depend on the contents of various classes of secondary metabolites such as essential oil, flavonoid, polyphenolic compounds, sterol, carotenoid, tannin, saponin, triterpene alcohol, polysaccharide, mucilage, and resin. In recent years, interest toward the antioxidant properties of *C. officinalis* extracts has increased due to their high content of polyphenols and carotenoids. As a result of studies conducted with *C. officinalis*, antimutagenic effect is found by saponins found in the plant. In addition, hypoglycemic and gastroprotective effects by triterpene oligoglycosides and calendasaponins A, B, C, D have been found. Also, many active compounds have been found to have wound healing and anti-inflammatory activity (Ćetković et al. 2004; Frankič et al. 2009; Preethi et al. 2006).

### 4.5.2 Antimicrobial

Efstratiou et al. have evaluated the antimicrobial activity of methanol and ethanol extracts of *Calendula officinalis* against clinical pathogens. Antibacterial action has been examined against bacteria such as *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Bacillus cereus*, *E. coli*, *Klebsiella aerogenes*, *Staphylococcus aureus*, *Enterococcus faecalis*, and *Klebsiella pneumoniae* by using disk diffusion test. Antifungal effects have been evaluated against pathogenic fungi such as *Candida albicans*, *Aspergillus flavus*, and *Exophiala*. The methanolic extract has showed better antibacterial effect than the ethanolic extract against most of the bacteria tested. Both extracts have been reported to have better antifungal activity against some fungal species tested compared to fluconazole (Efstratiou et al. 2012).

In another study, *Althaea officinalis* L. roots, *Arnica montana* L. flowers, *Calendula officinalis* L. flowers, *Hamamelis virginiana* L. leaves, *Illicium verum* Hook. fruits, and *Melissa officinalis* L. leaves have been evaluated for their antibacterial activities. In the study, the activity of methanol extract and 10% decoction of plants against anaerobic and facultative aerobic periodontal bacteria such as *Porphyromonas gingivalis*, *Prevotella* spp., *Fusobacterium nucleatum*, *Capnocytophaga gingivalis*, *Veillonella parvula*, *Eikenella corrodens*, *Peptostreptococcus micros*, and *Actinomyces odontolyticus* has been investigated. The methanol extracts of *H. virginiana*, *A. montana*, and *A. officinalis* were found to have inhibitory activity (MIC ≤2048 mg/L) against most of the species tested. *M. officinalis* and *C. officinalis* extracts have been found to have a lower inhibitory activity (MIC ≥2048 mg/L) against the species tested, with the exception of *Prevotella* sp. (Iauk et al. 2003).

Gazim et al. have tested the in vitro antifungal activity of essential oil obtained from *C. officinalis* flowers against *Candida albicans*, *C. dublini-*

*ensis*, *C. parapsilosis*, *C. glabrata*, *C. krusei*, and yeasts isolated from humans (*C. albicans*, *C. dubliniensis*, *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, *C. guilliermondii*, *C. krusei*, *Rhodotorula* spp.), using the disk diffusion method. In the study, the essential oil showed very good antifungal activity at a concentration of 15 µl/disk (Gazim et al. 2008).

Janssen et al. have stated that the essential oil obtained from the plant inhibits the growth of *Bacillus subtilis*, *E. coli*, *S. aureus*, *P. aeruginosa*, and *C. albicans.* In addition, they have stated that this effect is caused by terpene alcohols and terpene lactones. In another study, the essential oil of the plant has showed weak fungicidal activity against dermal fungi such as *Trichophyton mentagrophytes* var. *interdigitale*, *Trichophyton rubrum*, *Trichophyton concentricum*, and *Epidermophyton floccosum* (BWP et al. 2006). Flavonoids isolated from *C. officinalis* flowers (at a concentration of 1 mg/ml) have been shown to have an antimicrobial effect against *S. aureus*. In addition, different studies have showed that flavones are effective against *Klebsiella pneumonia*, *Sarcina lutea*, and *Candida monosa* (Gruenwald et al. 2007).

### 4.5.3 Antiviral

Kalvatchev et al. have examined the dichloromethane-methanol (1:1) extracts of *Calendula officinalis* flowers in terms of inhibiting HIV-1 replication. The plant extract has showed potential anti-HIV activity in vitro MTT/tetrazolium-based assay environment. In addition, uninfected Molt-4 cells in the presence of the extract (500 µg/ml) have protected from confluence and death following confluence along 24 hours when cultured with infected U-937/HIV-1 cells. It has been observed that *C. officinalis* flower extract causes a significant decrease in HIV-1 reverse transcriptase (RT) activity depending on the dose and time. RT inhibition has been achieved at a rate of 85% after 30 minutes of treatment in the cell-free system. According to the results obtained, the researchers have stated that *C. officinalis* flower extract is therapeutically interesting for its anti-HIV properties (Kalvatchev et al. 1997). In another study, chloroform extract obtained from plant flowers has inhibited the replication of HIV Type I in acutely infected lymphotic Molt-4 cells in vitro. In addition, chloroform extract has been shown to inhibit HIV-I reverse transcriptase activity in a dose-dependent manner (BWP et al. 2006).

In another study, it has been found that 70% hydroalcoholic tincture of *C. officinalis* flowers have showed high antiviral activity against influenza virus; it has significantly suppressed the growth of herpes simplex virus (ESCOP 2003).

### 4.5.4 Antioxidant

There are many in vivo and in vitro studies on the antioxidant activity of *Calendula officinalis* plant. Especially its effectiveness on hydroxyl radicals has attracted the attention of many researchers.

The influence of methanolic and water extracts of growing wild *C. arvensis* L. and cultivated *C. officinalis* L., in a concentration range of 0.1–0.9 mg/ml, has been evaluated on three different free-radical species, DPPH (2,2-diphenyl-1-picrylhydrazyl free radical), hydroxyl radical, and lipid peroxyl radical, using electron spin resonance spectroscopy. Extracts of both plants have showed scavenging effect on all radicals examined, depending on the concentrations they were applied to. Overall, *C. officinalis* extracts were found to be better radical scavengers than *C. arvensis* extracts. It has been determined that *C. officinalis* aqueous extracts showed higher activity than methanolic extracts. It has been observed that the 0.75 mg/ml aqueous extract of *C. officinalis* completely destroys the hydroxyl radicals in the Fenton system, and the same concentration of the extract scavenges 92% DPPH and 95% peroxyl radicals formed during lipid peroxidation. The antioxidant properties are thought to be related to the total phenolic substance composition (14.49–57.47 mg/g) and flavonoid composition (5.26–18.62 mg/g) in the extract. Both methanolic and water extracts have free radical scavenging properties like synthetic

antioxidant butylhydroxyanisole (BHA). The formation of o-semiquinone radicals from rutin and caffeic acid in the lipid peroxidation system has proven this mechanism (Ćetković et al. 2004).

Preethi et al. have examined the antioxidant effect of *C. officinalis* extract in vitro and in vivo in a study they conducted. The *C. officinalis* extract has been found to scavenge hydroxyl and superoxide radicals in vivo and inhibit lipid peroxidation in vitro. In addition, the extract scavenged ABTS (2,2-azobis-3-ethylbenzothiazoline-6-sulfonic acid) and DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals. IC50 (50% inhibitory concentration) values compared with ginger extract, which is a standard antioxidant extract, have been calculated as 6.5 and 100 μg/ml, respectively. Concentrations required for 50% inhibition of lipid peroxidation were found to be 500, 480, and 2000 μg/ml, respectively. Calendula extract also has showed a dose-dependent scavenging effect of nitric oxide in culture; the IC50 has been found to be 575 μg/ml. As a result of oral administration of calendula extract at doses of 100 and 250 mg/kg, it has been observed that superoxide formation in macrophages was inhibited by 12.6% and 38.7%. Oral administration of *C. officinalis* to mice for 1 month has showed a significant increase in catalase activity and liver and blood glutathione levels. After the application of calendula extract, glutathione reductase has increased and glutathione peroxidase has decreased. These results show that *C. officinalis* extracts have significant antioxidant activity in vivo and in vitro (Preethi et al. 2006).

The butanolic fraction of *C. officinalis* is rich in flavonoids and terpenoids; these compounds are thought to be the active ingredients of the plant. The fraction was therefore studied against reactive oxygen and nitrogen fractions. The amount of superoxide radicals and hydroxyl radicals decreased when treated with increasing concentrations of the butanolic fraction. Lipid peroxidation in liver microsomes induced by $Fe^{2+}$/ascorbate has been 100% inhibited by 0.5 mg/ml butanolic fraction. The total antioxidant potential (TRAP) of the extract has been calculated as 368.14 +/− 23.03 μM and the total antioxidant reactivity (TAR) as 249.19 +/− 14.5 μM. The results have showed that the butanolic fraction of *C. officinalis* contains several compounds with antioxidant properties, some of which have high antioxidant reactivity (Cordova et al. 2002).

The potential use of *C. officinalis* extract to protect against UV radiation-induced oxidative stress on the skin has been studied. In this study, the physicochemical composition of the hydroalcoholic extract has been determined, and its in vitro antioxidant effect has been investigated using different methodologies. In addition, the in vivo protective effect of the extract against UVB-induced oxidative stress in the skin of hairless mice has been investigated by monitoring the secretion/activity of metalloproteinase and determining reduced glutathione levels. Hairless male and female mice have been exposed to UVB (2.87 J/cm$^2$) irradiation, and a 44.5% reduction in glutathione levels has been seen. Subsequently, the extract has been administered orally to mice at doses of 150 mg/kg and 300 mg/kg. Glutathione levels have remained the same in hairless mice treated orally with the extract at the indicated doses relative to the control group not exposed to UVB rays. As a result, the extract has prevented UVB irradiation-induced GSH consumption of hairless mice after oral ingestion and has showed in vitro antioxidant activity against different radicals. According to the results, this study demonstrates the potential applicability of *C. officinalis* extract against UV-induced skin damage (Fonseca et al. 2010).

### 4.5.5 Immunomodulatory

It was observed that three polysaccharides (PS-I, PS-II, PS-III) isolated from 70% ethanol extract of *Calendula officinalis* flowers stimulated phagocytosis of human granulocytes at a concentration of 0.1–10 μg/ml by 40–57%, 20–30%, and 54–100%, respectively. This effect indicates that the plant may have an immunomodulatory effect (Varljen et al. 1989).

In another study, polysaccharide fractions (molecular weight in the range of 25,000–

500,000) obtained from *C. officinalis* flower have showed immunostimulating activity in granulocytes and carbon cleaning tests (Wagner et al. 1985).

The polysaccharide fraction of the aqueous extract obtained from *C. officinalis* flowers has been found to increase phagocytosis in the carbon clearance test in mice (ESCOP 2003). However, another study has been found that extracts of *Calendula* flowers did not show a direct mitogenic effect on human lymphocytes and thymocytes (Amirghofran et al. 2000).

### 4.5.6 Cytotoxic

The cytotoxic effect of the methanol extract of *Calendula officinalis* flowers on human cancer cells in vitro has been evaluated. The fraction of the methanol extract dissolved in ethyl acetate has showed a cytotoxic effect in vitro. As a result of the activity-guided isolation of the fraction, it has been determined that the effective compounds were calenduloside F6'-O-butyl ester and calenduloside G6'-O-methyl ester. Calenduloside F6'-O-butyl ester compound has showed a cytotoxic effect against leukemia, colon cancer, melanoma, kidney cancer, and breast cancer. Calenduloside G6'-O-methyl ester compound has been reported to be effective against all cancer cells mentioned above with GI50 ≤ 20 μmol, except for ovarian cancer and kidney cancer (Ukiya et al. 2006).

The extract prepared with water from *C. officinalis* flowers has been treated with laser radiation at 650 nm wavelength for 15 minutes. During the process, 100–200 g of flowers were taken, placed in 1 liter of water, periodically exposed to laser beams for 7–15 days, then filtered, and stored at −70 °C. The effect of this extract on enhancing human peripheral lymphocytes, cell life, and apoptosis has been investigated in vitro. Using tumor cells extracted from leukemia, melanoma, fibrosarcoma, lung, prostate, cervix, breast, pancreas, and colorectal region, viable cell numbers and tumor proliferation were measured. The extract has showed 70–100% inhibition on the proliferation of said cancer cells. However, it showed cytotoxic activity by increasing leukemia and NKL lymphocyte activation. It is thought that the inhibition mechanism stops the cell division in the G0/G1 phase and causes apoptosis by triggering caspase-3 (Jiménez-Medina et al. 2006).

In order to evaluate the selectivity of antitumor activity, the cytotoxic activity of tea made from *Matricaria recutita* and *Calendula officinalis* flowers has been tested against various malignant cells and healthy peripheral blood mononuclear cells (PBMC). Chemical structures of infusions and decoctions prepared from plants have been analyzed by liquid chromatography/mass spectrometry (LC/MS), and their total phenolic content and radical scavenging activity have been also determined. Results from the study reveal that tea made from *C. officinalis* and *M. recutita* flowers has a selective, dose-dependent cytotoxic effect against cancer cells. It is remarkable that the cytotoxicity of teas prepared from *C. officinalis* flowers is higher than that of *Matricaria recutita* tea. The cytotoxic effect on PBMC is very weak in *M. recutita* tea, while it is more pronounced in *C. officinalis* tea. *C. officinalis* teas have showed a highly selective antitumor effect against melanoma FEMX (malignant melanoma cell) cells compared to normal healthy PBMC. Chemical analysis shows that the predominant phenolic compounds in infusions and decoctions of *C. officinalis* and *M. recutita* flowers are flavonoid glycosides and hydroxycinnamic acid derivatives. No significant difference has been found between the infusions of both herbs in terms of total phenolic content and antioxidant activity (Matić et al. 2013).

### 4.5.7 Antitumor

The extract prepared with water from *C. officinalis* flowers has been treated with laser radiation at 650 nm wavelength for 15 minutes. During the process, 100–200 g of flowers were taken, placed in 1 liter of water, periodically exposed to laser beams for 7–15 days, then filtered, and stored at −70 ° C. The effect of the extract on the inhibition of Ando-2 melanoma tumor growth in nude

mice (without thymus) was studied. The mice have been randomly divided into groups with ten mice in each group. The first group orally has been administered with *C. officinalis* extract at a dose of 50 mg/kg three times a week for 12 weeks, the second group has been receiving the same extract intraperitoneally at a dose of 25 mg/kg twice a week for 9 weeks, and the third group intraperitoneally at a dose of 5 mg/kg Taxol twice a week for 3 weeks. The control group was fed with physiological saline both intraperitoneally and orally. Tumor growth inhibition was found to be 60% in both groups given *C. officinalis*; these results are similar to the Taxol given group. Considering the living rates at the end of the study, the survival rate was 0% in the control group, 75% in the group given extract orally, 60% in the group administered with the extract intraperitoneally, and 40% in the group given Taxol (Jiménez-Medina et al. 2006).

### 4.5.8 Wound Healing

The European Medicines Agency (EMA) has approved the use of lipophilic and aqueous alcoholic extracts of *Calendula officinalis* as a traditional medicinal product in the treatment of minor inflammatory diseases of the skin and as an aid in the healing of small wounds (Nicolaus et al. 2017).

The wound healing process involves several different stages in which the formation of new blood vessels (angiogenesis) plays an important role. In a study, the aqueous extract of *C. officinalis* flowers has been evaluated for angiogenic effect on the chick chorioallantoic membrane. It has been observed that the capillary density in the tissue treated with the extract increased significantly ($p = 0.0001$) compared to the control group. In addition, hyaluronan has been found to be positive in the group treated with the extract (Patrick et al. 1996).

The potential of topical *C. officinalis* extract on recovery of 5-fluorouracil (5-FU)-induced oral mucositis has been evaluated in 60 male hamsters. Oral mucositis in hamsters has been induced with 60 mg/kg 5-FU on days 0, 5, and 10. On days 12–17, they were treated with gels with and without 5% and 10% *C. officinalis* extract. It has been evaluated macroscopically and microscopically with the control group. As a result of the study, it was found that the formation of oral mucositis in hamsters treated with gel containing *C. officinalis* extract was lower and it accelerated healing (Tanideh et al. 2013).

Ethanol extract of *C. officinalis* flowers has been administered orally to female Wistar rats (150–200 g) with backburn at different doses, and improvement has been observed compared to the control group. The burn wound has been made on the shaved back of the rats under anesthesia, and the animals have been treated with 20, 100, and 200 mg/kg doses of *C. officinalis* extract. Animals treated with the extract have shown a significant improvement in recovery compared to untreated animals. Hexosamine and collagen hydroxyproline levels, which play an indicator role in wound healing, have increased. It has been found that the acute phase proteins haptoglobin and orosomucoid, which were elevated due to burn wound, were significantly reduced in animals treated with 200 mg/kg extract. Decreased antioxidant defense mechanism in the liver during burn wound was found to be increased in treated animals. In the treated group, tissue damage determining enzymes (alkaline phosphatase, alanine, and aspartate transaminase) have been significantly reduced in a dose-dependent manner. Histopathological analysis of skin tissue has supported the increased healing potential of the extract after a burn wound (Chandran and Kuttan 2008).

In a study, the angiogenic activity of *C. officinalis* ethanol extract and dichloromethane and hexane fractions has been evaluated, especially considering the healing activity. Chorioallantoic membrane of fertilized chicken eggs and cutaneous wounds of rats were used as a model in the study. Also, the effect of vascular proliferation has been tested to confirm the expression intensity of vascular endothelial growth factor (VEGF) in cutaneous wounds in rats. As a result of the study, the angiogenic activity of the extracts and fractions was proven in both experimental models. It has been stated that this effect is not directly

related to VEGF expression and may be related to other pro-angiogenic factors (Parente et al. 2011).

### 4.5.9 Analgesic

The hydroalcoholic extract of *Calendula officinalis* flowers was evaluated for analgesic activity in Swiss albino mice (25–35 g, male) using the formalin and writhing test. Orally, doses of 200, 400, and 600 mg/kg in the formalin test (2.5% formalin in 20 μL 0.9% saline, subplantar) and doses of 100, 200, and 400 mg/kg in the writhing test (1% acetic acid, 1 ml/100 g, i.p.) showed a significant analgesic effect according to the indomethacin (2.5 mg/kg, oral) standard (Behtash et al. 2010).

### 4.5.10 Anti-inflammatory

It has been stated that one of the main ingredients responsible for the anti-inflammatory effect is faradiol (Nicolaus et al. 2015). It has been proven that *Calendula officinalis* flowers show anti-inflammatory activity in inflammation caused by croton oil in the ear (Nicolaus et al. 2014). The aqueous-ethanolic extract of the plant at a dose of 1200 μg/ear has been shown to inhibit 20% in croton oil-induced mouse edema. The activity is attributed to the presence of faradiol-3-myristic acid, faradiol-3-palmitic acid, and 4-taraxasterol esters, which are among the most active compounds of triterpenes (Muley et al. 2009).

Ukiya et al. have investigated the effect of the ethyl acetate-soluble fraction of the methanol extract of *C. officinalis* flowers against 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation in mice. It has been shown to inhibit TPA-induced inflammation by 84% in mice compared to indomethacin used as reference drug. The compound responsible for the activity is thought to be triterpenic glycosides containing oleanolic acid (Ukiya et al. 2006).

*C. officinalis* flower extract has showed anti-inflammatory activity against acute paw edema induced by carrageenan and dextran in mice. The extract has been administered orally at doses of 250 and 500 mg/kg. It has showed 50.6% and 65.9% inhibition in carrageenan-induced edema and 41.9% and 42.4% inhibition in dextran-induced edema, respectively. In the chronic inflammation model created with formalin, it has showed 32.9% and 62.3% inhibition at the same doses, respectively. In the same study, a decrease was observed in the levels of proinflammatory cytokines IL-1β, IL-6, TNF-α, and IFN-γ and the levels of C-reactive protein from acute phase proteins. However, a decrease in lipopolysaccharide-induced cyclooxygenase-2 (COX-2) levels has been also observed in the spleens of mice. The results obtained from the study showed that the strong anti-inflammatory response of *C. officinalis* flower extract was achieved by the decrease in the levels of proinflammatory cytokines and COX-2 (Preethi et al. 2009).

A study has been conducted to investigate the efficacy of *C. officinalis* extract in the treatment of experimentally induced ulcerative colitis. Ten pure-blood German dogs (1–2 years old, 20–25 kg, female) with 6% acetic acid-induced ulcerative colitis were included in the study. Forty percent *C. officinalis* ethanol extract was administered to the first group at a dose of 3 ml/day for 30 days, and a solution containing saline solution has been administered to the second group at the same dose for the same period. At the end of the 45th day, it has been observed that ulceration, inflammatory cell and vascular dilatation, reduction of mucous cells, crypt abscess, inflammatory cysts, mucosal atrophy, and submucosal edema, indicating ulcerative colitis damage completely disappeared in the group that was applied with the extract (Mehrabani et al. 2011).

### 4.5.11 Hepatoprotective and Renoprotective

Potential hepatoprotective effects of *Calendula officinalis* and *Morus alba* extracts have been evaluated against cytotoxicity and oxidative stress in isolated rat hepatocytes induced by carbon tetrachloride ($CCl_4$). *Calendula officinalis* and *Morus alba* extracts at different concentrations (1, 10, 100, and 1000 μg/ml) have caused a decrease in the percentage viability of isolated rat hepatocytes. Treatment of hepatocytes with

extracts has improved the hepatotoxicity and oxidative stress caused by $CCl_4$; significant improvement in cell viability and ALT, AST, LDH, and GSH content has been detected (El-Tawil et al. 2010).

The efficacy of hydroalcoholic extract of *C. officinalis* flowers has been investigated on albino male Wistar rats whose livers were damaged by $CCl_4$ (carbon tetrachloride). A 28.5% reduction in hepatocytolysis has been observed due to glutamo-oxalate-transaminase (GOT) and glutamo-pyruvate-transaminase (GPT). However, when the histoenzymology was examined, it has been observed that there was a decrease in liver fattening with lactate dehydrogenase (LDH), succinate dehydrogenase (SDH), cytochrome oxidase (Cyox), and $Mg^{+2}$-dependent adenosine triphosphatase (ATPase). The effect of the same extract on cisplatin-induced kidney toxicity in Swiss albino mice was also studied. It has been observed that it decreases urea and creatinine levels in the blood and increases the levels of glutathione with superoxide dismutase and catalase, which are antioxidant system enzymes (Rusu et al. 2005).

In another study, the protective effect of ethanolic extract of *C. officinalis* flowers against $CCl_4$-induced acute hepatotoxicity and cisplatin-induced nephrotoxicity has been evaluated. The extract has been shown to reduce blood levels of serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), alkaline phosphatase (ALP) enzyme, and total bilirubin in female Wistar rats at doses of 100 mg/kg and 250 mg/kg. The effects of the same extract on cisplatin-induced kidney toxicity in Swiss albino mice were also studied. The extract decreased increased urea and creatinine levels in blood at doses of 100 mg/kg and 250 mg/kg, and it was observed to increase glutathione levels with antioxidant system enzymes superoxide dismutase and catalase. Results from the study show that *C. officinalis* flower extract plays a protective role against $CCl_4$-induced acute hepatotoxicity and cisplatin-induced nephrotoxicity. The extract has been found to contain several carotenoids dominated by lutein, zeaxanthin, and lycopene. It has been stated that the possible mechanism of action of the flower extract may be due to its antioxidant activity and the reduction of oxygen radicals (Preethi et al. 2009).

The effect of 80% methanol extract of *C. officinalis* leaves against acetaminophen-induced liver damage in 30 male albino mice has been investigated. Liver damage in mice has been induced by oral acetaminophen (640 mg/kg). Acetaminophen caused 100% death in mice at a dose of 1 mg/kg, while pretreatment of mice with *C. officinalis* (1.0 mg/kg) has reduced the mortality rate to 30%. Pretreatment of mice with leaf extract (500 mg/kg orally, four doses at 12-hour intervals) prevented acetaminophen-induced increase in serum transaminases (SGOT, SGPT), serum bilirubin, and serum alkaline phosphatase. Following treatment with three successive doses of leaf extract (500 mg/kg, every 6 hours), hepatic damage induced by acetaminophen has been limited. These results show that *C. officinalis* leaf extract has hepatoprotective effect (Ali and Khan 2006).

### 4.5.12 Antigenotoxic

In a study by Abdel-Aziem et al., genotoxicity was induced in rats by oxidative stress induced by aflatoxins. The effects of the generated genotoxicity on the antioxidant system, cytotoxicity, and DNA fragmentation were investigated. Ethanol extract prepared from *C. officinalis* flowers at a dose of 0.5 g/kg was orally administered to rats. After administration, the oxidative stress markers such as malondialdehyde, glutathione peroxidase, and superoxide dismutase were calculated. In the aflatoxin given group, malondialdehyde 135.1 ± 3.4 nmol/g, glutathione peroxidase 14.22 ± 1.2 U/mg protein, and superoxide dismutase were found as 166.42 ± 4.27 U/mg protein. In the group given *C. officinalis* extract with aflatoxin, malondialdehyde 63.7 ± 2.6 nmol/g, glutathione peroxidase 35.61 ± 1.43 U/mg protein, and superoxide dismutase were found as 281.57 ± 5.04 U/mg protein. Viability in the cytotoxicity study was calculated by the ratio of polychromatic erythrocyte/normochromatic erythrocyte. Viability was calculated as 0.48 ± 0.4 in the aflatoxin given group (blind: 1.01 ± 0.1), while it was calculated

as 0.88 ± 0.3 in the group given *C. officinalis* extract with aflatoxin. The rate of DNA fragmentation was 43% in the group given aflatoxin and 20.6% in the group given *C. officinalis* extract with aflatoxin. According to the results obtained from the study, it can be said that the extract has an antigenotoxic effect (Abdel-Aziem et al. 2014).

### 4.5.13 Cytoprotective

A study has been conducted to determine the protective effect of *C. officinalis* ethanolic extract on rats exposed to cigarette smoke. In the study, 21 Sprague-Dawley male albino rats (240–260 g) were exposed to cigarette smoke for 1 hour per day for 23 days. One group has been given the extract by intragastric administration at a dose of 100 mg/kg, and saline has been given intragastrically to the control group. The effect of *C. officinalis* administration on rats has been monitored by measuring malondialdehyde, protein carbonyl, glutathione, vitamin levels and glutathione peroxidase and superoxide dismutase activities. While the malondialdehyde level was 40.05 ± 2.70 nmol/g in the control group, it was 32.71 ± 3.06 nmol/g in the group fed with the extract; while the protein carbonyl level was 3.36 ± 1.04 nmol/mg in the control group, it was 1.84 ± 0.25 nmol/mg protein in the extract applied group; and while the reduced glutathione level was 3.20 ± 0.26 μmol/g in the control group, it was found to be 2.63 ± 0.44 μmol/g in the extract applied group. As a result of the obtained data, it has been found that *C. officinalis* extract provided protection against subacute cell damage caused by cigarette smoke (Özkol et al. 2012).

## 4.6 Clinical Studies

Studies on *Calendula officinalis* support its use among the public; however, it also has effects proven by clinical studies. Its effects supported in studies are its antioxidant, antiulcer, anti-inflammatory, antimicrobial, and antiviral effects. It has also been observed to have antimutagenic, hepatoprotective, hypolipidemic, anti-tyrosinase, anti-edematous, and anti-HIV effects. Its effects supported by clinical studies are wound healing, antioxidant, anticandidal, and cosmetic effects (Çolak 2018).

### 4.6.1 Wound Healing

It is the best-known pharmacological effect and is widely used among the public because of this effect. Numerous studies have been conducted on this effect and it has been proven in clinical trials. Clinical studies have shown that *C. officinalis* extract is effective in preventing acute dermatitis in patients treated with ultraviolet (UV). The therapeutic effect of *C. officinalis* is explained by the presence of flavonoids, especially rutin (Martins et al. 2014).

A study has been conducted in which 254 women who underwent surgery for breast cancer and will receive postoperative radiation therapy were included. In this study, the protective effects of ointment prepared with trolamine and *C. officinalis* against acute dermatitis were compared. In the study in which patients between the ages of 18 and 75 without metastatic breast adenocarcinoma were included, 126 patients were given ointment prepared with *C. officinalis* drug, and 128 patients were given ointment prepared with trolamine. With the application of *Calendula* ointment, it has been observed that there was a significant decrease in second-degree and higher degree dermatitis compared to trolamine. However, 30% of the patients using the ointment prepared with *C. officinalis* and 5% of the patients using the trolamine ointment have reported that topical application of the ointment was difficult. Two patients have stopped using the ointment because of these difficulties. However, in the prevention of redness, the ointment prepared from the plant was 69%, trolamine ointment 39%; in reducing pain, the ointment prepared from the plant provided 65% satisfaction, and the trolamine ointment 46%. As a result of the study, it has been observed that the ointment prepared from the plant was statistically signifi-

cantly more effective than trolamine ointment in preventing acute dermatitis of second degree or higher in postoperative breast radiotherapy (Pommier et al. 2004).

Thirty-four patients with venous leg ulcers have been studied to determine the therapeutic efficacy of *C. officinalis* extract in epithelialization of venous ulcers in the lower legs. The patients were divided into two groups. The first group (n:21) was treated with ointment containing *C. officinalis* extract prepared by Soxhlet extraction twice a day for 3 weeks. Saline solutions were applied to the control group of 13 patients for 3 weeks. While the total surface of all ulcers at the beginning of the treatment in the experimental group was 67.544 $mm^2$, at the end of the third week, the total surface of all ulcers was calculated as 39.373 $mm^2$ (41.71% reduction). Complete recovery was achieved in seven patients. While the total surface area of all ulcers at the beginning of the treatment was 69.722 $mm^2$ in the control group, the total surface area of all ulcers at the end of the third week was calculated as 58.743 $mm^2$ (14.52% reduction). All four patients recovered completely. A statistically significant difference has been found in wound healing in the experimental group compared to the control group ($p < 0.05$). As a result of the study, it has been reported that *Calendula* ointment has positive effects on venous ulcer epithelialization (Duran et al. 2005).

An observational study was conducted on 41 patients with pressure ulcers for more than 3 months. Wound healing after spray application with *C. officinalis* flower extract has been evaluated. After 15 weeks of treatment, 63% of the ulcers have completely healed, and there have been notable improvements in appearance compared to baseline. It had been observed that after 30 weeks, 88% of the wounds had healed completely. As a result of the study, it has been stated that the spray containing *C. officinalis* flower extract increased wound healing and no side effects were observed during the treatment (Buzzi et al. 2016).

A study was conducted to determine the effect of *C. officinalis* cream in healing bedsores. Twenty patients with bedsores were included in the study. The conditions of the patients such as the duration of the bedsores and the size of the wound were recorded. The bedsores were washed with saline solution, dried, and applied with *Calendula* cream three times a day for 4 weeks. The magnitude and rate of recovery were recorded each week. As a result of the study, the recovery rate in patients is 56.6%. Recovery time is $3.5 \pm 1.2$ ($p < 0.001$) in weeks. According to the results obtained from the study, it has been reported that *Calendula* cream can be used in the treatment of bedsores (Esmaili et al. 2008).

### 4.6.2 Antioxidant

A randomized controlled clinical study was conducted to evaluate the effectiveness of mouthwash containing *C. officinalis* 2% ethanolic flower extract on oropharyngeal mucositis. Forty patients with head and neck cancer who received chemotherapy and radiotherapy were included in the study. Patients were randomly divided into two groups (20 patients in calendula group and 20 patients in placebo group). Oropharyngeal mucositis severity was evaluated using Oral Mucositis Assessment Scale (OMAS) scores in all patients. After 2 weeks, a decrease in the severity of mucositis was noted in the group using the extract containing mouthwash. After 2 weeks, it was 5.5 points against the placebo value of 6.8 points ($p = 0.019$), after 3 weeks it was 8.25 points against the placebo value of 10.95 points ($p < 0.0001$), and after 6 weeks it was 11.4 points against the placebo value of 13.35 points ($p = 0.031$). For total antioxidant, polyphenol, and flavonoid contents and quercetin concentration for 2% *C. officinalis extract*, it was calculated as $2353.4 \pm 56.5$ µM, $313.40 \pm 6.52$ mg/g, $76.66 \pm 23.24$ mg/g, and $19.41 \pm 4.34$ mg/L, respectively. As a result of the study, it was concluded that *C. officinalis* was effective in reducing the intensity of oral mucositis, but could not completely prevent its occurrence (Babaee et al. 2013).

### 4.6.3 Anticandidal

A study was conducted to evaluate the safety and therapeutic effect of *C. officinalis* by topical route in the treatment of recurrent vaginal candidiasis. We studied 127 patients with an average age of 23.7 ± 5.2 and 95.2% active sexual life and recurrent vaginal candidiasis. Tincture prepared with 20% ethanol from *C. officinalis* flowers was applied topically three times a week for 2 weeks to randomly selected 46 patients. At the beginning of the study, 85.7% of the patients presented with vaginal discharge and 83.3% with itching. However, as treatment progressed, the number of these patients decreased significantly. Vaginal cultures of the patients were performed at the beginning, on the 21st and 30th days. As a result of the experiment, *Candida* was found in the vaginal cultures of only seven patients (16.7%) (Vázquez et al. 2010).

### 4.6.4 Cosmetic

A single-sided blind study has conducted with 21 healthy volunteers aged 24–35 years. A cosmetic face cream containing the extract of *C. officinalis* flowers prepared in ethanol was tested for 8 weeks in comparison with another cream without the extract. As a result of the study, it was determined that the cream containing the extract increased skin moisturization and firmness (Akhtar et al. 2011).

## 4.7 Toxicological Studies

*C. officinalis* has high economic value as an herbal medicine and has been recently approved for food use in the USA. It is on the list generally accepted as safe (GRAS) substances by the Food and Drug Administration (FDA) (Gazim et al. 2008).

### 4.7.1 Acute Toxicity

The acute toxic effects of hydroalcoholic extract of *Calendula officinalis* when taken orally on mice and rats and subacute toxic effects in rats and hematological, biochemical, and morphological effects have been evaluated. In the acute toxicity test, it has been observed that the extracts caused death in animals at oral doses above 5 g/kg. The extracts did not cause hematological changes on oral therapy at doses of 0.025, 0.25, 0.5, and 1.0 g/kg compared to the control group. However, it has been reported that blood urea nitrogen (BUN) and alanine transaminase (ALT), which are among the biochemical parameters, are increased. No damage was found in the morphological examination of the brain, kidney, and heart. However, inflamed areas have been found in the lungs and vessels associated with oral gavage and possible hepatotoxic effects. In conclusion, acute and subacute application of *C. officinalis* hydroalcoholic extract did not cause significant changes in most biochemical, hematological, and morphological parameters. However, the increase in BUN and ALT serum levels and histological change in the liver suggest the possibility of renal and hepatic overload (Silva et al. 2007).

When *C. officinalis* flower extract was administered intravenously to mice, the LD50 (50% lethal dose) was 375 mg/kg, and when administered intraperitoneally, the LD100 (100% lethal dose) was 580 mg/kg. The LD50 of hydroalcoholic extract (1:1) prepared with 30% ethanol has found to be 45 mg when administered subcutaneously to mice and 526 mg/100 g when administered intravenously to rats. Aqueous extract from the plant has been administered orally to mice at 0.15 g/kg body weight for 18 months and to rats for 22 months. As a result of this chronic application, the aqueous extract has been found to be nontoxic and noncarcinogenic (ESCOP 2003).

A study has been conducted to determine the acute and subchronic toxicity of aqueous extract of *C. officinalis* flowers orally in male and female Wistar rats. In the study, the animals' body weight, water and food intake, selected tissue weights, histopathological changes, and hematology and blood parameters have been examined. For acute toxicity, 2000 mg/kg of *C. officinalis* extract has been administered by oral gavage. For subchronic

toxicity, *C. officinalis* extract has been applied to drinking water at doses of 50, 250, and 1000 mg/kg/day for 90 days. In the acute study, there have been no signs of death or toxicity. The effects of *C. officinalis* extract in the subchronic regimen varied according to gender. However, hematology and biochemical parameters have been generally affected, causing mild abnormalities in liver tissues. Due to the lack of toxic effect in the acute toxicity test in the study, the NOAEL (no-observed-adverse-effect level) for acute gavage dose was found to be 2000 mg/kg. For histopathological changes in the liver, AST and ALT activities, and hematological variations, LOEL (lowest-observed-effect level) has been calculated as 50 mg/kg/day for subchronic exposure in both genders. The researchers reported that according to the results obtained from the study, the acute and subchronic toxicities of *C. officinalis* extract were low (Lagarto et al. 2011).

A study has been conducted on Wistar rats to determine the acute and subchronic dermal toxicity of *C. officinalis* essential oil. Hematological parameters, biochemical parameters, body weight change, relative organ weights (liver, kidney, brain), and histopathological parameters have been examined. Animals have been exposed to a dose of 20 mL/kg of *C. officinalis* essential oil for acute dermal toxicity. For the dermal subchronic toxicity study, they have been exposed to *C. officinalis* essential oil at doses of 2.5, 5, and 10 mL/kg, seven times a week for 90 days, respectively. As a result of the study, the hematological parameters, blood biochemistry, relative organ weights, and histopathological parameters were compared with the control group, and no significant change was observed. The NOEL (no-observed-effect level) and NOAEL (no-observed-adverse-effect level) values of *C. officinalis* essential oil were found to be 2.5 and 10 mg/kg/day, respectively. According to the data obtained from the study, *C. officinalis* essential oil did not cause a significant toxic effect; therefore, it has been reported that the essential oil can be considered safe for topical use and other intended cosmetic applications (Mishra et al. 2018).

### 4.7.2 Chronic Toxicity

Aqueous extract of *C. officinalis* flowers has not shown chronic toxicity to mice. *C. officinalis* flower extract has been administered orally at a dose of 0.15 g/kg to hamsters 18 months old and rats over 21 months old. No toxic effects have been observed in animals after administration. In addition, no toxicity was observed when calenduloside B at a daily dose of 200 mg/kg was administered orally for 2 months (ESCOP 2003).

There are no records of repeat dose toxicity (Demirezer et al. 2017).

### 4.7.3 Mutagenicity and Teratogenicity

In the Ames test using TA1535, TA1537, TA98, and TA100 strains of *Salmonella typhimurium*, 60% ethanol extract of *C. officinalis* flowers has not shown mutagenic effects at concentrations of 50–5000 μg/plate. Genotoxic effects with mitotic crossing over and chromosome disruption with *Aspergillus nidulans* diploid strain D30 were observed at concentrations higher than 1 mg/mL. There has been also an increase in cytotoxicity attached to concentration. After oral administration of the extract up to 1 g/kg for 2 days, no increase has been observed in any of the micronucleus polychromatic erythrocytes. These findings have not been confirmed in vivo in the mouse bone marrow micronucleus assay (EMA 2018). Six saponins isolated from *C. officinalis* flowers were not mutagenic in the Ames test with and without S9 activation with *Salmonella typhimurium* TA98. In carcinogenicity studies with *C. officinalis* flower extract, a daily dose of 0.15 g/kg was administered orally to rats for 22 months and to hamsters for 18 months. It has been found that the extract is not carcinogenic to either species (ESCOP 2003).

### 4.7.4 Pregnancy Toxicity

There are no data on drug interactions, drug and laboratory test interactions, teratogenic and non-teratogenic effects during pregnancy, breastfeed-

ing mothers, or pediatric use. Therefore, Calendulae flos should not be administered to children during pregnancy or when breastfeeding or without medical supervision (WHO 2002).

### 4.7.5 Reproductive Toxicity

Silva et al. have conducted a study to evaluate the effects of 70% ethanol extract of *C. officinalis* flowers on the reproductive function of Wistar rats. Male rats divided into four groups were treated orally with the extract at doses of 0, 0.25, 0.5, and 1.0 g/kg for 60 consecutive days. From the 53rd to the 60th day of treatment, rats have been mated with untreated and fertile female rats. Reproductive parameters such as testicular morphology, reproductive organ weights, fertility index, and offspring viability were evaluated. In the second part of the study, groups of pregnant rats were treated orally with the same doses of extract on days 1–6 (preimplantation period), 7–14 (organogenic period), or 15–19 (fetal period) of gestation. On the 20th day of gestation, rats have been killed to evaluate maternal and fetal parameters. The results have shown that treatment with the extract did not affect male reproductive parameters. In addition, no toxic effects have been observed in preimplantation and organogenic periods of pregnancy. However, when the extract was applied during the fetal period, it has caused a decrease in maternal weight gain. As a result of the study, it was reported that the extract did not affect male fertility and had no toxic effects in the early and middle periods of pregnancy, but caused maternal toxicity when administered during the fetal period of pregnancy (Silva et al. 2009).

## 4.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies

The herb has internal and external use. Decoction and other preparations prepared from the chipped drug can be used in topical application. It is also convenient to prepare tincture, liquid extract, and infusion. There are preparations in the form of powder, tea (in the form of infusion), tincture, cream, gel, ointment, ophthalmic solution, and shampoo (J. J. E. C. U. Gruenwald et al. 2000).

**Tea** 150 ml of hot water is added to one to two teaspoons of the drug and infused for about 10 minutes (Gruenwald et al. 2000).

- In sore throat and inflammation, 1 to 2 g of the drug is steep in 1 cup of water for 10 to 15 minutes (Gruenwald et al. 2000).
- In the peptic ulcer, 1 to 4 g of drug is steep in 1 cup of boiling water for 10 to 15 minutes; drink one glass three times a day (Gruenwald et al. 2000).

**Ointment** It is prepared as 2 to 5 g drug in 100 g of ointment (Gruenwald et al. 2000).

- 2% and 5% ointment are used as a wound healing. It is applied topically to the problematic area (Blumenthal et al. 1998).

**Tincture** It is prepared in 90% ethanol (v / v) at a ratio of 1:5 (Willoughby et al. 1996).

- For diaphoretic purposes, 2–4 ml of tincture is diluted to 250–500 ml of water or 0.5–1 ml of liquid extract is mixed with 40% ethanol (Gruenwald et al. 2000).
- Tincture is not diluted in the treatment of wounds. It is used for compresses, diluting the tincture with boiled water in a ratio of 1:3 (ESCOP 2003).

**Calendula Oil** Drug is kept in olive oil, diluted 1:10 with peanut oil, 1:1 with 40% ethanol, or 1:5 with 90% ethanol (Gruenwald et al. 2000).

There is no record of the pharmacokinetic properties of *Calendula officinalis* (EMA 2018).

## 4.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

*Calendula officinalis* is an important plant that has been in use for many years. It is commonly used in both traditional medicine and homeopathic medicine for the treatment of various ailments. In the past, the flowers of the plant have been used for intestinal diseases, liver ailments, and bug- and snakebites (Gruenwald et al. 2007). It is also used to support granulation; facilitate the healing of skin inflammations, wounds, and burns; and prevent the spread of infections. It is used both internally and externally in the form of infusions, tinctures, liquid extracts, cold-pressed oils, and ointments (Grieve 1970).

Studies on *C. officinalis* support its use among the public. Various phytopharmacological studies have been conducted on different *C. officinalis* extracts. With these studies, it has been proven that the plant has antioxidant, antiulcer, wound healing, anti-inflammatory, antimicrobial, and antiviral effects. It has also been observed that it has antimutagenic, hepatoprotective, analgesic, immunomodulatory, antigenotoxic, and anti-HIV effects (Çolak 2018).

Clinical studies with *C. officinalis* have been mainly performed with external administration. Patients with ulcerative extremity wounds and diabetic foot wounds have been selected in the studies. Besides its wound healing effect, the antiseptic feature of *C. officinalis* has also attracted attention in external application. Due to these effects, its effectiveness in oral infections has also been investigated (Çolak 2018).

Clinical studies have shown that it is highly effective in preventing acute dermatitis in cancer patients receiving postoperative radiation therapy (Pommier et al. 2004). Its cytotoxic effect on the in vitro tumor cell line and its in vivo anticancer activity are briefly summarized (Boucaud-Maitre et al. 1988). In a clinical study conducted to evaluate the therapeutic effect of *C. officinalis* in the treatment of vaginal candidiasis, it has been proven that the plant has anticandidal activity (Vázquez et al. 2010).

Aqueous extract of *C. officinalis* flowers, *Momordica charantia* and *Cassia tora* seeds, and oil of *Azadirachta indica* plant seed have been traditionally been used in the treatment of skin diseases such as psoriasis. While these herbs and oil are used individually safely, there are no studies on their use as a combination. In order to ensure the safety of the combination intended for use in the formulation, an acute toxicity study was conducted in rats. In the study, 5000 mg/kg oral single dose of herbal mixture has been applied to female rats, and 2 ml of distilled water has been given to the control group. As a result of the study, it has been reported that the herbal mixture did not show a significant toxicological effect under working conditions (Roopashree et al. 2009).

However, with interactions of the herb with drug and laboratory tests, there are insufficient data on teratogenic and non-teratogenic effects or pediatric use in pregnancy (WHO 2002). Therefore, more studies are needed to use the plant more safely.

## 4.10 Challenges and Future Recommendations as Potential Drug Candidate

*Calendula officinalis* is a plant traditionally used in the treatment of many diseases. German Commission E, British Herbal Pharmacopoeia, EMA, ESCOP, and WHO monographs contain information on the traditional use of the herb, in vivo and in vitro pharmacological studies and clinical studies conducted in recent years. Various studies have been conducted to evaluate the toxicity and safety of the plant. However, there are insufficient data on drug interactions, teratogenic effects, or pediatric use. Therefore, Calendulae flos should not be used in children under 12 years of age, during pregnancy, and when breastfeeding.

*C. officinalis* has been used in both traditional medicine and homeopathic medicine for many years. The plant is rich in many pharmaceutical active ingredients such as flavonoids, carotenoids, glycosides, and sterols. Its wound healing effect, anticandidal effect, analgesic effect, and

antioxidant activity have been supported by clinical studies. It has been proven by current clinical studies to be a potential phytotherapeutic drug in the treatment of various diseases. However, further research and further clinical studies are needed on the pharmacokinetics, pharmacodynamics, and toxicology of the herb.

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# *Camellia sinensis* (L.) Kuntze

5

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**Abstract**

*Camellia sinensis*, known for its widespread consumption, can be used in many medical fields, and is the most popular beverage after water worldwide. *Camellia sinensis* contains approximately 4000 bioactive substances, one third of which is polyphenols. Polyphenols are powerful antioxidants and they can be used in many health areas. It is known to have improving effects on reproduction due to its antioxidant properties. On the other hand, it has a protective effect on semen, oocyte, and reproductive tissues. In conclusion, *Camellia sinensis* has positive effects on reproductive system in animals. However, this needs to be detailed with toxicological and pharmacological studies. After these processes and its standardization, it can be recommended as an effective herbal drug candidate on reproduction.

**Keywords**

Antioxidant · *Camellia sinensis* · Reproduction

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## 5.1 Introduction

It is known that plants are used as a source of medicine since ancient times (Namita et al. 2012). Majority of people rely on traditional plants for their health needs (Gurib-Fakim 2006). Furthermore, there is an increased interest in the use of plants in the treatment of human diseases due to the increased demand for drugs due to population growth and the high cost of treatment for synthetic drugs and their side effects (Namita et al. 2012). *Camellia sinensis* (L.) Kuntze, known for its widespread consumption, can also be used in the medical field (Ferrara et al. 2001), and is the most popular beverage after water worldwide (Boehm et al. 2009; Moore et al. 2009; Jayasinghe and Kumar 2019). *C. sinensis* is the scientific name for tea (Bedrood et al. 2018) and belongs to the genus *Camellia* L. from family Theaceae (Namita et al. 2012). Its discovery is assumed to date back 4000 years (Ferrara et al. 2001). *C. sinensis* is an evergreen shrub-type plant with numerous branches, and has leaves with glossy dark green, serrate, elongate ovate, and short-petiolate (Mahmood et al. 2010). It can also grow up to 16 m tall (Ferrara et al. 2001). *C. sinensis* is commercially available and has extremely rich vitamin and mineral content (Boehm et al. 2009). There are three forms as green, oolong, and black produced from the same plant (Chopade et al. 2008; Boehm et al. 2009;



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Rahman et al. 2018). Moreover, it was reported that *C. sinensis* contains approximately 4000 bioactive substances, one third of which is polyphenols (Mahmood et al. 2010). Polyphenols (green tea polyphenols) exhibit antioxidant, antimicrobial, antihypertensive, antidiabetic, anticancer, and antimetabolic syndrome effects (Rahman et al. 2018). Due to these effects, it can be used in many health areas (Chopade et al. 2008; Sharangi 2009; Mahmood et al. 2010). As understood, *C. sinensis* is recognized as an important industrial and pharmaceutical raw material. It is also known to have improving effects on fertility in male and female (Khan et al. 2017; Rahman et al. 2018).

This manuscript aimed to investigate the healing effects of *Camellia sinensis*, which has a traditional importance in herbal medicine, on reproduction. It also aimed to highlight the use of *C. sinensis* in the pharmaceutical industry with an ethnobotanical approach.

### 5.1.1 Origin, Distribution, and Cultivation

*Camellia sinensis* plant grows most ideally in tropical and subtropical regions with slightly acidic soils, and sufficient rainfall and drainage. In addition, it is generally cultivated in the highlands (Chan et al. 2007). It is reported that *Camellia sinensis* originated in South Asia (Mahmood et al. 2010) and spread around the world (Mondal 2009). Furthermore, it is known that the native country of tea is China. Tea agriculture began in India and Sri Lanka, which are leaders of tea production, in 1823 and 1824, respectively. In Turkey, the tea cultivation began in 1924 (Alkan et al. 2009). At the present time, it is known that it is cultivated in more than 30 countries including Turkey, India, Sri Lanka, China, Kenya, former Soviet Union, Indonesia, Iran, Japan, Bangladesh, Vietnam, Malawi, and Argentina (Bedrood et al. 2018). In Turkey, tea cultivation is widely practiced in the Eastern Black Sea Region, and it creates a source of income for the people there.

### 5.1.2 Economic Importance

*Camellia sinensis* is of high economic importance in many ways (Mondal 2009; Jayasinghe and Kumar 2019). Tea reveals the economic importance of the *Camellia* genus (Mondal 2009). In addition to being a direct contributor to the national economy, it also creates a significant employment opportunities for people. For example, approximately 10% of Sri Lanka's population works in the tea industry (Jayasinghe and Kumar 2019). Turkey is among the leading countries in the production of tea and ranks sixth after China, India, Sri Lanka, Kenya, and Indonesia (Alkan et al. 2009). In Turkey, *C. sinensis* is cultivated in the Eastern Black Sea Region with a total of 76,654 ha area, and therefore has economic importance for the region (Adiloğlu and Adiloğlu 2006). On the other hand, since *C. sinensis* is used as medicine and pharmaceutical raw material, it is also of economic importance in this aspect (Mondal 2009).

### 5.1.3 Chemical Components

The chemical components of *Camellia sinensis* (green tea) leaves include fibers (26%), proteins (15%), lipids (2–7%), and vitamins and minerals (5%). Moreover, it contains pigments, polyphenols (30–40%), and methylxanthines (3–4%) as secondary metabolites (Roychoudhury et al. 2018). It also contains many other factors including vitamin C, carotenoids, minerals (such as Se, Zn, Mn, and Cr), and some phytochemical compounds (Rahman et al. 2018). One of the most important contents of tea responsible for beneficial effects on health is polyphenols (Sharangi 2009; Gale et al. 2015). Theaflavins, catechins, and thearubigins are the main polyphenols found in green tea (Gale et al. 2015). However, it is known that polyphenol content differs in green tea (30% to 40%) and black tea (3% to 10%) (Sharangi 2009). It was also reported that catechins are the most important bioactive phytochemicals of *C. sinensis* (green tea) (Bedrood et al. 2018; Fig. 5.1).

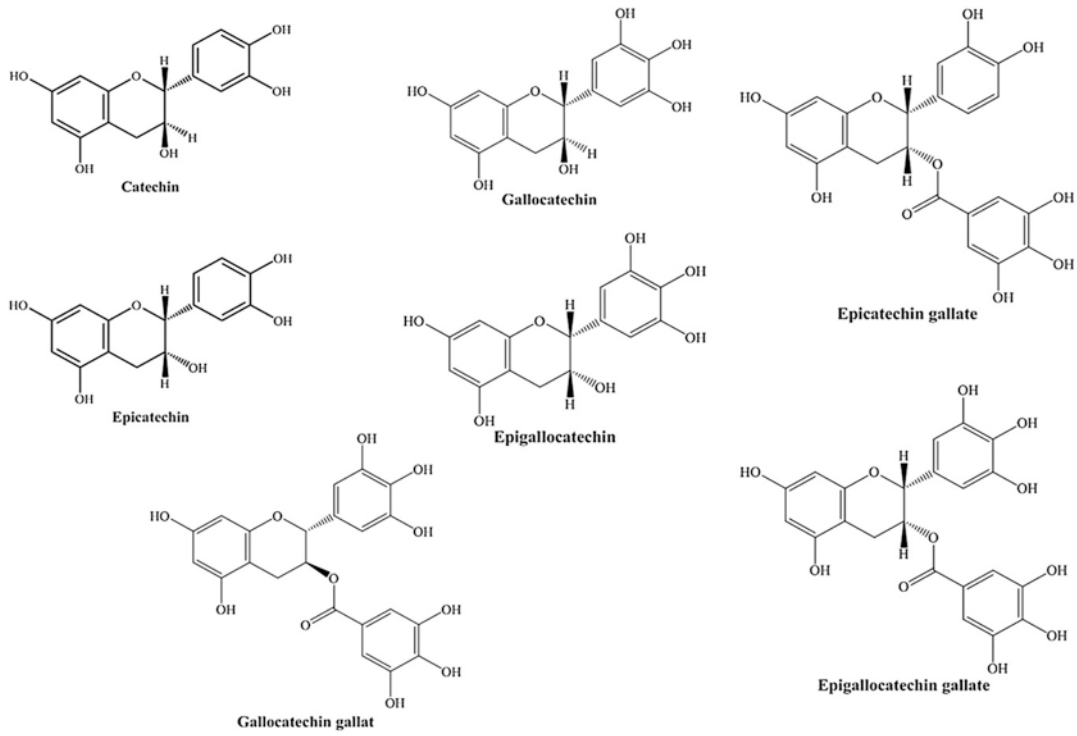


**Fig. 5.1** Main polyphenol compounds and chemical structures of *Camellia sinensis* (green tea) (Bedrood et al. 2018)

### 5.1.4 Biological Activities

The major component of *Camellia sinensis*, the isoflavonoid catechins, and lesser amounts of quercetin, kaempferol, and myricetin are the most important sources of biological activity of this plant (Kirk and Othmer 1947). Immunostimulatory activity of *C. sinensis* is regulated by catechin polysaccharide complex in its structure. Immunomodulatory effect leads to induction of lymphocyte proliferation, and its immunomodulatory effect is very similar to the commercially produced anti-inflammatory drugs (Chattopadhyay et al. 2012). On the other hand, components in *C. sinensis* extract are protective against sepsis (Scoparo et al. 2016). Its protective activity against sepsis is regulated with ameliorating the level of MPO, iNOS, COX-2, and anti- and pro-inflammatory cytokines. These mentioned activities explain the immunomodulatory activity of *C. sinensis*. In vitro studies demonstrate that homogen polysaccharide extract of *C. sinensis* expresses its antitumoral activity with upregulating the Bax/Bcl-2 ratio and caspase-3 expression level, thus leading to apoptosis in cancer cells. Moreover, it is argued that *C. sinensis* is effective on tumor related miRNA level (Yang et al. 2019). Experimental studies show that *C. sinensis* has antidiabetic activity with downregulating the blood glucose level when the animals were exposed to streptozotocin for induction of experimental diabetes (Gomes et al. 1995). Experimental diabetic in vivo studies indicated that *C. sinensis* shows its antihyperglycemic activity with protecting insulin-secreting pancreatic $\beta$-cells and provoking insulin secretion (Anderson and Polansky 2002). Although its antidiabetic and antihyperglycemic mechanism has not been clarified yet, it is known that hyperglycemia reduces the activity of antioxidant enzymes and induces oxidative stress, thus causing pancreatic $\beta$-cell damage. One of the subtypes of catechins, i.e., epigallocatechin gallate (EGCG), is protective against cytokine-related $\beta$-cell damage, and pancreatic cell cluster atrophy in experimental diabetes that induced with the

repeated doses of streptozotocin (Han 2003; Song et al. 2003). Until today, antimicrobial activity of *C. sinensis* was confirmed in various pathogenic and nonpathogenic bacteria (Toda et al. 1991). In vitro studies also demonstrated *C. sinensis* to have antiviral-like functions in rotavirus- and enterovirus-infected cultured monkey kidney cells. As a matter of fact, the antiviral-like function of *C. sinensis* was explained with blocking the adsorption of viruses into the cell (Mukoyama et al. 1991). There are also strong evidences for this plant to be protective and curative against influenza virus (Hamilton-Miller 1995). Besides its antitumor, anti-inflammatory, and antimicrobial properties, *C. sinensis* is believed to have radioprotective properties. It was observed that its extract reduces the pathological changes in the nucleus caused by radiation in the oral mucosal cells of dental patients when used for mouthwash prior to panoramic radiography (Trevenzoli et al. 2018).

### 5.1.5 Traditional Uses

*C. sinensis* has traditionally been used for many different purposes (Chopade et al. 2008; Naveed et al. 2018). Traditionally, green tea (*C. sinensis*) was used as a diuretic and stimulant and to control bleeding, aid wound healing, and improve heart health in Chinese and Indian medicine. In addition, it was reported that its traditional uses include treating flatulence, regulating blood sugar and body temperature, improving mental processes, promoting digestion (Chopade et al. 2008), and increasing milk production in women who have just given birth (Latorre and Latorre 1977). *C. sinensis* was also reported as a traditional remedy for various digestive problems (Sharangi 2009), and type 2 diabetes (Naveed et al. 2018).

### 5.1.6 Medicinal Uses

Different studies were conducted on medicinal use of *Camellia sinensis* (Chopade et al. 2008; Mahmood et al. 2010), and it was observed that it contributes to prevention and recovery of many diseases (Chopade et al. 2008). It is known that *C. sinensis* has an antimicrobial effect against many bacteria (Hamilton-Miller 1995; Mahmood et al. 2010; Saeed et al. 2017). Additionally, it has many beneficial effects such as antiarthritic, anti-inflammatory, anticarcinogenic, antimutagenic, anti-infective, hypocholesterolemic, anti-cancerous, antifungal, antiparasitic, anticoccidial, antiprotozoal, and hypolipidemic effects and resistance to capillary congestion (Saeed et al. 2017). It was also reported that *C. sinensis* has antiviral properties (Saeed et al. 2017) that prevent enterovirus and rotavirus infection in monkey kidney cells in the tissue culture study (Hamilton-Miller 1995). Since it has strong anti-inflammatory and antihistamine properties, it is recommended in the treatment of asthma. Moreover, its polyphenols have insulinomimetic activity and suppress blood glucose level. Hence, it improves insulin activity by increasing the insulin glucose ratio (Naveed et al. 2018). *C. sinensis* is a rich source of antioxidants (Saeed et al. 2017).

## 5.2 Effect of *Camellia sinensis* on Reproduction

It is known that *Camellia sinensis* has some reproductive effects and improves reproduction in mammals. It has been reported that this effect is due to its antioxidant properties (Opuwari 2013). Moreover, it is known that antioxidants have positive effects on reproductive functions (Kurt 2019; Eşki et al. 2021). Similarly, it has been stated that green tea polyphenols, which are substances having antioxidant properties, improve important semen parameters including sperm motility, sperm concentration, morphology, and DNA damage. So, it increases the quality of male and female gametes and fertility (Rahman et al. 2018). Several experimental studies have shown that *C. sinensis* improved fertility in male and female experimental animals. Sheteifa and Morsy (2014) reported that green tea increased semen quality in rabbits. Another study showed that it has a protective effect on

semen quality against the negative effects of heat stress in mice (Abshenas et al. 2011). It was also stated that *C. sinensis* (black tea brew) has an aphrodisiac effect in male rats and can be used in sexual inadequacies such as premature ejaculation (Ratnasooriya and Fernando 2008). Furthermore, it has been reported that *C. sinensis* has a protective effect against cadmium-induced inhibition of δ-ALA-D in bovine ovary tissue. Cadmium has detrimental effects on reproductive tissues and developing embryos (Soares et al. 2013). *C. sinensis* provides benefits in combating the effects of these damages, and thus it is also understood that *C. sinensis* protects reproductive tissues against toxicity. Similarly, it was reported that *C. sinensis* reduced the harmful effects of cadmium chloride and improved some sperm parameters in male Wistar rats (Mahmoudi et al. 2018). Moreover, it was thought that green tea extract would benefit in the process of in vitro embryo production, and the addition of green tea as an antioxidant substance to the maturation medium improves the in vitro maturation of sheep oocytes and embryo development (Barakat et al. 2014). Therefore, it is thought that *C. sinensis* would have beneficial effects in in vitro fertilization studies. On the other hand, *C. sinensis* can also be used as a cryopreservation agent. Park et al. (2018) informed that *C. sinensis* supplementation during the freezing process increased success in cryopreservation of boar sperm.

## 5.3 Conclusion and Recommendation for Future Research

*Camellia sinensis* has positive effects on health in many ways. It is also thought that *C. sinensis* can be used for the health of reproductive tracts. The future studies should be conducted to explain the effects of *C. sinensis* on the antioxidant system in a comprehensive way, and to relate the data obtained with reproduction. However, this needs to be detailed with toxicological and pharmacological studies. After these processes and its standardization, it can be recommended as an effective herbal drug candidate on reproduction.

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# *Capsella bursa-pastoris* (L.) Medik.

6

Ceyda Sibel Kılıç

**Abstract**

*Capsella bursa-pastoris* (L.) Medik. is a cosmopolite species belonging to Brassicaceae family. The plant has a long history of worldwide traditional usage and the studies on the plant justify these usages. The plant is called "poor man's pharmacetty" due to its nutritional content and it is eaten in various countries. In this chapter, ethnomedicinal and ethnobotanical usages, composition, and biological activities of *C. bursa-pastoris* are focused on.

**Keywords**

*Capsella bursa-pastoris* · Brassicaceae · Cruciferae · Mustard family

## 6.1 Introduction

*Capsella bursa-pastoris* (L.) Medik. is a cosmopolite species belonging to Brassicaceae (formerly known as Cruciferae) – mustard family. The plant is annual/biennial, 4–50 cm long with a thin root. Basal leaves form a rosette on the ground and their shapes vary from lyrate to pinnatifide; entire leaves can also be observed (Hedge 1965). The plant has a terminal raceme-type inflorescence and small heart-shaped silicula-type fruits; a single fruit can accommodate numerous seeds up to 40,000 seeds/plant (Defelice 2001) (Fig. 6.1).

The plant is reported to originate in Eurasia during the preglacial times and introduced to the New World, Australasia, and southern Africa by the colonists (Wesse et al. 2020).

The name of the genus comes from the Latin word "capsa" which means little box. The plant is usually known by the name "shepherd's purse," since the fruits resemble the leather bags or purses used by shepherds to carry their meals. The names of the plant in different languages are given in Table 6.1.

## 6.2 Distribution and Status of the Species

*C. bursa-pastoris* is a cosmopolite plant growing in Europe, Asia, America, Australasia, and Africa. The species might show variations in respect to its morphological properties like size and leaf shape; however, it can be identified with its terminal racemose inflorescence having small white flowers and toothed rosette leaves (Aksoy et al. 1998). The plant is considered to originate in Central Italy and Western Greece, but now can be found in temperate regions of the world (Defelice

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**Fig. 6.1** General appearance of *Capsella-bursa-pastoris* (Photo by C.S. Kılıç)

**Table 6.1** Vernacular names of *Capsella bursa-pastoris* in different languages

| Language | Vernacular name | Reference |
|---|---|---|
| English | Mother's heart, clapped pouch, peppergrass, poor man's pharmacetty, St. James's weed, toywort, blindweed | Defelice (2001) |
| German | Hirtentachelkraut | EMA (2011) |
| French | Bourse a Pasteu | |
| Dutch | Herderstasie | |
| Spanish | Bolsa de pastor | EMA (2011), Defelice (2001) |
| Turkish | Çobançantası, Çıngıldaklı ot, Kuşkuş otu, Çobankesesi, Medik, Hırındik, Acıgıcı | Baytop (1999); Yıldız (2021); Aksoy et al. (2016); Kadıoğlu et al. (2020) |
| Arabic | Madakat el Raee, Kess el Raee, Sharabat el Raee, Gezdan ell Raee, Karmala | Al-Snafi (2015) |
| Japanese | Nazuna | https://www.verywellhealth.com |
| Korean | Naengi | |

2001). Furthermore, the species is considered to be among the most widely distributed plants in the world (Hintz et al. 2006).

According to the Plant List, the following taxa are found naturally throughout the world:

- *C. bursa-pastoris* (L). Medik.
- *C. bursa-pastoris* subsp. *thracicus* (Velen.) Stoj. & Stef.
- *C. draboides* (Korsh.)
- *C. x gracilis* Gren.
- *C. grandiflora* (Fauché & Chaub.) Boiss.
- *C. lycia* Stapf.
- *C. mexicana* Hemsl.
- *C. orientalis* Klokov.
- *C. puberula* Rupr.
- *C. rubella* Reut.

Though usually found as a wild plant, *C. bursa-pastoris* is also reported to be cultivated (Ran et al. 2018).

## 6.3 Traditional/ Ethnomedicinal Uses

*C. bursa-pastoris* is known to have various traditional uses throughout the world such as anticancer, antithrombin, antimicrobial, wound-healing, antioxidant, antibleeding, etc. (Qayyum et al. 2018). It even has a place in the folklore of some countries. For example, according to a Yorkshire folkloric tale, when the plant is found, a fruit pod is opened to reveal the color of the seed inside. If the seeds are yellow, you will be rich, but if the seeds are green, then you will be poor (Defelice 2001).

The plant has a long history that intersects with the history of mankind, for example, seeds were found in Çatal Höyük, Turkey, and found to date back to 5950 BC. The seeds were also found in the stomach of the Tollund Man dating back to approximately 400 BC in Denmark (Defelice 2001). Thus, the plant has been known to mankind and has a history of ethnobotanical/traditional medicinal usage in every country that it grows naturally. Some examples for ethnobotanical/traditional uses of the species are as tabulated in Table 6.2:

In addition to these medicinal uses, the plant is also used for culinary purposes. For example, the plant is eaten as raw, or in salads; rice meals and rice soups are also prepared by using the plant along with pastries and pancakes in the Black Sea region of Turkey (Ozbek et al. 2017); young shoots are eaten as raw in Kars, Turkey (Kadıoğlu et al. 2020); the stem and leaves are eaten when fresh around Konya, Turkey (Tugay et al. 2012); and leaves are also consumed in Samsun, Turkey (Demir et al. 2020). The leaves have peppery taste and the name "peppergrass" comes from the taste of the leaves (Defelice 2001), and the characteristic aroma of the edible parts of the plant is found to contain sulfur-containing compounds (Lee and Choi 1996).

The plant has other ethnobotanical usages, as well. Leaves and flowers of the plant are used as animal fodder in Erzincan, Turkey (Korkmaz et al. 2016); the leaves of the plant are used as wound healer in ethnoveterinary medicine in British Columbia (Lans et al. 2007); and the fruits of the plant are used as toy in Bulgaria (Kültür and Sami 2008-2009).

## 6.4 Composition

The plant is called poor man's pharmacetty and this is due to the secondary metabolites, vitamins, minerals, etc. (Defelice 2001) that the plant contains and can be held responsible for its pharmacological activities.

The composition of the plant in respect to individual plant parts is given in Table 6.3.

Fixed and essential oil compositions of different parts of the plant were also investigated in different studies. The results of these studies are tabulated for a more clarified presentation in Table 6.4.

Fixed oil obtained from the seeds of the plant was also examined. According to a study by Kılıç et al. (2007), major fatty acids of the seeds were determined to be oleic acid (22.86%), palmitic acid (18.168%), linoleic acid (20.59%), linolenic acid (12.2%), and 11-eicosenoic acid (11.14%); palmitic acid (44.1%), oleic acid (16.1%), linolenic acid (13.4%), azelaic acid (10.0%), and stearic acid (9.6%) for the roots. In another study by Moser et al. (2010), seed oil was found to contain linoleic acid (20.5%), oleic acid (14.2%), and gondoic acid (9.8%) as major components. Furthermore, in another study by

**Table 6.2** Ethnomedicinal usages of *C. bursa-pastoris*

| Plant part | Preparation method | Usage/activity | Country | Reference |
|---|---|---|---|---|
| NA | NA | Uterine tonic and hemostatic | Romania | Neagu et al. (2019) |
| Leaves and seeds | NA | Antidiarrheic, wound healer, astringent, diuretic, stimulant | Pakistan | Qayyum et al. (2018) |
| Entire plant | Decoction: 50 g plant is boiled in 200 ml water. 50 ml is drank four times a day with meals | Prostatic enlargement | Palestine | Jaradat et al. (2017) |
| Aerial part | NA | Uterine cancer | Kashmir/India | Tariq et al. (2015) |
| Entire plant | Decoction | Bloody urine and diarrhea, against ulcers, tumors, and uterine cancer | Himalaya/India | Khan et al. (2009) |
| NA | NA | Anti-inflammatory, hepatoprotective | Peru | Bussman (2013) |
| NA | NA | Edema and hypertension | Korea | Cha et al. (2017) |
| Aerial part | NA | Edema, enteritis, nephritis | China | Lan et al. (2017) |
| Aerial part | Infusion | Diuretic, nosebleed | Turgutlu (Manisa)/Turkey | Güler et al. (2015) |
| Leaves, stem, flower | Tea | Against varicose veins, regulates circulation in cardiovascular diseases, against bladder inflammation | Gazipaşa (Antalya)/ Turkey | Aksoy et al. (2016) |
| Aerial part, seed, leaves, flower | NA | Hemostatic, used in urinary tract disorders, breaks down kidney stones, diuretic, regulates menstruation, analgesic | Aegean and South Marmara regions/Turkey | Sarı et al. (2010) |
| Leaves and seeds | Boiled in water and used as gargle | Reduces toothache and bleeding of the gums | Anatolia/Turkey | Gürsoy and Gürsoy (2004) |
| Aerial parts | Internally | Diabetes mellitus | Trabzon/Turkey | Sarıkaya et al. (2010) |
| Aerial parts | Infusion/internally Pounded/externally | Against kidney stones, antitussive, diuretic, against diabetes, astringent | East Anatolia/ Turkey | Altundağ and Ozturk (2011) |
| NA | NA | Antidiarrheic, diuretic | Hatay/Turkey | Ayanoglu et al. (1999) |
| Aerial parts | Boiled in water | To pass kidney stones, analgesic | Ordu/Turkey | Türkan et al. (2006) |
| Leaves | Poultice | Antihemorrhoidal, wound healer | Alaşehir (Manisa)/Turkey | Ugulu (2011) |
| NA | Tea (boiled in water), juice | Reduces blood sugar, hemostatic in gum and nosebleed, passes kidney stones if drank 1 spoonful a day, a few drops of juice is administered to the nose in nosebleed | Pozantı (Adana)/Turkey | Bagcı et al. (2006) |
| Leaf, stem | Tea | To pass kidney stones, antihemorrhoidal, in menstruation | Eskişehir/ Turkey | Yaşar et al. (2019) |
| Aerial parts | Infusion | Diseases of the female reproductive system | Cappadocia (Nevşehir)/ Turkey | Akgül et al. (2016) |
| Aerial parts | Infusion | Suppressor, obesity, internal bleeding, hemostatic | Gülnar (Mersin)/Turkey | Sargin and Büyükcengiz (2019) |

(continued)

**Table 6.2** (continued)

| Plant part | Preparation method | Usage/activity | Country | Reference |
|---|---|---|---|---|
| Aerial parts | Tea, tincture | Kidney and urinary tract disorders, hemorrhoids and wounds, headache, muscle disorders, hypotension, cardiac disorders, superficial burns, and skin disorders with bleeding | Kumru (Ordu)/ Turkey | Gül and Seçkin Dinler (2016) |
| Aerial parts | Crushed and salve, applied once a day | Antihemorrhagic | Dalaman (Muğla)/Turkey | Sağıroğlu et al. (2013) |
| Aerial parts | Infusion – Used internally | Women's health | Aladağlar (Niğde)/Turkey | Özdemir and Alpınar (2015) |
| Leaves | Decoction, one tea cup three times a day for 8 days | Hypertension | Turkey | Olcay and Kültür (2020) |
| Aerial parts | Decoction | Antidiabetic | Turkey | Karaman and Elgin Cebe (2016) |

NA: Not Available

Singh et al. (2014), linoleic acid (30.59%), linoleic acid (18.81), and oleic acid (16.08%) were found to be major components of the fixed oil of the seeds. On the other hand, Grosso et al. (2011) determined that major components were palmitic acid, stearic acid, and oleic acid; however, these fatty acids were found in plant extract, not in the fixed oil obtained from the seeds. These results were found to be in parallel with the study by Bekker et al. (2002) in which palmitic and stearic acids were found to be the major components, as well.

When the mineral content of the plant was examined, leaves of the plant were found to contain Na, K, Ca, Mg, P, Fe, Cu, Zn, and Mn. Among these, K was the mineral with the highest amount, and furthermore, oxalic acid content of the plant was found to be low, so consumption of the leaves would not pose a threat to human health (Guil-Guerrero et al. 1999). Though not in the former study, the plant was also found to contain selenium, which is an important element in respect to human health. The plant was also found to accumulate selenium more by converting inorganic selenium into organic selenium, which would contribute to human health if incorporated into human diet (Ran et al. 2018).

## 6.5 Pharmacological Activities

As a result of the composition of the plant, it is being used for different purposes such as antimicrobial, anticancer, anti-inflammatory, antioxidant, acetylcholinesterase inhibition and acts on smooth muscles, fertility, etc. (Kuroda and Kaku 1969; Dar et al. 2021; Al-Snafi 2015). Studies on the biological (pharmacological) activities of the plant and/or plant parts are given below:

### 6.5.1 Acetylcholinesterase Inhibitory Activity

Acetylcholinesterase inhibitors are important in the treatment of Alzheimer's disease. Methanol and methanol/water extracts of the aerial parts of *C. bursa-pastoris* had high acetylcholinesterase activity in the study by Grosso et al. (2011) and therefore could be an important agent in the treatment of the disease in addition to its nutritional importance.

In another study by Zengin Kurt et al. (2016), hexane extract of the aerial parts of the plant exhibited the highest AChE inhibitory activity compared to ethanol and water extracts of the plant with an $IC_{50}$ value of 7.24 μg/mL and might have the potential to be used as a natural food supplement.

**Table 6.3** Chemical composition of *C. bursa-pastoris*

| Plant part | Chemical composition | Reference |
|---|---|---|
| Aerial parts | Fumaric acid | Kuroda et al. (1976) |
| Aerial parts | Polar lipids (pheophytin a and b), monoacylglycerols, diacylglycerols, sterols, chlorophyll a and b, triterpenols, waxy esters | Bekker et al. (2002) |
| Leaves | Ascorbic acid | Kılıç and Coşkun (2007) |
| Aerial parts | Flavonoids (quercetin-6-C-glucoside, quercetin-3-*O*-glucoside, kaempferol-3-*O*-rutinoside, quercetin, kaempferol), organic acids (oxalic, citric, malic, quinic, shikimic, fumaric acid), amino acids (asparagine, serine, threonine, glycine, valine, proline, arginine, isoleucine, leucine, tryptophan, phenylalanine, cysteine, ornithine, lysine, histidine, tyrosine), sterols (cholesterol, campestrol, stigmasterol, β-sitosterol, ergosta-4,6,8(14),22-tetraen-3-one, lupeol, stigmasta-3,5-dien-7-one, stigmasta-4-en-3-one) | Grosso et al. (2011) |
| Aerial parts | 4′,7-Dihydroxy-5-hydroxymethyl-8-prenylflavonoid, 4′,7-dihydroxy-5-hydroxymethyl-6,8-diprenylflavonoid, chrysoeriol-7-O-D-glucopyranoside, acacetin-7-O-d-glucopyranoside, quercetin, sinensetin, licoflavonol, icaritin, 6,8-diprenylgalangin | Ma et al. (2016) |
| Aerial parts | Apigenin-7-*O*-*β*-*D*-glucopyranoside, uridine, Luteolin-7-*O*-*β*-*D*-glucopyranoside, α-adenosine | Lan et al. (2017) |
| Aerial parts | 7*S*,8*R*,8'*R*-(-)-Lariciresinol-4-4′-bis-*O*-glucopyranoside, lariciresinol4'- *O*- β-D-glucoside, salidroside, 3-(4-β-D-glucopyranosyloxy-3,5-dimethoxy)-phenyl-2*E*-propanol, coniferin, capselloside, pinoresinol-β-D-glucoside, β-hydroxy-propiovanillone 3-O- β-D-glucopyranoside | Cha et al. (2017) |
| Aerial parts | Phacadinanes B, foveoeudesmenone, (10*R*)-13-noreudesma-4,6-dien-3i1-dione, (5R,7S,10S)-5-Hydroxy-13-noreudesma-3-en-2,11-dione, 3-epi-Phomadecalin D, 8α-monoacetoxyphomadecalin D, 5βH-Elem-1,3,7,8-tetraen-8,12-olide, (4S,5R,8R,10S)-1-Nor-10-hydroxy-8-methoxyeremophil-7(11)-en-12,8-olide,]. Hypocreaterpenes A, 6α-hydroxy-4-epi-septuplinolide, 6α-hydroxy-isoalloalantolactone, 1β-hydroxyalantolactone | Ma et al. (2018) |
| Aerial parts | Quercetin, kaempferol-7-O-rhamnopyranoside, quercetin-3-O-glucopyranoside, quercetin-6-C-glucopyranoside, kaempferol-3-O-rutinoside | Peng et al. (2019) |
| Aerial parts | Chlorophyll, β-carotene, lycopene | Demir et al. (2020) |
| Aerial parts | Acacetin, sinensetin, icaritin | Hwang et al. (2021) |
| Leaves | Phytoalexins (camalexin, 6-methoxycamalexin, N-methylcamalexin) | Jimenez et al. (1997) |
| Leaves | Carotenoids, oxalic acid | Guil-Guerrero et al. (1999) |
| Leaves | Ascorbic acid | Kılıç and Coşkun (2007) |
| Leaves | Lipophilic antioxidants (carotenoids, chlorophylls, tocopherols) | Sırcelj et al. (2018) |
| Aerial parts, seeds, and rosette leaves | Ascorbic acid | Kılıç and Coşkun (2007) |
| Seeds | Tocopherols (α-, β-, γ -, δ-tocopherol), phytosterols (cholesterol, brassicasterol, campesterol, stigmasterol, β-sitosterol, Δ5-avenasterol, cycloartenol | Moser et al. (2010) |
| Seeds | Sulforaphane (49.3 ± 3.8 μg/g) | Hur et al. (2013) |

**Table 6.4** Major components of essential oils obtained from different parts of *C. bursa-pastoris*

| Plant part | Major components | % | Reference |
|---|---|---|---|
| Aerial parts | $nC_{22}H_{46}$<br>Camphor<br>Cis-3-hexen-1-ol<br>α-Phellandrene | 25.5<br>20.2<br>14.7<br>7.8 | Miyazawa et al. (1979) |
| Roots | $nC_{22}H_{46}$<br>Camphor | 47.5<br>6.9 | |
| Leaves | Phytol<br>6,10,14-Trimethylpentadecan-2-one | 16.34<br>7.78 | Lee and Choi (1996) |
| Roots | Tetracosane | 6.75 | |
| Leaves | Phytol<br>1,2-Benzenedicarboxylic acid<br>Octadecanoic acid | 21.12<br>13.07<br>11.40 | Choi et al. (2006) |
| Roots | Triacontane<br>Ethyl acetate<br>Phytol | 14.12<br>11.93<br>6.69 | |
| Aerial parts | 1,1-Dimethylcyclopentane<br>2,4-dimethyl hexane<br>Cyclohexane | 16.67<br>10.36<br>8.46 | Kamali et al. (2015) |
| Leaves | Guanidine-succinimide<br>Phytol<br>Pentadecanone, 6,10,14-trimethyl | 21.28<br>18<br>9.6 | Gao and Zhou 2009 |

### 6.5.2 Antibacterial Activity

Antibiotic resistance has become an important health issue; thus, natural sources started to be examined in order to discover new antibacterial agents. In a study performed on methanol, methanol/water, and dichloromethane extracts of the aerial parts of *C. bursa-pastoris*, methanol/water extract was found to be effective against Gram (+) bacteria such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Micrococcus luteus*, and *Bacillus cereus*, and methanol extract was found to effective against *S. epidermidis* and *M. luteus*. This finding was deemed to be important since immunocompromised patients are considered to be more vulnerable to *S. epidermidis* and *M. luteus*. This activity was considered to be related to the presence of phenolic compounds, and high content of quercetin was also reported to be responsible for the high antibacterial activity of the methanol/water extract (Grosso et al. 2011).

Water, ethanol, and methanol extracts of the aerial parts of the plant were tested for their antibacterial activities against some bacteria, and ethanol extract was found to show weak inhibition against Gram (−) bacteria like *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (Birinci Yildirim et al. 2012).

Aqueous and ethanol extracts of the plant were tested against eight different bacterial species (Gram (+), *Staphylococcus aureus* and *Enterococcus faecalis*, and Gram (−), *Escherichia coli*, *Proteus vulgaris*, *Serratia marcescens*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*) and were found to be active against most of these bacteria (Hasan et al. 2013).

Ethanol extract of the aerial parts and roots was tested against oral pathogenic bacteria (*Staphylococcus mutans*, *S. sanguis*, *Actinomyces viscosus*, and *Enterococcus faecalis*), and it was found that the plant inhibited the growth of these bacteria and this effect was seen as the most prominent with the bacterium *S. mutans*. Furthermore, its mixture with *Glycyrrhiza glabra* L. is reported to form a promising mixture in respect to controlling dental caries and oral infections (Soleimanpour et al. 2013).

Water extract prepared from the plant was tested against vancomycin-resistant enterococci and *Bacillus anthracis* and was found to be effective against these two bacteria due to sulforaphane that it contains (Choi et al. 2014).

Ethanol extract of different parts of the plant was shown to have antibacterial activity against oral pathogens and concluded to be used in the treatment of oral infections. Furthermore, its mixture with ethanol extract of the fruits of *Tribulus terrestris* L. was reported to exhibit better activity (Soleimanpour et al. 2015).

In a study by Sadat et al. (2020), methanol extract of the whole plant was tested against methicillin-resistant *Staphylococcus aureus* (MRSA); however, inhibitory effect was not observed against MRSA isolates.

In addition, ethanol extract prepared from the leaves of the plant was reported to be used against leishmaniasis, which is an important skin disease (Hameed et al. 2019).

### 6.5.3 Anticancer Activity

*C. bursa-pastoris* is known to be used against cancer in traditional medicine (Khan et al. 2009; Tariq et al. 2015; Qayyum et al. 2018), and anticancer effect of the plant was confirmed with some studies, as well.

One of the earliest studies on the anticancer effect of *C. bursa-pastoris* belongs to Kuroda et al. (1974) in which they studied the aqueous extract of the aerial parts against hepatocarcinogenesis induced by 3′-methyl-4-(dimethyl amino) azobenzene in rats (1974). Though the agent used in the study was a strong hepatocarcinogen, the extract was reported to have strong inhibitory activity in the development of carcinogenesis.

Kuroda et al. performed another study on liver catalase activity (1975) in rats that were fed with 3′-methyl-4-(dimethyl amino)azobenzene, which was an azo dye hepatocarcinogen. Liver catalase activity on the other hand was reported to be effective in the prevention of azo dye carcinogenesis, and aqueous extract of the aerial parts of the plant was found to prevent reduction in liver catalase activity.

Kuroda et al. (1976) also studied the inhibitory effect of the ethanol extract of the aerial parts of the plants and found that the extract resulted in 50–80% inhibition in the growth of Ehrlich solid tumor in mice. During the study, fumaric acid was reported to be present in the extract, and this acid was reported to be responsible for the anticancer effect of the plant.

In a study performed with water, ethanol, and methanol extracts prepared from the aerial parts of the plant, antitumor activity was tested, and the extracts were found to have weak to moderate activities (42.9% inhibition was observed for the water extract and 29.5% and 42.9% inhibition were determined for ethanol and methanol extracts, respectively) (Birinci Yildirim et al. 2012).

In a study by Lee et al. (2013), methanol extract of the plant was tested against HSC-2 human oral cancer cells and was determined to inhibit cell growth and induce apoptosis. This activity was observed to be mediated by Sp1 protein and thus, the plan was concluded to be a promising agent in oral cancer.

The plant was reported to contain sulforaphane at a concentration of 49.3 ± 3.8 μg/g. This finding is quiet important since this compound is a naturally occurring sulfur-containing isothiocyanate that can provide protection against various types of cancers, diabetes, atherosclerosis, neurodegenerative diseases, cardiovascular diseases, and respiratory diseases. Therefore, this compound might be considered to be responsible for the anticancer and anti-inflammatory activities of the plant, as well (Hur et al. 2013).

Furthermore, the essential oil of the plant is reported to contain an organosulfur compound, allyl isothiocyanate. This compound is also important since it is found in the plant as a defense system against herbivores. However, it is also considered to be a cancer chemopreventive agent and therefore might contribute to the anticancer activity of the plant itself (Kamali et al. 2015).

### 6.5.4 Antihemorrhoidal Activity

*C. bursa-pastoris* is reported to be used against hemorrhoids in Turkey; therefore, a study was performed on the aerial parts of the plant related to this effect. Ethanol and water extracts prepared from the plant were tested in croton oil-induced

hemorrhoid model in rats, and water extract was found to have the highest antihemorrhoidal activity (Apaydin Yildirim et al. 2020).

### 6.5.5 Anti-inflammatory Activity

The plant is reported to have anti-inflammatory activity and traditionally used for this purpose. In order to reveal the anti-inflammatory potential and justify the traditional usage of the plant, Cha et al. (2017) performed a study in which they isolated eight phenolic glycosides from the aerial parts of the plant and found that among these phenolic glycosides, pinoresinol-β-D-glucoside, salidroside, salidroside, 3-(4-β-D-glucopyranosyloxy-3,5-dimethoxy)-phenyl-2*E*-propanol, β-hydroxy-propiovanillone 3-O- β-D-glucopyranoside, and coniferin showed in vitro anti-inflammatory activity against LPS-induced neuroinflammation model.

Since the plant was traditionally used in China against edema, nephritis, and enteritis, Lan et al. (2017) tried to reveal the anti-inflammatory potential of the plant and found that ethyl acetate extract of the aerial parts exhibited important anti-inflammatory activity in experimental animals at a dose of 300 mg/kg. They also found that the compounds isolated from the ethyl acetate extract given in Table 6.3 were responsible for the activity.

In a study by Peng et al. (2019), ethanol extract of the whole plant was reported to reduce NO and $PGE_2$ production and meanwhile inhibited TNF-α and Il-6 production in the development process of inflammation and thus, exhibited strong anti-inflammatory activity. This activity was previously confirmed with a study by Choi et al. (2014) in which sulforaphane-containing solution prepared from the plant showed significant anti-inflammatory activity which was demonstrated by decrease in the levels of nitric oxide (NO), cytokines (interleukin 1$\beta$- IL-1$\beta$), IL-6 and IL-10, and prostaglandin $E_2$ ($PGE_2$). Furthermore, the solution also reduced inducible NO synthase and cyclooxygenase-2 (COX-2) levels which also supported the anti-inflammatory activity of the solution.

### 6.5.6 Antioxidant Activity

In 2011, Gross et al. found that while methanol/water extract of the aerial parts of the plant scavenged lipid peroxyl radical more than superoxide radical and nitric oxide radical, the plant possessed concentration-dependent antiradical activity against DPPH, superoxide radical, and lipid peroxy radical and was concluded to have the highest activity against nitric oxide radical.

Antioxidant activity of the essential oil isolated from the aerial parts of the plant was examined in a study performed in 2015 by Kamali et al.; however, the essential oil was not found to be a good antioxidant.

In another study by Neagu et al. (2019), antioxidant activities of *C. bursa-pastoris* plants collected from two different localities in two different seasons were compared with each other, and the effect of abiotic factors influencing the activity was examined.

### 6.5.7 Antihemorrhagic Activity

Postpartum hemorrhage (PPH) is a life-threating condition and also among the three main causes of maternal mortality in the world. *C. bursa-pastoris* is known to increase the contraction of uterine smooth muscles, and since the plant contains tannins and has astringent activity, it is found to be used orally in the treatment of heavy menstrual bleeding. It can be used in uterine bleeding that can occur between periods, as well. Hydroalcoholic extract of the plant was used sublingually in a study performed to determine its effectiveness in PPH and was found to reduce early PPH. Furthermore, it reduced menstrual bleeding in uterine leiomyoma patients (Ghalandri et al. 2017).

This activity was also confirmed with another study performed by Naafe et al. (2018). The plant was used in heavy menstrual bleeding which led to iron deficiency anemia and resulted in hysterectomy, and it was found that hydroalcoholic extract of the plant reduced the volume of menstrual bleeding. These studies probably justify the usage of the plant in Europe during the World

War as ergot in the treatment of uterine bleeding and postpartum hemorrhage.

### 6.5.8 Cholesterol-Lowering Activity

In a study performed with the ethanol extract of the aerial parts of the plant along with the polyphenolic substance icaritin, ethanol extract of the plant was reported to decrease PCSK9 gene expression and thus attenuated serum total and LDL cholesterol levels in obese mice. As a result of this study, both icaritin and ethanol extracts of the aerial parts of the plant were suggested to be alternative therapeutics in the treatment of hypercholesterolemia (Hwang et al. 2021).

### 6.5.9 Hepatoprotective Activity

Ethanol extract prepared for the aerial parts of the plant was subjected to isolation, and nine compounds were obtained at the end of the study carried out by Ma et al. (2016). These isolated compounds were tested for their hepatoprotective activities, and four of them (4′,7-dihydroxy-5-hydroxymethyl-6,8-diprenylflavonoid, chrysoeriol-7-O-D-glucopyranoside, sinensetin, 6,8-diprenylgalangin) were found to possess moderate hepatoprotective activity.

Furthermore, ethanol extract of the plant was found to improve high-fat diet-induced hepatic steatosis via inhibiting histone acetyltransferase activity; therefore, this finding might lead to the discovery of novel treatments including *C. bursa-pastoris* in the prevention and treatment of nonalcoholic fatty liver disease (Choi et al. 2017).

### 6.5.10 Neuroprotective Activity

In a study by Ma et al. (2018), 12 flavonoids were isolated from the ethanol extract of the aerial parts of the plant, and among these flavonoids, phacadinanes B, 8α-monoacetoxyphomadecalin D, hypocreaterpenes A, and 6α-hydroxy-4-epi-septuplinolide were reported to have significant neuroprotective activity.

### 6.5.11 Sexual Function

In a study by Sehhati et al. (2018), women complaining from heavy menstrual bleeding following the administration of intrauterine device (IUD) were given 700 mg of the plant from the first day of the period once every 8 hours till bleeding stopped. The results of this study suggested that the plant could be an effective alternative in the reduction of abnormal menstrual bleeding. Since the plant did not have any side effect, it was considered to be preferable among women who preferred complementary medicines, and also the plant increased sexual functioning due to its oxytocin synergistic effects.

### 6.5.12 Other Activities/Usages

The plant was examined as a biomonitor of heavy metals and was found to be effective in environmental monitoring of heavy metals that are found in the soil and was found to demonstrate short-time changes in pollution especially in urban areas (Aksoy et al. 1999).

Methanol extract of the whole plant was found to inhibit melanin synthesis more than 50% at a dosage of 50 μg/mL. This effect is important in respect to discovering safe depigmentation agents that might be used for medical or cosmetic purposes (Hwang and Lee 2007).

Ethyl acetate extract prepared from the whole plant was found to be highly phytotoxic compared to hexane, dichloromethane, and n-butanol extracts and could be used in annual ryegrass control as a weed control agent (Seal et al. 2009).

The plant is a cadmium accumulator and was found to have high tolerance to cadmium; therefore, it was concluded to have a potential in remediating cadmium-contaminated farmland soils in the winter (Liu et al. 2015).

Corrosion is an important and common problem in metals and controlling corrosion is an

expensive process. Since preparation of plant extracts is inexpensive and since they provide other benefits, ethanol extract of the plant was tested for its inhibitory effect on the corrosion of Q235 carbon steels, and the results showed that the extract was an effective inhibitor (Hu et al. 2015).

## 6.6 Side Effects

The plant is usually considered to be safe; however, in a study by East (1955), dried and ground aerial parts of the plant were added to the diets of mice of both sexes, and the plant was reported to prevent ovulation and resulted in temporary infertility in both male and female mice.

The plant has uterotonic activity; therefore, it should not be used by pregnant women (Fleming 2000).

## 6.7 Toxicity

In a piggery found in South Africa, four pigs died suddenly within a period of 24 h, and as a result of the *postmortem* examination, the pigs were reported to die due to nitrate and nitrite poisoning provisionally. Pigs are known to be highly susceptible to nitrite poisoning, rather than nitrate poisoning. *C. bursa-pastoris* was tested for its nitrate and nitrite content, and was found to contain 8020 ppm nitrate and 4630 ppm nitrite. Though the death of the pigs was attributed to the plant, the authors also specified that unusual circumstances have to be present for the plant to become toxic (Wiese and Joubert 2001).

The plant was also considered to have harmful effects on livestock due to the bursine alkaloid that it contains (Töngel 2005). This alkaloid was also mentioned in another study performed by Balabanli et al. (2006). These studies conflict with the study of Korkmaz et al. (2016) where the authors reported that the plant was used as animal fodder in Erzincan, Turkey.

## 6.8 Commercial Formulations

### 6.8.1 Commercial Preparations Related to Well-being

Commercial preparations of the plant are usually found as food supplements such as Potter's Antitis Cystitis Relief for helping in the minor complaints of the urinary tract, Health Embassy Shepherd's Purse Herb, Shepherd's Purse Tincture Alcohol-free extract for healthy cardiovascular system, and homeopathic medicine of *C. bursa-pastoris*. The plant is also being sold as herb in different countries.

In 2018, Federal Institute for Drugs and Medical Devices in Germany (BfArM) registered the plant as the first coated tablet for the reduction of heavy menstrual bleeding in women with regular menstrual cycle (https://www.diapharm.com).

### 6.8.2 Cosmetic Preparations

An under eye cream by W-Lab Cosmetics contains *C. bursa-pastoris* (https://estacosmetic.nl).

## 6.9 Gap between Ethnomedicinal and Scientific/Clinical Evidences

When we review the literature on *C. bursa-pastoris* in respect to the comparison between ethnomedicinal and scientific/clinical evidences, we can say that the traditional usages of the plant are generally justified by studies on the composition and/or pharmacological activities of the plant.

*C. bursa-pastoris* is an important plant having a history of traditional usage, and pharmacological studies performed on the plant showed increase in the recent years. The plant has the potential to be used medicinally due to scientific claims and requires more attention in this respect.

## 6.10 Challenges and Future Recommendation

*C. bursa-pastoris* has many and important biological activities and moreover, since it is a ruderal plant, it is quiet easy to cultivate. The plant is called pickpocket since it can produce thousands of seeds and grow easily in farms, thus reducing crop yields. Due to this easy growing nature of the plant, it is considered to be a weed-causing problem in many countries of the world. It is also considered to be an alternate host for some plant diseases, viruses, and insect pests, as well (Defelice 2001).

Nevertheless, the plant has important components that can have beneficial effects on human health, and since it is not an endangered species – and definitely not predicted to go extinct in the near and far future – studies on different biological activities of the plant should be increased The plant should especially be tested in various diseases and in all kinds of cancer cell lines to find a cure for important, quality of life deteriorating and/or fatal diseases that we suffer from.

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# *Capsicum annuum* L.

7

Hafize Yuca

**Abstract**

*Capsicum annuum* is a well-known spice in different areas of the world from old times due to its specific taste, color, and aroma. It has been used in most of the kitchens and dietary products. The objective of this chapter is to review the medicinal and pharmacological properties along with botanical properties and chemical composition of *C. annuum*. It contains capsaicinoids (capsaicin, dihydrocapsaicin), carotenoids (lutein, zeaxanthin, capsorubin, $\beta$-carotene), flavonoids (quercetin, kaempferol, catechin, epicatechin, rutin, luteolin), and steroid saponins (capsicidine, capsicoside E, F, G). Major constituents of *C. annuum* essential oil are capsiamide and acetic acid identified using GC/MS. It has been reported that *C. annuum* has antioxidant, antibacterial, antiviral, antiproliferative, antiadipogenic, antimutagenic, enzyme inhibitory, anti-inflammatory, hepatoprotective, antidiabetic, renoprotective, hypocholesterolemic, antitumor, anti-obesity, analgesic, food craving, and anti-reflux activities. *C. annuum* has been accepted with GRAS status through FEMA and is confirmed through the FDA for usage as "spices and other natural seasonings and flavorings" and "color additive" in food.

**Keywords**

Solanaceae · Chili · Capsaicin · Red pepper · Cayenne · *Capsicum annuum*

## 7.1 Introduction

### 7.1.1 Description of *Capsicum annuum* L.

*Capsicum annuum* is a yearly shrub and shoots up to 0.75–1.8 m with many angled branches. The stem is 20–80 cm, erect, branched. Leaves are glabrous, long-petiolate, ovate to lanceolate, top is acuminate. Flowers are pedicellate, calyx teeth are too short; the corolla is white and sometimes green or purple stained. Fruits are 1–25 cm, in many different shapes. They are plenty-seeded berries that might be cylindrical, long, oblong, obtuse, or ovoid. They are red when mature, with a glabrous shining surface (Fig. 7.1) (Baytop 1978; Kirtikar and Basu 1975).

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**Fig. 7.1** Taxonomical aspect with photograph of *Capsicum annuum.* (Photos of by İsmail Gerçek from Ortaklı Village/İslahiye/Gaziantep/Turkey; by Ali Atmaca from Birecik/Şanlıurfa/Turkey)

### 7.1.2 Taxonomical Aspect with Photograph

### 7.1.3 Synonyms

1. *Capsicum abyssinicum* A. Rich.
2. *C. chlorocladum* Dunal.
3. *C. odoriferum* Vell.
4. *C. angulosum* Mill.
5. *C. ceratocarpum* Fingerh.
6. *C. annuum* var. acuminatum Fingerh.
7. *C. purpureum* Roxb.
8. *C. annuum* var. fasciculatum (Sturtev.) Irish.
9. *Piper indicum* Garsault.
10. *C. annuum* var. aviculare (Dierb.) D'Arcy & Eschbaugh.
11. *C. axi* Vell.
12. *C. ovatum* DC.
13. *C. annuum* f. violaceum Kuntze.
14. *C. bauhini* Dunal.
15. *C. annuum* var. conicum (Lam.) Voss.
16. *C. pomiferum* Mart. ex Steud.
17. *C. baccatum* Rodschied.
18. *C. pubescens* Dunal
19. *C. annuum* var. conoides (Mill.) Irish.
20. *C. bicolor* Jacq.
21. *C. annuum* var. glabriusculum (Dunal) Heiser & Pickersgill.
22. *C. caerulescens* Besser.
23. *C. annuum* var. grossum (Willd.) Sendtn.
24. *C. cerasiforme* Willd.
25. *C. annuum* f. leucocarpum Kuntze.
26. *C. indicum* var. aviculare Dierb.
27. *C. cerasiforme* Mill.
28. *C. nigrum* Willd.
29. *C. annuum* var. *longum* (DC.) Sendtn.
30. *C. cereolum* Bertol.
31. *C. comarim* Vell.
32. *C. oliviforme* Mill.
33. *C. hispidum* var. glabriusculum Dunal
34. *C. conicum* Lam.
35. *C. purpureum* Vahl ex Hornem.
36. *C. torulosum* Hornem.
37. *C. conicum* G. Mey.
38. *C. hispidum* Dunal
39. *C. annuum* f. *luteum* Kuntze.
40. *C. conoideum* Mill.
41. *C. hamiltonii* G. Don
42. *C. conoideum* var. chordale Fingerh.
43. *C. grossum* L.
44. *C. conoideum* var. sulcatum Fingerh.
45. *C. globosum* Besser
46. *C. tomatiforme* Fingerh. ex Steud.
47. *C. globiferum* G. Mey.
48. *C. tournefortii* Besser
49. *C. cordiforme* Mill.
50. *C. crispum* Dunal.
51. *C. tetragonum* Mill.
52. *C. frutescens* var. queenslandicum Domin
53. *C. curvipes* Dunal.
54. *C. ustulatum* Paxton
55. *C. milleri* Roem. & Schult.
56. *C. frutescens* var. *longum* (DC.) L.H. Bailey.
57. *C. cydoniforme* Roem. & Schult.
58. *C. velutinum* De Wild.
59. *C. pyramidale* Mill.
60. *C. sphaerium* Willd.
61. *C. sonitpurense* Jintu Sarma & G. Dutta
62. *C. frutescens* var. glabriusculum (Dunal) M.R. Almeida.
63. *C. dulce* Dunal.
64. *C. fasciculatum* Sturtev.
65. *C. violaceum* Desf.
66. *C. frutescens* var. *conoides* (Mill.) L.H.Bailey.
67. *C. silvestre* Vell.
68. *C. quitense* Willd. ex Roem. & Schult.
69. *C. minimum* Mill.
70. *C. frutescens* var. *cerasiforme* (Mill.) L.H.Bailey.
71. *C. petenense* Standl.
72. *C. indicum* var. *conoideum* (Mill.) Dierb.
73. *C. longum* DC.
74. *C. micranthum* Link
75. *C. luteum* Lam.
76. *C. frutescens* var. *fasciculatum* (Sturtev.) L.H. Bailey.
77. *C. odoratum* Steud.
78. *C. narunca* Dunal
79. *C. annuum* f. *chlorocarpum* Kuntze.
80. *C. frutescens* var. grossum (L.) L.H. Bailey. (http://powo.science.kew.org/taxon/urn:lsid:ipni.org:nams:316944-2).

### 7.1.4 Local Names

Acı kırmızı biber, isot (Turkish), poivre rouge, piment enrage, piment fort, piment-aiseau, poivre de cayenne (French), lombok, cabe, cabai (Indonesian), mit'mit'a, berbere (Amharic), hari mirch (green) (Hindi), jolokia (Assami), lanka, morich (Bengali), nga yut thee, nil thee (Burmese), peperone, diavoletto, peperoncino, pepe di caienne, pepe rosso picante (Italian), lup-chew (Chinese), chili (Danish), cayenne pepper, red pepper, chilli, chili (English), kibe paprika (Estonian), chilipippuri (Finnish), la1 mirch (red), roter pfeffer, cayenne-pfeffer, chili-pfeffer, beißbeere (German), macskakpöcs paprika, aranybors, ördögbors, chilipeppar (Swedish), chili-paprika (Hungarian), la1 marcha (red), lila marcha (green) (Gujarati), aji (Spanish), pisi hui, prik khee, prik (Thai), spaanse peper, cayenne-peper (Dutch), felfel, bisbas (Arabic), lalmarach (Urdu), mulagu (Tamil), togarashi (Japanese), ot (Vietnamese) menashinakayi (Kannada), mak phet kunsi (Laotian), lada merah (Malay), mulagu (Malayalam), la1 mirchya (red), hirvya mirchya (green) (Marathi), lankamaricha (Oriya), mirapakaya (Telegu), murgh (Pashto), pimentao, piri-piri, pimenta de caiena (Portuguese), lal-mircha (Punjabi), marichiphala, ujjvala (Sanskrit), rathu mitis, gasmiris (Singhalese), siling labuyo, sili (Tagalog), sipeo marpo, si pan dmar po (Tibetan), pilpel adom (Hebrew), csili-paprika, cayenne bors, cayenni bors, chilipipar, cayennepipar (Icelandic), chile, guindilla, cayena inglesa, pimienta de cayena, pimienta picante, pilipili hoho (Swahili) (Basu and De 2003; Singletary 2011).

### 7.1.5 Occurrence/Habitat

*Capsicum annuum* is cultivated throughout Asia, Africa, America, and Mediterranean countries as a spice and vegetable, in fields or under glass, for its unripe green or ripe red fruits. The many forms cultivated for this purpose bear mainly Turkish names and are named after the shape of the fruits in Turkey. They may be grouped under two cultivars *longum* and *grossum*. Some other varieties are grown in pots as ornamentals for their showy, lasting fruits (Baytop 1978; Khan et al. 2014).

### 7.1.6 Importance

*Capsicum annuum* is a well-known spice in different areas of the world from old times due to its specific taste, color, and aroma. It has been used in most of the kitchens and dietary products. Also, its medicinal importance is well established. Its fruit is used as a circulatory stimulant. In addition, chili has various pharmacologically substantial compounds such as capsaicinoids. Due to its carotenoids, it is used for coloring of soaps, sauces, and cosmetics as commercial products (Basu and De 2003; Khan et al. 2014).

### 7.1.7 Objective of This Chapter

The objective of this chapter is to review the medicinal and pharmacological properties (internal and external uses, method of administration, adverse effects, contraindication, etc.) along with botanical characteristics and chemical compounds of *Capsicum annuum* plant.

## 7.2 Distribution and Status of Species

*Capsicum* genus taxonomy is confounded within certain species complexes. It is generally believed that about 20 *Capsicum* species are spread worldwide. Five major species of *Capsicum* cultivated are *Capsicum annuum*, *C. pendulum*, *C. frutescens*, *C. pubescens*, and *C. chinense* (Basu and De 2003). *C. annuum* grows naturally in Central America and Native of Mexico. It is cultivated throughout Asia, Africa, America, and Mediterranean countries such as Turkey (Baytop 1978).

## 7.3 Comparison of Traditional/Ethnomedicinal/Local Uses: In Turkey and Throughout the World (Asia and Europe)

In Turkey, it is used internally as an appetizer, urine enhancer, and stimulant and externally as a flushing and blood collector. It is also widely used as a spice and in the preparation of fenu-

greek adorned on pastirma. Internally, red pepper powder (1–2 g) is taken by mixing with honey per day. Externally, against rheumatism pains, a mixture of 10 g of the powder in 60 g of alcohol (50%) is rubbed onto the skin (Baytop 1999).

Fruits of *Capsicum* were maybe the most commonly used for the longest time as a diet ingredient in the ancient civilization in Mexico and northern South America. Chilies were used to increase food intake, through increased salivation, hotness, and blush in the mouth due to their very strong and stimulant effect (Govindarajan and Sathyanarayana 1991). In the central region of Peru, leaves of the *C. annuum* are used against breathing difficulties, vomiting with blood, headache, epilepsy, madness, and chills through a smoke/steam bath. In North America *C. annuum* fruits with *Rosmarinus officinalis*, *Clematis* sp., *Chrysanthemum* sp., *Larrea tridentate*, *Centella asiatica*, *Oplopanax horridus*, and *Ginkgo biloba* are used for promoting memory and against asthma, emphysema, eczema, and aging. In Tlanchinol Hidalgo, Mexico, fruits are used against cough. In Eastern Nicaragua, decoction prepared from leaves and fruits are used against back and postpartum abdominal pain topically. In Dominican Republic, tea prepared from leaves is used for painful menses. In Costa Rica, decoction of root is used against colic and stomach discomfort (Meghvansi et al. 2010).

In India, *C. annuum* is used for sciatica, hoarseness, arthritis, coughs, and gout. It is utilized against malaria, scarlet fever, yellow fever, and typhus for lowering temperature. It is utilized for cholera, anorexia nervosa, edema; loss of dyspepsia, appetite, and diarrhea; and alcoholism (Cayenne with cinnamon and sugar) (PDR for Herbal Medicines 2000). In Indian central Himalaya, fruit and oil are used against dog bite. The fruits are used against eye diseases of cattle in Kalahandi, Orissa, and against ascites in Lakhimpur, Assam (Northeast India). In Central India and Agasthiayamalai Biosphere Reserve, fruit powder is applied topically, and root extract is given orally on snake bite and wounds. In Nagaland, fruits are used against pruritus and as counterirritant (Meghvansi et al. 2010). In Uttarakhand Himalaya, fruit powder blended within *Piper nigrum* and *Syzygium aromaticum* in water is used against skin disease (Shah et al. 2008). In Uttar Pradesh, raw fruits stirred within *Zingiber officinale*, $Na_2SO_4$, *Allium cepa*, NaCl, and $NaHCO_3$ are used against indigestion (Ali 1999).

In Europe, *C. annuum* fruits are used as cardiotonic and aperitif in Central Italy as well as antirheumatic, antihypertensive, and anti-fever and against evil eye in Southern Italy. In Calabria region (Southern Italy), the fruit poultice is used as revulsive (Meghvansi et al. 2010). In Northern Basilicata (Italy), fruits with or without *Leopoldia comosa* bulbs are used as anti-fever (Pieroni et al. 2002).

In Africa, fruits are used as stimulant in Enugu State (Nigeria). In Ekiti State (Nigeria), stem is used for oral and dental healthcare (Meghvansi et al. 2010). In Wonago Woreda (Ethiopia), fresh/dry fruits are used against ascariasis by chewing and swallowing (Mesfin et al. 2009).

In Asia, fruit is used against dysentery, fever, and skin diseases in Nawalparasi region (Nepal) (Ghimire and Bastakoti 2009).

In Palestine, fruits are used as rubefacient for arthritis, counter-irritant, digestive tonic, condiment, and carminative and for rheumatism (Jaradat 2005).

## 7.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques (Classification and Structures of Few Representatives)

Fruits of *Capsicum annuum* contain capsaicinoids as capsaicin (32–38%), dihydrocapsaicin (18–52%), norhydrocapsaicin, nordihydrocapsaicin, homohydrocapsaicin, homodihydrocapsaicin, homocapsaicin (Hamed et al. 2019; Korkutata and Kavaz 2015; PDR for Herbal Medicines 2000; Vera-Guzmán et al. 2017), carotenoids (0.3–0.8%), capsanthin, $\alpha$-carotin, capsanthin-5,6-epoxide, violaxanthin, $\beta$-cryptoxanthin, antheraxanthin, $\alpha$- and $\beta$-carotene, lutein, capsorubin, zeaxanthin, phytoene, cucurbitaxanthin A phytofluene, and neoxanthin (Civan and Kumcuoglu 2019; Hornero-Méndez et al. 2000; PDR for Herbal Medicines 2000; Rodríguez-Rodríguez et al.

2020), flavonoids such as apiin, luteolin-7-*O*-glucoside, luteolin-7-*O*-(2-apiofuranosyl-4-glucopyranosyl-6-malonyl)-glucopyranoside, quercetin 3-*O*-*α*-L-rhamnopyranoside-7-*O*-*β*-D-glucopyranoside, catechin, quercetin, kaempferol, epicatechin, rutin, luteolin, myricetin, luteolin 7-*O*-[2-(*β*-d-apiofuranosyl)-*β*-D-glucopyranoside, apigenin 6-*C*-*β*-D-glucopyranoside-8-*C*-*α*-L-arabinopyranoside luteolin 6-*C*-*β*-D-glucopyranoside-8-*C*-*α*-L-arabinopyranoside, apigenin (Materska et al. 2003; PDR for Herbal Medicines 2000; Vera-Guzmán et al. 2017), as well as essential oil (0.1%).

Compounds of essential oil are acetic acid (14.43%), 1-methoxy-4-(1-propenyl)-benzene (5.67%), 10s,11 s-himachala-3 (12),4-diene (41.14%), 2-methoxy-3-isobutyl pyrazine, N-(13-methyl tetradecyl)acetamide (capsiamide), and 2,4a,5,6,7,8,9,9a-octahydro-3,5,5-trimethyl-9-methylene-1H-benzocycloheptene (5.74%) (Cao and Zhang 2011; PDR for Herbal Medicines 2000).

Seeds of *C. annuum* contain steroid saponins such as capsicidine; capsicosides E, F, and G; and furostanol saponin (Iorizzi et al. 2002; PDR for Herbal Medicines 2000; Sung et al. 2018).

## 7.5 Scientific Evidences: Pharmacological Activities (All Major Therapeutic Activity with In Vitro and In Vivo Studies and Mechanism of Action)

### 7.5.1 In Vitro Studies

#### Antioxidant Activity

Extracts prepared from five cultivars of *Capsicum annuum* (El Dorado, Tula, Grande, El Rey, and Sayula) were investigated for their antioxidant activities. Grande pepper indicated the highest free radical scavenging effect (87 %). Grande and El Dorado peppers showed reducing power with 0.85% and 0.81%, respectively, while standard antioxidant BHT showed 0. 97% reducing power at 100 μg/mL (Farhoudi et al. 2019).

Carotenoid extracts obtained from dried fruits of *Capsicum annuum* (guajillo, pasilla, and ancho peppers) were evaluated for their antioxidant activity. Guajillo pepper carotenoid extracts demonstrated highest antioxidant effect in $DPPH^+$ scavenging assay (24.2%) (Hernández-Ortega et al. 2012).

#### Antibacterial Activity

Water, methanol, and ether extracts prepared from *Capsicum frutescens*, *C. annuum* var. glabriusculum, and *C. annuum* were investigated for their antimicrobial activity by using microdilution method on *Arcobacter cryaerophilus*, *A. butzleri*, *A. skirrowii*, *Campylobacter jejuni*, and *Helicobacter pylori*. *C. annuum* methanol extract was efficient on *H. pylori* and *C. jejuni*, whereas water extract was potently efficient on *A. cryaerophilus* (Doğan et al. 2018).

#### Antiviral Activity

Methanolic extract of *Capsicum annuum* was evaluated for antiviral activity on Vero cells for anti-HSV-1 and ant-HSV-2 effects via plaque assay. It was found that $IC_{50}$ value of extract toward Vero cells was 1078.69 μg/mL in the MTT assay. It indicated considerable anti-HSV-1 and anti-HSV-2 activities at 25 μg/mL (Hafiz et al. 2017).

#### Antiproliferative Activity

Different polarity extracts prepared from *Capsicum annuum* were investigated for cytotoxic effect toward MCF-7 cell line in MTT assay.

It was seen which cell viability was lowered in specimens, and apoptotic induction was raised in MCF-7 cell line. When methylene chloride and ethyl acetate extracts were applied to the cells, the effect was caused by down-regulation of Bcl-2, Her-2 expression genes, and this mechanism was confirmed by RT-PCR. Additionally, the pre-apoptotic genes (Bax and P53) were increased (Bazid et al. 2019).

#### Anti-Adipogenic Activity

Capsicosides A and G were purified from the ethanolic extract of *Capsicum annuum* seeds,

and they were evaluated for the anti-adipogenic activity on intracellular lipid accumulation in 3 T3-L1 adipocytes. It was shown which they reduced accumulation at 1–20 μg/mL. Capsicoside G showed significantly greater inhibitory effect than capsicoside A on 3 T3-L1 adipocyte differentiation at 20 μg/mL (Sung et al. 2015).

### Antimutagenic Activity

Eight oleoresin extracts (water, methanol, ethanol, propanol, acetone, dichloromethane, diethyl ether, and *n*-hexane) from chili were evaluated for antimutagenicity activity by Ames test. *n*-Hexane oleoresin showed the strongest activity. Carotenoids and capsaicinoids were isolated from *n*-hexane oleoresin. Carotenoids showed significant antimutagenicity ($r = 0.89$, $P < 0.05$). Cryptocapsin showed the strongest activity (Shinn-Nen et al. 1998).

### Enzyme Inhibitory Activity

*Capsicum annuum* extracts prepared from various parts were assessed for inhibitory effects for key enzymes of hyperglycemia (α-glucosidase and α-amylase) and hypertension (angiotensin-converting enzyme). Extracts from the stalk had high phenolic and capsaicin content and showed considerable α-amylase and α-glucosidase inhibition activities. The extracts of placenta and pericarp showed potent ACE inhibitory and α-glucosidase inhibitory effects (Chen and Kang 2014).

Methanol extract from *C. annuum* showed high inhibitory activity on acetyl coenzyme A carboxylase. The active compounds found were (*E,E*)- and (*E,Z*)-9-oxooctadeca-10,12-dienoic acids. The $IC_{50}$ values of the specimens were 1.4 $x10^{-6}$ and 1.5 $x10^{-6}$ M, respectively (Watanebe et al. 1999).

## 7.5.2 In Vivo Studies

### Anti-inflammatory Activity

The hydroalcoholic extract of *Capsicum annuum* was investigated for anti-inflammatory effect on carrageenan-induced hind paw model. The extract showed demonstrable anti-inflammatory effect in rats at 100 mg/kg bw (Vijayalakshmi et al. 2010).

### Hepatoprotective Activity

Ethanolic extract of *Capsicum annuum* was investigated for the hepatoprotective activity on paracetamol-induced liver damage in male Wistar rats. The ethanolic extract was given orally to rats. Silymarin was used as reference standard. The rats were separated to five groups. Group 1 rats (G1) served as healthy control and receive no treatment. G2 served as toxic control and receive paracetamol orally at 750 mg/kg at an interval of 72 h for 21 days. G3 received standard silymarin 50 mg/kg for 21 days and simultaneously administered paracetamol. G4 received ethanolic extract of *C. annuum* 250 mg/kg for 21 days and simultaneously administered with paracetamol. G5 received ethanolic extract of *C. annuum* 500 mg/kg for 21 days and simultaneously administered with paracetamol. According to the results, a significant decrease was seen in serum enzymes (ALT, AST, and ALP) (Priya and Anitha 2017).

### Antidiabetic Activity

Acetone fraction (AF) obtained from ethanolic extract of *Capsicum annuum* fruit was evaluated for antidiabetic activity on rats with type 2 diabetes. 150 or 300 mg/kg bw of the AF were administered orally to animals once a day for 4 weeks. The results indicate that AF at 300 mg/kg showed antihyperglycemic and antihyperlipidemic activities, glucose intolerance and insulin resistance were improved, and pancreatic morphology was restored. Additionally, the alterations of other organ related serum markers were ameliorated (Mohammed et al. 2017).

### Renoprotective Activity

Aqueous extract of *Capsicum annuum* (red paprika) (AqCA) was evaluated for renoprotective potential toward EtOH-induced oxidative imbalance and renal toxicity. At a random manner, the male Wistar rats were grouped as EtOH-entreated, CA125, CA250, EtOH pre-entreated with CA, control, and entreated for 30 days.

TUNEL assay and Western blotting were done for evaluation. Earlier therapy within CA prevented EtOH-induced changes in tissue and parameters of serum (Das et al. 2021).

### Hypocholesterolemic Activity

*Capsicum* oleoresin (CO) was investigated for hypocholesterolemic activity on dietary hypercholesterolemia in male gerbils. It was given to animals at 75 mg/kg bw/day. CO reduced serum cholesterol (70%) and triglycerides (66%), while liver cholesterol and triglycerides were reduced by 70.9% and 68.7%, in turn. CO avoided cholesterol and triglyceride accumulation in the liver and aorta. In oleoresin-fed gerbils, cholesterol and triglyceride fecal excretions potently increased (Gupta et al. 2002).

### Antitumor Activity

Capsanthin, capsanthin 3,3′-diester, and capsanthin 3′-ester were isolated from red paprika. The carotenoids were evaluated for antitumor activity in mouse skin two-stage carcinogenesis assay by utilizing 7,12-dimethylbenz[a]anthracene and TPA. The isolated compounds promoted significantly antitumor activities (Maoka et al. 2001).

### Anti-Obesity Activity

*Capsicum annuum* and capsanthin (major carotenoid in *C. annuum*) were evaluated on diet-induced obese mice with impaired lipid metabolism. Forty male mice were grouped to 4: normal diet, high-fat diet (HD), HD within *C. annuum*, and HD within capsanthin. At the end of the eighth week, weight gain was significantly reduced, and the liver and adipose tissue hypertrophy was ameliorated in the red paprika and capsanthin groups. In addition, serum lipid profile and adipokine secretion were improved, and hepatic steatosis via suppressor hepatic lipogenesis, fatty acid oxidation, and gluconeogenesis was ameliorated. Adipogenesis was inhibited and lipid droplet size was decreased in epididymal adipose tissue (Kim et al. 2017).

### Analgesic Activity

Carotenoids extracts obtained from dried fruits of *Capsicum annuum* (guajillo, pasilla, and ancho peppers) were determined for analgesic activity. Carotenoid extracts from guajillo pepper displayed potent peripheral analgesic effect at 5, 20, and 80 mg/kg and induced central analgesia at 80 mg/kg (Hernández-Ortega et al. 2012).

### Gastric Acid Secretory Activity

Aqueous extract of *Capsicum annuum* was investigated on aspirin-induced acute injury of gastric mucosa in rats. *C. annuum* increased acid secretion (0.93 mL 0.1 N HCl) to about seven times the basal excretion (0.14; $p < 0.005$) (Vasudevan et al. 2000).

## 7.6 Clinical Studies (Ongoing, Proposed, and Completed)

### 7.6.1 Food Craving Activity

Foods containing chili peppers were evaluated for determining neurotic cycles underlying spiced food craving. It was compared with brain response in extreme cravers and non-cravers and assessed on the Questionnaire of Spiced Food Craving. The pictures of foods with visible chili peppers or no chili peppers indicated extreme cravers ($n$ = 25) and non-cravers ($n$ = 26). They attended in an fMRI cue-reactivity paradigm. There was no discriminatory activation on amygdala and orbitofrontal cortex (Zhou et al. 2019).

### 7.6.2 Anti-Reflux Activity

Chili was investigated on gastric accommodation (GA) in gastroesophageal reflux illness patients. 2 g of chili or placebo in capsules were given to 15 healthy volunteers (HV) and 15 pH-positive non-erosive patients within a week. It was determined by single-photon emission computed tomography. Symptoms of upper gastrointestinal were determined through a visual analog scale. Patients had considerably more GA after taking chili when comparing to HV. In addition, the postprandial gastric volumes were potently more than HV at 10, 20, and 30 min in patients (Patcharatrakul et al. 2020).

### 7.6.3 UV-Induced Skin Damage Suppression Activity

Extract of *Capsicum annuum* xanthophylls was evaluated for activity on UV-induced depredation on skin. A randomized double-blind placebo-controlled investigation was performed and compared to healthy volunteers ($n = 46$). The minimal erythema dose (MED) was determined for all individuals before the study. A xanthophylls capsule (9 mg) or a placebo was taken daily for 5 weeks. The MED, minimal tanning dose (MTD), and facial skin and skin physiology parameters were detected at 0, 2, and 4 weeks. The verum group MED was potently higher at 2 and 4 weeks compared to placebo group. The UV-induced skin darkening suppression was considerably higher than placebo group at 4 weeks (Nishino et al. 2018).

### 7.6.4 Anti-Obesity Activity

Xanthophylls from red paprika were evaluated on decreasing the abdominal fat parts in the healthy and overweight volunteers (BMI = 25–30 kg/m$^2$). Xanthophyll capsules (9.0 mg) or placebo capsules were given to volunteers orally for 12 weeks. The abdominal visceral fat parts were found smaller in xanthophyll group than in the placebo group. In addition, abdominal subcutaneous fat parts, total fat parts, and BMI were decreased significantly. Adverse effects were not seen through intake of xanthophyll capsules (Kakutani et al. 2018).

## 7.7 Toxicological Studies (Dose and Safety Profile; Acute, Chronic, and Mutagenicity Studies to Demonstrate Broad Spectrum Safety; GRAS Status)

### 7.7.1 Dose and Safety Profile

#### Internal Usage

The decoction of 5 g powder of red pepper, 3 g powder of *Cascarilla* bark, and 5 g powder of rhubarb root is prepared in 2/3 liter of water for internal usage and can be consumed 2 cups per day (PDR for Herbal Medicines 2000).

#### External Usage

A 22 × 14 cm medicated plaster should contain 390–552 mg of soft extract of *Capsici fructus* (11 mg capsaicinoids, as 35 μg/cm$^2$ capsaicin), and a 12 × 18 cm medicated plaster should contain 171–240 mg of soft extract (4.8 mg capsaicinoids, as 22 μg/cm$^2$ capsaicin) for adolescent, adult, and elderly usage. A maximum of one plaster should be applied on the affected area for at least 4 and up to 12 hours for daily usage. At least a 12-hour interval is recommended before a novel plaster is administrated at the same part. It is not recommended to use in children under the age of 12 (EMA Monographs 2014).

Semi-solid dosage forms should contain 0.6–1.9 g of soft extract (40–53 mg capsaicinoids/100 g) for adult and elderly usage. It is given two to four times a day as in the form of a thin layer on the affected parts. It is not recommended to use in children and adolescents under the age of 18 (EMA Monographs 2014).

Capsules should contain 400, 445, 450, 455, or 500 mg of extract. Cream form should contain 0.25% or 0.75% capsaicin. A liquid extract is prepared via percolating 100 g medication within 60 g EtOH. Moreover, *Capsicum*-oleoresin within 90% EtOH and a tincture within 90% EtOH are the other usage forms. 10 g of medication, tincture (1:10), or semi-solid preparations (max of 50 mg capsaicin in a 100 g base) are used externally in a day. The cream is given to the affected parts not more than three or four times daily (PDR for Herbal Medicines 2000).

#### Method of Administration

The method of administration is cutaneous use (EMA Monographs 2014).

#### Contraindications

If there is any hypersensitivity to the active substance or other capsaicinoids, it must not be used. It must not be applied on broken skin or wounds (EMA Monographs 2014).

#### Interactions with Other Medications

When used at the same time with aspirin (acetylsalicylic acid) and salicylic acid, the extract of

*Capsicum annuum* (100 mg of capsaicin per gram) reduced their bioavailabilities resulted by capsaicin effects in the gastrointestinal system (Cruz et al. 1999).

### Pregnancy and Lactation

There is no data from the usage of the plaster in pregnant women. In animal researches, reproductive toxicity has been observed after high subcutaneous doses of capsaicin. As capsaicin may pass in the placenta and into breast milk, according to an attentive risk-benefit evaluation, the plaster should only be used afterward throughout lactation and pregnancy. Data is not available on fertility.

For semi-solid form, safety has not been utilized during pregnancy and lactation, so it is not recommended to use throughout pregnancy and lactation (EMA Monographs 2014).

### Works that Required Attention

Not relevant (EMA Monographs 2014).

### Overdose

Toxic dosages affect the thermoreceptors and cause life-threatening hypothermias. Chronic gastritis, liver damage, kidney damage, and neurotoxic effects occurred when using high doses of the medication (or the plant) when consumed over broad times. The symptomatic treatment is applied for poisonings (PDR for Herbal Medicines 2000).

### Duration of Use

If symptoms continue throughout using the medicinal product, it should be consulted to a doctor or a pharmacist. The medication should be used for a maximum of 3 weeks until the pain is gone. After 3 weeks, it should have a break for at least 2 weeks (EMA Monographs 2014).

## 7.7.2 Acute, Chronic, and Mutagenicity Studies to Demonstrate Broad Spectrum Safety

### Acute Toxicity

The data about acute toxicity on herbal preparations are not available. For capsaicin, the acute toxicity order in mice was firstly intravenous application, followed by intraperitoneal, subcutaneous, oral, and dermal, respectively (EMA Monographs 2014).

### Chronic Toxicity

According to the EFSA Panel on Food Additives and Nutrient Sources, paprika extract (E 160c), a natural dye, is permitted like a food additive in Europe. For toxicological, there are two studies: a 13-week oral toxicity investigation and one chronic toxicity and carcinogenicity research. It was concluded that paprika extracts (DN-933) used as food colors do not raise a genotoxicity, and in the chronic toxicity and carcinogenicity study, paprika extract (E 160c) was not found carcinogenic for use as an admissible daily intake (ADI). According to panel, the ADI was determined as 24 mg/kg bw/day for paprika extract (E 160c). For paprika extract (DN-933), the total carotenoid content was standardized as 7.1% and ADI was determined as 1.7 mg carotenoids/kg bw/day (EFSA Panel on Food ANS 2015).

Paprika color as a food additive was evaluated for chronic toxicity and carcinogenicity in female and male F344 rats. It was given to animals at concentrations of 0%, 0.62%, 1.25%, 2.5%, and 5% during 52-week toxicity study and at concentrations of 0%, 2.5%, and 5% during 104-week carcinogenicity research. As a result, no toxicological effects were seen in the chronic toxicity study. In addition, paprika color didn't induce specific tumors in the carcinogenicity investigation (Inoue et al. 2008).

### Mutagenicity and Teratogenicity

Toxicity, genotoxicity, and carcinogenicity studies have not been performed on herbal preparations. The mutagenicity and carcinogenicity studies were insufficient for capsaicin. Capsaicin was not teratogenic in rats when administered subcutaneously.

However, there was a case in which capsaicin passes the placenta and performs a toxic action on the peripheral nerves of fetuses. High subcutaneous doses (50 mg/kg) of capsaicin given to prenatal treatment of rats caused functional neuronal defects. However, it was concluded that as body growth and sexual maturation were retarded,

mating frequency was decreased and gestations were reduced (EMA Monographs 2014).

### 7.7.3 GRAS Status

*Capsicum annuum* L. has been accepted with GRAS status through FEMA and is confirmed through the FDA for usage as "spices and other natural seasonings and flavorings" and "color additive" in food. Its FEMA number is 2833; CAS number is 84625-29-6; and CFR codes are 21CFR73.340 and 21CFR182.10.

https://www.femaflavor.org/flavor-library/paprika-capsicum-annuum-l

https://www.ecfr.gov/cgi-bin/text-idx?SID=e956d645a8b4e6b3e34e4e5d1b690209&mc=true&node=pt21.3.182&rgn=div5

## 7.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies (with Special Focus on Bioavailability and Metabolism of Active Constituents)

### 7.8.1 Commercial Formulations/Products

- **CVS Medicated Heat (Patch)**
- **Ingredient:** chili pepper (*Capsicum annuum* L.)
- **Uses:** It is used for relieving minor pain of muscles and joints related within: strains, arthritis, simple backache, bruises, and sprains, temporarily.
- **Administration method:** It is used topically for adults and children (12 years of age and older). It should be applied to clean and dry affected parts. Patch is removed from film and applied to affected area no more than three to four times daily. Patch must not be worn for more than 8 hours.
- **Hysan Deguo Porous Capsicum (Plaster).**
- **Ingredient:** chili pepper (*Capsicum annuum* L.)
- **Uses:** It is used for relieving minor pain of muscles and joints related within: sprains, arthritis, bruises, simple backache, and strains, temporarily.
- **Administration method:** It is used topically.
- **SinolM Fast Headache Pain Relief All-Natural (Nasal Spray).**
- **Ingredient:** chili pepper (*Capsicum annuum* L.)
- **Uses:** It provides fast relief from headache pain, cluster, migraine, tension, premenstrual and menstrual, and sinus headaches.
- **Administration method:** The bottle should be shaken before each use. It is sprayed once or twice into each nostril and sniff deeply up into the nasal cavity. It provides relief within minutes. If headache is severe, it can be used two to three times as directed. Then cap is replaced after use.

### 7.8.2 Pharmacokinetic Studies

The metabolic ratio of 5 g of raw chili pepper was investigated in Thai women. It immediately increased after ingestion and lasted for up to 30 minutes (Chaiyata et al. 2003). In a study, *Capsicum* gel capsules (5 g) were given orally. Capsaicin was first determined in the plasma at 10 min within a Cmax = 2.47 ± 0.13 ng/mL, Tmax = 47.08 ± 1.99 min, area under the curve (0-t) = 103.6 ± 11.3 ng.min/mL, and $T_{1/2}$ = 24.87 ± 4.97 min (Weerapan Khovidhunkit 2009).

Capsaicin is absorbed through the skin and metabolized primarily in the liver and eliminated in the form of metabolites in the urine and feces (EMA Monographs 2014). When a 3% solution of capsaicin is given topically, it was rapidly absorbed and attained optimal concentration. The capsaicin shelf-life was approximately 24 hours (Ahuja and Ball 2006). In a study, capsaicin was completely metabolized with 20 min in microsomes of rat and human (Chanda et al. 2008). The

highest levels were detected in blood and intestines at 1 h, hepatic at 3 h, and renal at 6 h (Suresh and Srinivasan 2010). About 6.3% of administered capsaicin was eliminated in feces within a period of 4 days, within the peak excretion being on the initial day of oral intake. For this reason, almost 94% capsaicin is digested when taken orally. Just a little portion of capsaicin was eliminated in urine (0.095%) (Mózsik et al. 2009). Capsaicin absorption was rapid in the gastrointestinal system, and almost 85% of it was absorbed within 3 h (Kawada et al. 1984). Furthermore, the capsaicin is carried to the portal blood (nearly 85%) and partly metabolized to 8-methyl nonanoic acid (Reyes-Escogido et al. 2011). The other metabolites were determined as 16- and 17-hydroxy capsaicin and 16- and 17-dihydrocapsaicin (Cortright and Szallasi 2004).

## 7.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

*Capsicum annuum* is a well-known spice in many parts of the world. Its utilization began quite in the early days, and it is considered to have its resource in America. In spite of its dietary significance, the folklore of its medical significance is also well known. In traditional medicine, *C. annuum* has a lot of uses as appetizer and against rheumatism, epilepsy, asthma, painful menses, cough, eye diseases, fever, skin diseases, ascariasis, etc. administered topically or orally or through smoke bath. Wide literature is present on several investigation areas; however, several parts are still not broadly discovered. Thus, further researches to utilize this widespread and economic fruit for the best therapy of disorders are taken and suggested. Additionally, in traditional medicine, it was observed that the combinations of *C. annuum* with honey and other herbs were used. This combination also should be evaluated scientifically and may be used to develop new herbal products.

## 7.10 Challenges and Future Recommendations as a Potential Drug Candidate

When capsaicin is administrated orally, it shows a lot of unlikeable side effects, such as eye tearing, sweating, gastric pain, and ulcers. Additionally, it has short shelf-life and low bioavailability; therefore, most patients stop using it, making clinical trials useless. New drug formulations of capsaicin should be developed for oral intake (Batiha et al. 2020).

Most of the studies are only focused on capsaicin. More studies should be performed about *C. annuum*'s standardized extract and other compounds for novel pharmacological efficient components and their formulations to be utilized in pharmaceuticals and functional foods. Additionally, the dose and target population should be determined with clinical studies.

The use of phytochemicals obtained from *C. annuum* as food preservative is also hopeful. Combinations of capsaicin and dihydrocapsaicin with non-thermal process techniques, within other natural antimicrobials or salt, might ensure consumers a safer production that does not include chemical protectors (Salehi et al. 2018).

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# *Cedrus libani* A. Rich

8

Meltem Güleç, Selin Aktar Kiremitci, and Abdullah Olgun

**Abstract**

*Cedrus* is a vital member of the Pinaceae family, with elegant, decorative, evergreen, high, and monoecious conifer members that grow widely on mountains, particularly in the South, Southeast Mediterranean, and Western Himalaya. *Cedrus libani* (A. Rich), one of the four species, is currently found in only a few locations around the Eastern Mediterranean. It is a biologically significant species with one of the earliest ethnobotanical values in history of mankind, and it still attracts attention due to the ethnobotanical uses prevalent in its expanding range. Numerous studies on various parts of *Cedrus libani* shed light on its chemical composition (mostly terpenic structures) and pharmacological properties (antidiabetic, antimicrobial, wound healing, and cytotoxic activities); however, there are undoubtedly many more discoveries to be made with further studies.

**Keywords**

Cedar · *Cedrus* · Tar · Chemical composition · Biological activity · Pinaceae

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## Vernacular Names

English: cedar of Lebanon, Lebanon cedar (Farjon 2017)

Turkish: Gamalak (Kahramanmaraş); Hamalak, Kartan (Adana); Kamalak (Kahramanmaraş, Kayseri); Katran (Antalya); Katran ağacı (Adana, Antalya); Mezda (Kayseri); Sedir (Mersin, Muğla); Sedir ağacı (Mersin); Toros sediri (Tuzlacı 2011).

Arabic: Arez, Ariz lebnani (El-Beyrouthy et al. 2008; Baydoun et al. 2015).

The synonyms of *Cedrus libani* A. Rich can be listed as follows:

*C. libanensis* Jussieu ex Mirbel; *C. libanitica* Trew ex Pilger; *C. libanotica* Link; *C. cedrus* Huth; *C. patula* K. Koch, *Cedrorum libani* Hist.; *Pinus cedrus* Linnaeus, *Larix cedrus* Miller; *L. patula* Salisbury; *Abies cedrus* Poiret (Boydak and Calikoglu 2008, Davis 1970, Vidakovic 1991).



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## 8.1 Introduction

Cedros is the old Greek name for the resinous tree. The genus *Cedrus* is an essential part of the family Pinaceae with numerous historical and scriptural references consisting of graceful, ornamental, evergreen, tall, and monoecious conifers growing extensively on the montane or high montane slopes of mountains, especially South, Southeast Mediterranean, and Western Himalaya.

These trees usually have a dense or moderate density crown with an erect or bent top (Fig. 8.1). The branches are not produced in whorls, and the bark is initially smooth on young trees but becomes scaly and dark gray over time. The leaves are needlelike, persistent for 3–6 years, differing in length between species. Although the trees are monoecious, the male and female cones grow in different branches; both are erect, ovate to cylindrical-shaped, 5–10 cm long, and initially greenish, but after maturing in the second or third year, the color turns light purple. They fall off when they grow ripe. Each ovuliferous scale of female cones includes two soft, oily, and resinous seeds with a large winged shape (Davis 1970, Vidakovic 1991, Pijut 2000, Welch and Ouden 1991). The trees live long and contribute to the creation of essential forest ecosystems.

The *Cedrus* genus comprises four closely related species: *C. atlantica*, *C. libani*, *C. brevifolia*, and *C. deodara*, distributing on discontinuous regions between the western limit lying in Morocco, namely, Atlas Mountain, and eastern limit in the Himalayan Mountains, Nepal (Fig. 8.2). The range where the origin of *Cedrus* species belong forests composed four widely separated areas of Asia and North Africa:

1) Atlas and Riff Mountains (Algeria and Morocco) (*Cedrus atlantica* Manetti).
2) Mountainous area of Paphos, Troodos, and Tripylos in Cyprus (*Cedrus. brevifolia* Hen.)
3) Turkey and the border of the Mediterranean Sea in Syria and Lebanon (*Cedrus libani* A. Rich).
4) The Karakoram, Hindu Kush, and Indian Himalayas (*Cedrus deodara* Loud.). (Farjon and Filer 2013, Qiao et al. 2007, Vidakovic 1991).

The fossil records belonging to the genus reveal an Asian origin and migration to Europe and North Africa; accordingly, the characteristics that help determine species are habitual and because of environmental parameters like climate change. As a result of that affinity, the genus

**Fig. 8.1** *Cedrus libani* in the Taurus Mountains of Southern Turkey (Farjon and Filer 2013)

**Fig. 8.2** The genus *Cedrus* distribution (Farjon and Filer 2013)

*Cedrus*, so-called True Cedars, has three species in Farjon, although four different species are recognized traditionally. It is also claimed that the distribution propounds a decrease of a formerly more extended area of possibly one to two species. Besides, isozyme analysis of *Cedrus* diploid tissue serves as supporting information, detecting no differentiating gene marker between species *C. atlantica* and *C. libani.* Another study on allozyme differentiation established that *C. libani* and *C. atlantica* should be considered as two different taxa (Farjon and Filer 2013; Pijut 2000; Panetsos et al. 1992; Scaltsoyiannes 1999). Aside from disagreement on the number of species, we approve all four species following the traditional aspect.

Among the species, *Cedrus libani* is native to Turkey, Cyprus, Lebanon, and Syria and resides in the largest geographic area (Fig. 8.3) (Boydak and Calikoglu 2008), but since ancient times, it was planted in assorted areas around the Mediterranean. The species epithet implies Lebanon from where it was first defined and signed. It also appears in the flag of Lebanon as a symbol.

They are dignified trees attaining 15 to 40 m in height and up to 3 m in diameter when mature; developing usually monopodial, massive and columnar trunk, and wide-spreading branches. The habit of *Cedrus libani* is pyramidal in juvenile stage but evolves into a wide umbrella-shaped, flat-topped crown. The first-order branches grow massive, very thick, long, often erect, and tiered on young trees, becoming horizontal with age resulting a more spreading and rounded habit (Fig. 8.4) (Hillier 1991, Pijut 2000, Davis 1970, Farjon 2017, Vidakovic 1991).

Today, more than 90% total distribution of natural *Cedrus libani* forests are present in Turkey, in the mountains of South Anatolia (elev. 1000–2300 meters above sea level, mainly in the Taurus Mountains, Nur, Ahir, Babadağ, and Canik Mountains). In Lebanon, the country it receives the common name from, it can be found in 12 scattered forests located on the western slope of Lebanon Mouth and, in Syria, in forests situated in the Jabal an-Nusayriya on a highly reduced area (Farjon and Filer 2013, Hajar et al. 2010, Kurt et al. 2008).

*Cedrus libani* belongs to the class "vulnerable" in the IUCN Red List of Threatened Species, which means a high risk of extinction in the wild (Gardner 2013; IUCN 2012). The exploitation of the genus results from several impacts like climate change, overuse by people (construction, pasturage), forest fires, and wars (Boydak and Calikoglu 2008).

## 8.2 Ethnobotanical Use

*Cedrus libani* is a notable species of historical, cultural, and biological value and one of the oldest ethnobotanical species in human history since the dawn of civilization. This timber tree is in the Egyptian papyri list of ailments and treatments (Alamgir 2017), and it is believed that Egyptian people used its oil in their perfumes and cosmetics with other herbal ingredients. It was also preferred for mummification (preservation) of Pharaoh's corpses by indigenous people (González-Minero and Bravo-Díaz 2018) because cedar is generally resistant to pathogens and insects. They had often chosen cedarwood to create related objects like sarcophagi or cedar

**Fig. 8.3** *Cedrus libani* distribution (Farjon and Filer 2013)

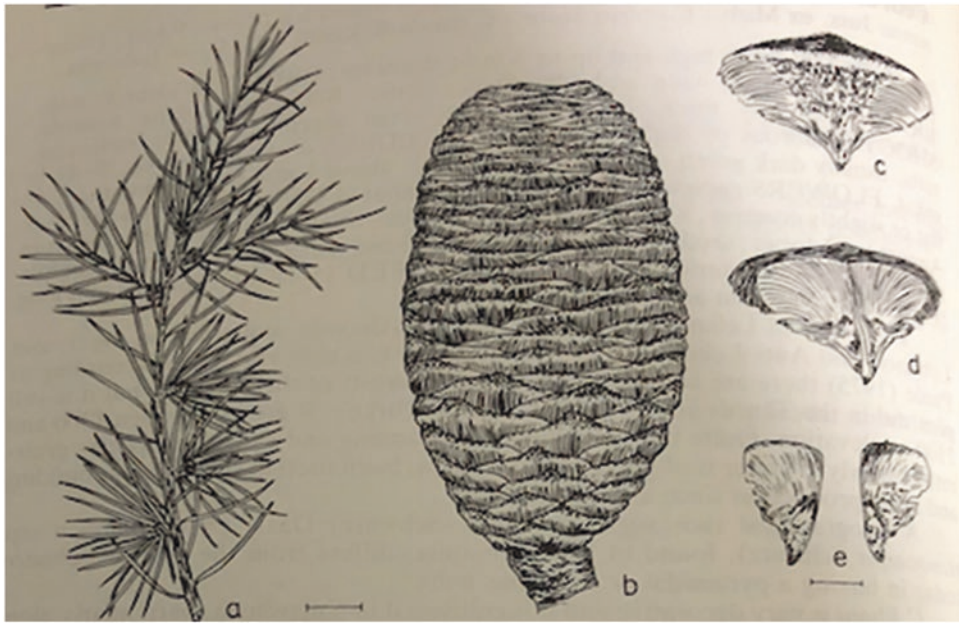


**Fig. 8.4** (**a**) Shoot, (**b**) cone, (**c**) fertile scale, (**d**). fertile scale with two seeds, e. seed winged on both sides (Vidakovic 1991)

resin to coat papyrus and coffins (Chaney and Basbous 1978).

The wood has unique features such as light, soft, highly resistant to decay, exceptional color and odor, and accessible to processing. Although the cedar wood's fragrance tends to disappear after 4–5 years, the smell is felt again when the wood's surface is grated (Boydak and Calikoglu 2008). Thanks to its impressive durability, fragrance, and remarkable development, cedar trees

were realized even by ancient people. This early awareness caused exploitation which also advanced into modern times. The earliest written evidence of the international wood trade belongs to Pharaoh Snefru (BD 2750), importing cedar from Phoenicia (today's Lebanon) to build a ship. They also bought cedar timbers for construction of pharaohs' palaces and temples in exchange for papyrus, gold, silver, or metalwork. The export of cedarwood enriched the Phoenician people providing prosperity (Chaney and Basbous 1978). Although the ship of Pharaoh Snefru is the earliest record for cedar wood usage, it has undoubtedly an older history in similar ways of usage. Mesopotamians, Nebuchadnezzar, the Assyrians, King David, Herod the Great, King of Babylonia, the Romans, and the Turks exploited cedar timber. It is also mentioned in the Old Testament of the Bible more than a hundred times, and it is reputed that Solomon's first Temple in Jerusalem has been built with it (Fig. 8.5). Besides all these, the cedar had a significant role in mythological passages and epics like Gilgamesh (Mayer and Sevim 1959, Boydak and Calikoglu 2008, Farjon 2017).

Studies on ethnobotanical knowledge in Lebanon has been very limited, causing loss of valuable information, and the species is experiencing serious threats there. The most extensive distribution of species exhibits in Turkey, resulting in various ethnobotanical usages against different disorders by the country's indigenous people (Table 8.1).

*Cedrus libani* is one of the best-known trees preferred for tar production. Records of modern ethnobotanical usage refer to yellow tar (thin tar), obtained from the tree's root and stem wood that grows in the mountains of Southern Anatolia. It is a fluid with a reddish-dark brown color, syrup consistency, and flammable complex mixture of hydrocarbons, resins, alcohols, and other compounds, which has a unique and pungent odor.

It is used externally to remove some parasites (such as ticks, lice, flies) in the skin of humans and animals. It is put in beehives in small amounts to prevent hive moth. It is a more valuable tar than black tar (*Pinus brutia* Ten) (Baytop 1999; Reunanen et al. 1993; Kilic Pekgozlu et al. 2017). A sort of tar from steam wood and resinous root of *C. libani* is used in animals against skin parasites (i.e., aphids) and insects (Saab et al. 2018).

Local people prefer dry resinous wood from large and dead tree roots for a better quality which they cut into pieces of 10–25 cm in length and 2–3 cm in width. They utilize a traditional distillation method with the help of two holes they excavate: one for ignition and one for collection connected with a discharge channel. During extraction, temperatures in the hole for ignition are usually over 300 °C. Slowing the burning process, controlling the air accession in the ignition part, and including less water content provide a better-qualified tar (Kurt et al. 2008).

The tar is used externally (by rubbing it on the stomach) to relieve abdominal pain, as a diaphoretic by applying to the chest and back, to treat skin diseases (treat wounds, scabies, and fungal diseases), and as an antiseptic. Other parts of the tree (cones, roots, branches) prepared as decoction or infusion are consumed by people to treat diseases like ulcers, prostate, and different skin diseases or relieve abdominal pain (Tuzlacı 2016). The leaves and the wood are used as antiseptic and expectorant to disinfect the respiratory tract (Chevallier 1996). Mountain people in Lebanon utilize the volatile oil from cones to remedy lumbago, muscular, sciatica, and rheumatism (El-Beyrouthy et al. 2008). (Table 8.1).

## 8.3 Chemical Composition

The chemical compounds contained in the extracts obtained from different parts of the *Cedrus libani* plant by different methods were determined in various studies.

Studies showed that the essential oil contained monoterpenes, diterpenes, sesquiterpenes, and sesquiterpene alcohols (Yılmaz et al. 2005). *C. libani* bark and cones were reported to contain oleoresin in one study (Hafizoglu 1987). In another study, ether extract of cones was reported to contain abietane-type resin acids and pimarane-type diterpenoids. Research shows that resin acids (abietic, neo- and dehydroabietic, sandaracopimaric, levopimaric, palustric acid, etc.),

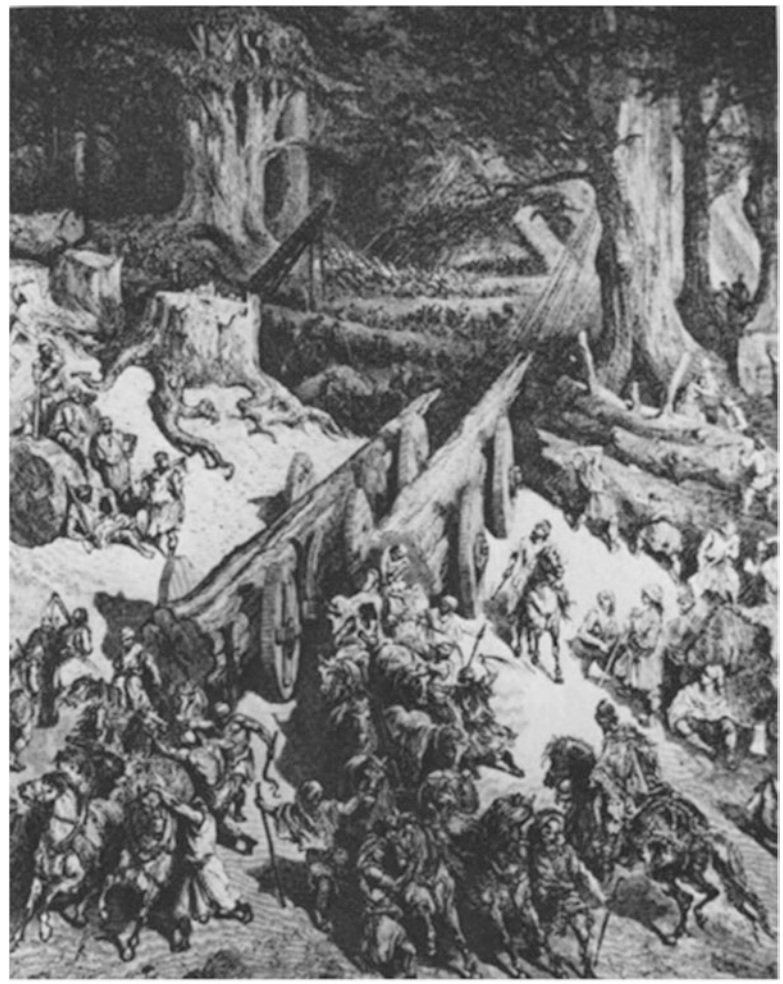

**Fig. 8.5** Drawing of Gustave Dore – people cutting cedars of Lebanon for Solomon's temple (Chaney and Basbous 1978)

alkanes, fatty acids, and terpene hydrocarbons are the main compounds (Norin and Winell 1971; Hafizoglu 1987).

In a different study, in addition to different from above α-and β-pinene, α-terpineol, limonene, sclarene, manool, myrcene, terpinen-4-ol, p-cymene, and kaur-16-ene, contents were determined from cones respectively. Phytochemical composition studies show that *C. libani* ethanol extract has different compounds such as α-pinene, β-myrcene, 7,13-abietadiene, terpinolene, and limonene (Yılmaz et al. 2005; Loizzo et al. 2008; Zgheib et al. 2020).

It has been reported that the essential oils obtained from wood and root samples are α-, β-, and γ-himachalene, himachalol, allohimachalol, −α- and β-atlantone, β-cedrene, and (E)-10,11-dihydroatlantone (Loizzo et al. 2008, Zgheib et al. 2020). Himachalol is specific marker of *C. libani* wood oils (Saab et al. 2018). β-Himachalene oxide and longiborneol were found to be main constituents of cedarwood extract. Manool was found from *C. libani* stem and bark samples analysis (Fleisher and Fleisher 2000; Zgheib et al. 2020).

In another study, high amounts of alpha and beta pinene were found in chloroform extract obtained from seeds. These compounds are considered to be the main ingredients. The main components of the ethanol extract have been reported as oleic acid, methyl oleate, and ethyl oleate. Abietol-neoabietol, abietal, and abieta-7,13-diene, which are among the diterpenes, are other detected compounds (Zgheib et al. 2020).

**Table 8.1** Traditional usage of *Cedrus libani*

| Vernacular name | Part used | Traditional usage | Preparation | Administration | Place | Reference |
|---|---|---|---|---|---|---|
| Arez | Twigs | Rheumatism | Decoction | Rub liquid (Ext) | Lebanon: Chouf | (El-Beyrouthy et al. 2008) |
| Arez | Essential oil | Rheumatism | Mix with olive oil | Local application (Ext) | Lebanon: Chouf, Jezzine | (El-Beyrouthy et al. 2008) |
| Ariz lebnani | Bark, cones | Wounds | Decoction | External use | Lebanon | (Baydoun et al. 2015) |
| Ariz lebnani | Bark, cones | Sciatica and lumbago | Decoction | Internal use | Lebanon | (Baydoun et al. 2015) |
| Ariz lebnani | Bark, cones | Rheumatism | Oil, hydrate | External use | Lebanon | (Baydoun et al. 2015) |
| Ariz lebnani | Bark | Astringent on wounds | Powdered | External use | Lebanon: Jabal Niha | (Arnold et al. 2015) |
| Mezda, kamalak | Shoot | Peptic ulcer | | Internal use | Turkey: Kayseri | (Sezik et al. 2001) |
| Katran, Sedir | Resin, tar (from seed) | Gastrointestinal pain, analgesics | Cataplasm decoction | Consumed 2–3 times a day for 2–3 weeks | Turkey: Mersin | (Sargin and Büyükcengiz 2019) |
| Sedir, Katran | Resin, seed tar | Alopecia, wound-boil treatment hive disinfection, anti-varroa, bee diseases | Cataplasm decoction | Apply once a month | Turkey: Mersin | (Sargin and Büyükcengiz 2019) |
| Andız, Sedir | Bark of stem | Skin diseases | Decoction | Internal use | Turkey: Denizli | (Bulut et al. 2017) |
| Katran ağacı | Cones, resin | Lung diseases | Oil extraction | External use | Turkey: Adana | (Güneş et al. 2017) |
| Sedir ağacı | Stem | Callus treatment | | | Turkey: Kahramanmaraş | (Kocabaş and Gedik 2016) |
| Katran ağacı | Resin | Psoriasis | Oil extraction | External use | Turkey: Niğde | (Paksoy et al. 2016) |
| Katran ağacı, sedir, sedir ağacı | Pix, resin, cambium | Gastrointestinal diseases,pyrosis, reflux, ulcer, boil | Decoction, eaten raw, resins chewed, infusion, cinder, lixivium | Drink one glass twice a day for 2–3 weeks/chew half handful a day for 1–3 weeks/ apply 2–3 times a day for 2–3 weeks | Turkey: Mersin | (Sargin 2015) |
| Sedir | Stem, branch | Timber, firewood | – | – | Turkey: Antalya | (Senkardes and Tuzlaci 2014) |
| Sedir | Branches | Abdominal pain | Infusion | Drink one cup on an empty stomach in the morning | Turkey: Elazığ | (Hayta et al. 2014) |
| | Bark of stem | Skin diseases, antiseptic | Oil extraction | External use | Turkey: Elazığ | (Dogan and Bagci 2011) |
| Sarı katran | Tar of bark | Skin lesion, topical antifungal for skin, antiseptic | _ | External use | Turkey: Antalya | (Fakir et al. 2009) |

In another study, a total of 137 components were determined, while α- and β-pinene were the major compounds in the oil. The other major components were 1-hexen-3-yne and Bicyclo[2.2.1]heptan-2-ol (Bilir and Avci 2013).

In different studies on *C. libani* leaf ethanol extracts, β-caryophyllene and germacrene D were detected as the richest compounds and specific markers. Other main components are fenchone, α- and β-thujone, 4(14)-salvialen-1-one, camphor, 1-borneol, γ-cadinene, trans-α-bisabolene, γ-muurolene, and endobornyl acetate which were the main constituents in *C. libani* leaf essential oils. Moreover, myrcene was detected in low concentrations in leaf oils (Saab et al. 2018; Zgheib et al. 2020). α-and β-pinene, myrcene, and limonene constituted a bulk of needle volatiles (Fleisher and Fleisher 2000).

In another study, chemical compositions of different wood and bark samples were studied. Wood cell wall components were determined to be holocellulose, cellulose, α-cellulose, and lignin. Also, cell wall components of bark samples were found to be hollocellulose, cellulose, and lignin (Usta and Kara 1997). In another study, 14 components were identified from heartwood, among which α-, β-, γ-isomers of himachalene and himachalol were dominant. Low concentrations of α-, β-, and γ-atlantone were also detected (Saab et al. 2005).

The chiral monoterpene, (-)-α-pinene, was reported as the dominant enantiomer released by *C. libani* (Raber et al. 2021). When the essential oils obtained from the leaves were analyzed, β-caryophyllene, γ-muurolene, germacrene D, γ-cadinene, trans-α-bisabolene, and 4 (14)-salvialen-1-one were reported as the main components. Myrcene was found in low concentrations. Himachalol was detected in wood oils (Saab et al. 2018).

Studies show that abiotic factors had an important role in the chemical polymorphism of the essential oils of *C. libani* cones (Zgheib et al. 2020).

## 8.4 Pharmacological Activities

One of the major sesquiterpenes of *C. libani*, himachalol (7-HC), had in vitro anticancer activity when tested in some human cell lines (brain SF-268 and colon HT-29 cells). It prevented inducible skin carcinogenesis in mice. It also displayed dose-dependent anti-inflammatory activity in rat monocytes by inhibiting LPS-induced COX-2 (Elias et al. 2019, Shebaby et al. 2020).

The essential oils from and seed of *C. libani* showed in vitro antiproliferative and erythroid differentiation activity in human K562 CML cells. The essential oil was cytotoxic against CCRF/CEM and CEM/ADR5000 acute lymphoblastic leukemia cells (Saab et al. 2018, Saab et al. 2012a, b, Saab et al. 2011). Ethanol extracts and essential oils obtained from wood and cones had in vitro anti-diabetic activity (Saab et al. 2018).

*C. libani* essential oil's antimicrobial activity (MIC) was reported to be 64 μg/mL against *S. aureus* and *T. rubrum* and 512 μg/mL against *C. albicans* (Fahed et al. 2017). Its larvicide activity was also reported (Saab et al. 2018).

Some extracts (acetone, ethyl acetate, and ethanol) from the needles and shoots of *C. libani* showed acetylcholinesterase (except needle ethanol extract) and butyrylcholinesterase (BChE) inhibitory activity and metal-chelation capacity. Needle-acetone extract was the most effective in inhibiting BChE and shoot ethyl acetate extract had the highest metal-chelation capacity (Senol et al. 2015).

Essential oil of *C. libani* had remarkable wound healing activity in rats and mice in accordance with ethnobotanical records (Tumen et al. 2011).

Essential oil from wood – but not from leaves or cones – of *C. libani* showed anti-amylase activity (Loizzo et al. 2007). Essential oil from wood and ethanol extracts of cones and leaves displayed antiviral activity against herpes simplex virus type 1 (HSV-1) in vitro (Loizzo et al. 2008).

Resins' ethanol extracts from root and stem showed strong antimicrobial activity against many different microorganisms (Kizil et al. 2002). Extracts (methanol, acetone, and chloroform) of fruits, leaves, barks, resins, and cones showed antimicrobial activity against many bacterial strains – including genera *Bacillus*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Listeria*, *Mycobacterium*, *Proteus*, *Pseudomonas*, and *Staphylococcus* – tested (Diğrak et al. 1999).

Extracts of the cones showed antimicrobial activity against *Helicobacter pylori* (Yeşilada et al. 1999).

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# *Chelidonium majus* L.

9

Gamze Göger


## Abstract

*Chelidonium* genus (Papaveraceae) is widely distributed in the world. The only species of the genus is *Chelidonium majus*. The drug and the herb mainly carry isoquinoline alkaloids of the benzophenanthridine type; some of the alkaloids it carries are chelidonine, chelerythrine, and sanguinarine; and protopine can be listed as protoberberine, berberine, stylopine, and protopine. All parts of the plant carry isoquinoline-type alkaloids in varying amounts.

*Chelidonium majus* is a drug registered in the European Pharmacopoeia under the monograph name *Chelidonii herba*. The European Pharmacopoeia standardizes the drug on the total alkaloids calculated on the chelidonine and requires a minimum of 0.6% alkaloids in aerial parts. The amount of alkaloids is quite high in the latex of the plant. This latex, rich in alkaloids, turns orange-red when it comes into contact with air.

The first medical records on the plant date back to the time of Dioscorides. Latex has a strong antiviral effect and is used in the treatment of warts. The tinctures prepared from aerial parts are used as antispasmodic and cholagogues in Europe. Until now, extracts of *C. majus* and a few isolated compounds have been determined to be primarily antispasmodic and cholekinetic. Apart from these, it has been determined that the extract and the isolated alkaloids have anticancer properties and are effective against pathogenic microorganisms. *Chelidonium majus* and isolated alkaloids show anti-inflammatory effects. In this study, literature data on *Chelidonium majus* were investigated, and phytochemical and phytotherapeutic properties of the plant were discussed.



## Keywords

Greater celandine · *Chelidonium majus* · Ethnomedicinal · Bioactive composition · In vitro and in vivo studies · Toxicity · Mode of action · Commercial formulations


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## 9.1 Species (Family)

*Chelidonium majus* L. (Papaveraceae)

## 9.2 Synonym(s)

Common celandine, garden celandine, swallow wort.

## 9.3 Botanical Description

*Chelidonium majus* is a perennial herbaceous plant about 30–120 cm long and identified by small yellow flowers, its pinnate leaves, and a yellow latex, or milky juice. The flowers contain four yellow petals with two sepals each about 1 cm long. The flowers bloom from May to July. The leaves are about 15 cm long, thin, and pinnate. The roots are brownish and branched and consists of several heads. Stems are 50 cm long, yellowish, and hairy. Fruits are long, linear, and capsular with two valves. Long and cylindrical capsule contains small and black seeds. Each has an elaiosome that attracts ants (Arora, D., & Sharma;).

## 9.4 Part(s) Used

Flowering stage of aerial parts of *Chelidonium majus* L. was used for therapeutic purposes (European Pharmacopoeia). Root, stems, and yellow color latex (juice/sap) are also used in some regions in Central and Eastern Europe (Zielinska et al. 2018).

## 9.5 Distribution of *Chelidonium majus* L.

*Chelidonium majus* L. (Papaveraceae) is a perennial herbaceous plant. It is widely distributed in most of regions of Europe and Western Asia (Armenia, Azerbaijan, Kazakhstan, Mongolia, Siberia, Iran, and Turkey) (Baytop 1999). It is also found in North Africa in Macaronesia, Algeria, and Morocco and introduced in Georgia from West America (Bozhadze et al. 2013).

## 9.6 Local Names

The plant is referred to by many common names such as great celandine, celandine poppy, swallow-wort, elon-wort, felonwort, and rock poppy tetterwort (Gilca et al. 2010; Maji and Banerji 2015). In China, *C. majus* is known as bai-qu-cai (Gilca et al. 2010). It also grows in North Anatolia of Turkey (Davis 1965) and known as "Kırlangıç otu, Sultan otu, Sarılık otu, Yaraotu, Temra otu, and Mayasıl otu" in Turkish folk medicine (Baytop 1999; Kültür 2007).

## 9.7 Comparison of Traditional/Ethnomedicinal/Local Uses: In Turkey and Throughout the World (Asia and Europe)

*Chelidonium majus* L. is used for traditional medical treatment in many countries of the world, especially in Europe and China. Traditional uses of *C. majus* throughout the world were listed in Table 9.1.

## 9.8 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques (Classification and Structures of Few Representatives)

*Chelidonium majus* is known for its alkaloids. The amount of alkaloids is 2% in the aboveground parts and 3–4% in the root. The amount of alkaloids in

**Table 9.1** Traditional uses of *Chelidonium majus* throughout the world

| | | Uses of plant | References |
|---|---|---|---|
| Chinese medicine | | Blood stasis, menstrual pain, peptic ulcer, prevention of cramps and cough ascites, anti-jaundice, diuresis in edema | Gilca et al. (2010) |
| Europe | The juice of the plant | Liver diseases, oral infections,<br>Gastric ulcer, and tuberculosis.<br>The juice of the plant is used externally to eliminate opacities of the cornea and warts and to heal skin ulcers | Gilca et al. (2010) |
| Northern Albanian | | Anti-jaundice | Pieroni et al. (2005) |
| North-West Greece | | Spasmolytic of bronchi; stimulates cardiac function; increases blood pressure, relieves stomachache and diseases,<br>Liver spasms, epidemic hepatitis; regulates bile secretion;<br>Treats skin diseases (herpes, foot corns) | Vokou et al. (1993) |
| Turkey | The aerial parts of plant and latex | Blister rashes, scabies, and warts | Baytop (1999) |
| Turkey | Latex | Hemostatic, itching, eczema, and inflamed wound and warts | Kültür (2007) |
| Turkey | Aerial parts | Hepatitis | Kültür (2007) |

the plant varies according to different plant organs. The amount of alkaloid changes in the plant during the day. When the aboveground and underground parts are compared, the amount of alkaloids is higher in the root part. The highest alkaloid content is found in latex. The alkaloid content in latex is about 30 times higher than in leaves and 10 times higher than in root. Moreover, while the amount of alkaloid decreases in the plant at night, it increases during the day (Zielinska et al. 2018).

Alkaloids are isoquinoline-type alkaloids and can be classified into two subgroups: benzophenantridine type (chelidonine, chelerythrine, sanguinarine) and protoberberine type (coptisine, berberine). The most abundant in the plant are chelidonine, berberine, and coptisine, while the roots contain more sanguinarine and chelerythrine. In addition, *C. majus* carries organic acids, terpenes, and flavonoids (Seidler-Lozykowska et al. 2016).

Generally, there are five groups of alkaloids in the plant: phenanthridine, protoberberine, protopine, quinolizidine, and aporphine (Kadan et al. 1990, 1992; Pavao and Pinto 1995; Petruczynik et al. 2002; Necas et al. 2005; Sarközi et al. 2006a, b; Zhou et al. 2012; Kedzia et al. 2013; Grosso et al. 2014; Poormazaheri et al. 2017).

Phenanthridine derivative alkaloids are chelidonine and derivatives, (+) chelidonine, α-(+)-homochelidonine, 10-hydroxychelidonine, 10-hydroxy-homochelidonine, isochelidonine, norchelidonine, oxychelidonine, and dihydrochelidonine. Phenanthridine derivative alkaloids are **chelerythrine** and derivatives, dihydrochelerythrine and 8-hydroxydihydrochelerythrine, and **sanguinarine** and its derivatives, oxysanguinarine, dihydrosangunarine, 8-hydroxydihydrosangunarine, sanguinarine, and N-demethyl-9,10-dihydrooxysanguinarine.

| Other components | Parts of *C. majus* | Components | References |
|---|---|---|---|
| **Caffeoyl acid derivatives** | Aerial parts | Rosmarinic acid | Grosso et al. (2014) |
| **Hydroxycinnamic acids and derivatives** | Aerial part | Caffeic acid, p-coumaric, ferulic<br>Caffeoyl-threonic acid, Caffeoyl-glyceric acid, Caffeoylmalic acid | Hahn and Nahrstedt (1993) |
| | Aerial part | Genistic, *p*-hydroxybenzoic | Wojdyło et al. (2007) |
| | Aerial part | Caffeoyl-threonic acid, Caffeoyl-glyceric acid, Caffeoylmalic acid | Grosso et al. (2014) |
| **Flavonoids** | Steams, leaves, and flowers | 5′-Methoxyflavonol<br>6′-Methoxyflavonol | Stancic-Rotaru et al. (2003) |
| | Aerial part | Kaempferol rutinoside<br>Quercetin rutinoside<br>Isorhamnetin glucoside | Grosso et al. (2014) |
| **Triterpenes** | **Aerial part** | 1-oxo-3α-hydroxy-22(30)-hopen-29-oic acid<br>3α-hydroxy-22(30)-hopen-29-oic acid | Deng et al. (2016) |
| **Organic acids** | | Chelidonic, citric, malic, succinic | Kopytko et al. (2005) |
| **Micro- and macro-elements** | **Fresh aerial part** | B, Ca, Cr, Cu, Fe, K, Li, Mg, Mn, Na, S, Zn | Then et al. (2000); Arora & Sharma (2013) |
| | **Crude material (aerial part and root) Infusion, decoction and alcoholic extracts** | Al, As, B, Ba, Ca, Cd, Co, Cr, Cu, Fe, Hg, K, Li, Mg, Mn, Mo, Na, Ni, P, Pb, S, Ti, V, Zn | Sarközi et al. (2005) |
| | **Commercial product** | Ca, Mg K and Na | Stef et al. (2010) |
| **Carotenoid** | **Flower** | Lutein, zeaxanthin diepoxide, flavoxanthin, chrysanthemoxanthin | Horvath et al. (2010) |
| **Proteins-lectin** | **Seed** | Lectin | Peumans et al. (1985) |
| | **Latex** | Phytocystatin as chelidocystatin | Rogelj et al. (1998) |
| | Root and leaf latex | 21 proteins | Nawrot et al. (2007a, b; 2008; 2013; 2014; 2017a, b) |

(−)-turkiyenine is an alkaloid that was isolated from Turkish *Chelidonium majus* (Kadan et al. 1990).

## 9.9 Other Components

For the isolation of alkaloids from plants by conventional methods, generally, the dried and ground herbal drug, which is thought to contain alkaloids, is extracted with an apolar solution. In this way, fixed oils and other fatty acids are removed from an oily plant part such as a seed.

The plant material, whose apolar metabolites have been removed, is re-extracted with methanol, ethanol, or their aqueous solutions. Removing the solvent of the filtered extract under reduced pressure yields a crude extract rich in alkaloids and possibly some other phenolic substances. To separate alkaloids from this crude extract, weak diluted acids are used. These acidic solutions, added to the extract with a solvent immiscible with water, for example, ethyl acetate or chloroform solution, will cause the alkaloids to form salts. The alkaloids in the salt form will dissolve in the aqueous part. In the

organic phase that does not mix with water, more basic or neutral alkaloids will be found (Zielinska et al. 2018).

In ESCOP 2003, *Chelidonium* monograph, it is stated that the water-soluble alkaloid salts of the plant are consumed in the form of infusion. Studies have determined that 60% of methanol extract made with aerial parts of *C. majus* contains almost 0.8% alkaloids (Boegge et al., 1996). In another study conducted with different plant samples, it was determined that the total amount of alkaloids increased by 1.6% with the alcohol ratio increasing to 70% (Vahlensieck et al., 1995). For traditional use in Europe, 45%, 25%, and 70% ethanol tinctures of *Chelidoni herba* are used (Barnes et al. 2007; EMA, 2011).

Modern techniques were also used for the extraction of *Chelidonium* alkaloids, and one of them is supercritical fluid extraction (SFE). SFE is a technique that is used in the properties of supercritical fluids between liquid and gas states, so that the solvent diffuses rapidly like a gas but dissolves like a solvent. Carbon dioxide ($CO_2$) is generally used for this purpose.

In a study, the effects of adding volatile polar solvents into $CO_2$ on alkaloid yield and composition were investigated. The results showed that high-intensity $CO_2$ is sufficient for chelidonine, the main alkaloid of the plant. Other *Chelidonium* alkaloids were found to be obtained by using isopropanol as a modifier. It was observed that the extract yield was the highest when the isopropanol/diethylamine mixture was used as a modifier (Ganan et al. 2016a, b). Solid phase extraction (SFE) has been also found effective in the isolation of chelidonine, coptisin, sanguinarine, and berberine (Kursinszki et al. 2006).

Sarkozi et al. used the conventional methods described above together with ultrasound-assisted extraction (USAE) techniques for the isolation of alkaloids from the *Chelidonium majus* (Sarközi et al. 2006a, b).

Zhou et al. extracted *Chelidonium* alkaloids using ultrasonic extraction, heat reflux extraction, and microwave-assisted extraction techniques and compared the results. They determined that microwave-assisted extraction is the most efficient method under the correct parameters among the three techniques (Zhou et al. 2012).

## 9.10 Scientific Evidences: Pharmacological Activities (all Major Therapeutic Activity with In Vitro and In Vivo Studies and Mechanism of Action)

### 9.10.1 Antibacterial Activity

Ethanol (EtOH) extract of *Chelidonium majus* was determined to have antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}Ra$ and was found at minimum inhibitory concentration (MIC) with 50 μg/mL (Tosun et al. 2004). The antibacterial activity of chelerythrine (100 mg/mL) against *Streptococcus mutans* 25,175 was found (Cheng et al., 2006). EtOH extract (80.0%) from roots of *C. majus* was tested against *Escherichia coli*, *Bacillus cereus* (MIC = 15.63 μg/mL), *Pseudomonas aeruginosa*, *Staphylococcus aureus* (MIC = 62.50 μg/mL), and *Candida albicans* (MIC = 62.50 μg/mL). Extract from aerial part was found as not active (Kokoska et al., 2002).

The alkaloids, 8-hydroxydihydrosanguinarine and 8-hydroxydihydrochelerythrine from *C. majus*, were potently active against methicillin-resistant *Staphylococcus aureus* with MICs/MBCs ranging from 0.49 to 15.63/1.95 to 62.50 μg/mL, respectively (Zuo et al., 2008).

Methanol (MeOH) extracts of aerial parts and roots of *C. majus* were tested against *Pseudomonas aeruginosa* ATCC 14452, *Klebsiella pneumoniae* ATCC 700603, *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 6538, and *Candida albicans* ATCC 10231. MeOH extracts of aerial parts and roots were found to be effective against Gram-positive bacteria with MIC of 31.25–62.5 mg/L. Individually tested alkaloids, sanguinarine, protopine, coptisine, chelidonine, chelerythrine, berberine, and allocryptopine, were found to be active against *S. aureus* and *P. aeruginosa* in the range of between 1.9 and 125 mg/L and between

31.25 and 62.5 mg/L against *C. albicans* (Zielinska et al. 2019).

Moricz et al. (2015) tested isoquinoline alkaloid components as chelidonine, sanguinarine, chelerythrine, berberine, coptisine, corydine, stylopine, and their dihydro and 6-acetonyldihydro derivatives by direct bioautography via thin-layer chromatography method against *Bacillus subtilis* ATCC 6633 and *Escherichia coli* ATCC 25922. Chelidonine, sanguinarine, and chelerythrine showed antibacterial effect against *E. coli* (Moricz et al., 2015).

Biofilm formation of inhibition activity of chelerythrine and sanguinarine was evaluated against *S. aureus* ATCC 6538P and *S. epidermidis* ATCC 35984. Sanguinarine ($EC_{50}$ = 24.5 μM) and chelerythrine ($EC_{50}$ = 15.2 μM) possessed a similar inhibitory activity against *S. aureus* (Artini et al. 2012).

### 9.10.2 Antiviral Activity

The antiviral effects of *Chelidonium* extracts are due to the anti-reverse transcriptase activity of alkaloids such as protoberberine and benzophenanthridine (Tan et al., 1991). The alkaloids chelidonine ($IC_{50}$ = 200 μg/mL) and berberine ($IC_{50}$ = 100 μg/mL) were active against HIV-I reverse transcriptase enzyme (Tan et al., 1991). In vitro study notified that the benzophenanthridine alkaloidal fractions of different parts of *C. majus* displayed virucidal effect against herpes simplex (HSV-1) and adenovirus types 5 and 12 [Kery et al., 1987].

The crude extract of *C. majus* was found to inhibit HIV-1 and this effect contributed to its sulfated polyglycosaminoglycan ingredient (Gerencer et al., 2006). In addition, alkaloid-rich extracts of C. majus showed antiviral activity against various virus strains. Ethanol extract of

| Brand name | Supplier | Active ingredients |
|---|---|---|
| Vesevedo | Naturland (Hungary) | *Chelidonium majus, Solidago virgaurea L., Urtica dioica L., Equisetum arvense L., Agrimonia eupatoria L.* |
| Choleodoron | Weleda GmbH & Co. KG (Austria) | *Chelidonium majus, Javanese turmeric* |
| Demerung | Laboratorio Biotecnoquímica (Venezuela) | *Fucus, Chelidonium majus Coffea arabica, Equisetum arvense L.* |
| Choleodoron | Weleda AG (Switzerland) | *Chelidonium majus, Javanese turmeric* |
| Syrop Sosnowy Złożony | Aflofarm Farmacja Polska (Poland) | *Calcium lactate, Chelidonium majus Codeine phosphate, Pimpinella anisum, Scots pine* |
| Iberogast | Bayer Vital GmbH (Germany) | *Iberis Amara, chamomile Mentha × piperita L., Chelidonium majus Silybum marianum L., Melissa officinalis L. Carum carvi L., Glycyrrhiza glabra L. Angelica archangelica L.* |
| Iberogast | Bayer A/O Russia (Russia), (Switzerland), Poland, Spain, Netherlands, Czech Republic | *Iberis Amara, Angelica archangelica L. Chamomile, Carum carvi L., Silybum marianum* L., *Melissa officinalis L., Mentha × piperita L. Chelidonium majus, Glycyrrhiza glabra L.* |
| Herpesil | Naturland (Hungary) | *Chamomile, Chelidonium majus Melissa officinalis L., Solidago virgaurea L. Pulmonaria, Thymus vulgaris L, zinc sulfate* |
| Aporil | Qualiphar SA (Belgium) | *Salicylic acid, acetic acid, lactic acid, Thuja Chelidonium majus* |
| Stago nouvelle formule | F. Uhlmann-Eyraud SA (Switzerland) | *Chelidonium majus, Curcuma longa L. Cynara [see artichoke], boldo [see Boldo]* |

(continued)

| Brand name | Supplier | Active ingredients |
|---|---|---|
| Artecholin N Supplier | Phytopharm Kleka (Poland) | *Artemisia abrotanum, Silybum marianum* L. *Mentha × piperita* L. *Cnicus benedictus* L. *Chelidonium majus, Achillea millefolium L. Taraxacum officinale* F.H. Wigg. |
| Lanagogum | Landson, PT Pertiwi Agung Pharmaceutical Industries Ltd. (Indonesia) | *Chelidonium majus, Curcuma longa L. Spinaceae, lecithin, Peppermint oil Curcuma longa oil* |
| Enterosol | Phytopharm Kleka (Poland) | *Achillea millefolium L., Chelidonium majus Quercus robur bark, Salix purpurea L. Salvia officinalis L., Thymus vulgaris L Artemisia vulgaris* |

plant is highly effective on HSV-1 (Monavari et al., 2012).

**Available commercial formulations/products, uses, administration methods, and pharmacokinetic studies (with special focus on bioavailability and metabolism of active constituents)**

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# *Cichorium intybus* L.

# 10

Okan Arıhan

**Abstract**

Chicory (*Cichorium intybus* L.) is a biennial plant belonging to the Asteraceae (compositae) family. It has a woody character with a height reaching about 1 meter as a branched herb. Its flowers are bright blue in color. Although it originated from the Mediterranean region, it is cultivated in various regions in the world. This plant is well known for its use in ethnomedicine, and different activities of the plants were assessed with animal studies. Plant is a rich source of different chemicals, and apart from its potential medicinal properties, it is used for different purposes such as food ingredient, livestock, and cosmetic preparations.

**Keywords**

*Cichorium intybus* L · Asteraceae · Daisy family · Chicory · Hindiba · Biological activity

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## 10.1 Introduction

Chicory (*Cichorium intybus* L. – abbreviated as CI from now on) is a biennial plant belonging to the Asteraceae (compositae) family. CI is classified under family Asteraceae, sub-family Cichoriodeae and genus *Cichorium* (Choudhary et al). Although it is a perennial herb, it has a woody character and its height reaches around 1–2 meters as a branched herb. Its strong taproot goes to a length of 75 cm (Bais and Ravishankar 2001, Van Wyk et al. 1997, FAO). Its flowers are bright blue in color (FAO). Cichorium is a Greek word which refers "field". Mediterranean region is the origin of this plant but cultivated in various suitable climatic conditions in the World (Al-Snafi 2016). This plant can exist in extreme temperatures (Bais and Ravishankar 2001) which can explain its worldwide distribution (Fig. 10.1).

The names of the plant in different languages are given in Table 10.1.

## 10.2 Distribution and Status of the Species

Chicory (Cichorium intybus L.; Asteraceae) is distributed in most parts of Europe and Asia including Turkey and Iran. However due to its agricultural importance it is now dispersed to different continents and countries such as Australia,



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**Fig. 10.1** General appearance of *Cichorium intybus*. (Photo by O. Arıhan)

**Table 10.1** Vernacular names of *Cichorium intybus* in different languages

| Language | Vernacular name | Reference |
|---|---|---|
| English | English chicory, coffee chicory, succor | Choudhary et al |
| German | German Chicoree, Kaffeezichorie | |
| French | French Chicon, chicoree sauvage, endive | |
| Turkish | Hindiba, Hindibahar, Yabani hindiba | Baytop (1999) |
| Arabic | Arabic Hindaba bariah, Shikoryah | Choudhary et al |

Siberia, South America and South Africa (Bais and Ravishankar 2001; Vahabinia et al. 2019).

Species is listed as Least Concern according to IUCN (https://eunis.eea.europa.eu/species/152694).

## 10.3 Traditional/ Ethnomedicinal Uses

CI is widely used in modern Chinese herbal medicine. Ancient medical texts reveal its ethnomedicinal use in ancient China, Greece and Egypt and China. (Imam et al. 2019). CI is also an important plant in Ayurvedic of medicine and treatment of inflammatory conditions with CI roots are among many of them (Rizvi et al. 2014). CI is also used in traditional medicinal practices including heart disease (Sedighi et al. 2021a, b). CI roots are widely used in Ayurveda tradition in illnesses such as constipation, gallstones and gastro-enteritis (Saxena et al. 2011). CI is used in Iranian ethnomedicine as hepato-protective and blood purifier. In addition, it is also used for enhancing fertility (Dorostghoal et al. 2019). Apart from its use for medicinal purpose CI was also used as a coffee substitute and this is one of the main reasons for its domestication (Imam et al. 2019).

Infusions of CI root (Radix Cichorii intybi) in its 1–5% infusion forms is known for their diaphoretic, diuretic, stomachic and tonic effects (Baytop 1999). The powder of the roasted roots has also been used as a coffee substitute in Europe (Öğe 1946).

## 10.4 Composition

The composition of the plant according to individual plant parts is given in Table 10.2.

When the elemental content of the plant was examined following elements, Potassium, Calcium, Phosporus, Magnesium, Sodium were found in a decreasing order (Barry 1998).

## 10.5 Pharmacological Activities

Chicory which is well known for its culinary use it is also used for its diverse biological activities. Studies concerning biological (pharmacological) activities of the plant are given below:

### 10.5.1 Antidiabetic Activity

CI is a commonly used plant in India for the treatment of diabetes mellitus in Indian enthomedicine. Experimental diabetic rats (with 50 mg/kg STZ) were administered with 125 mg/

**Table 10.2** Chemical composition of *C. intybus*

| Plant part | Chemical composition | Reference |
|---|---|---|
| Root | Inuline, essential oil, glycosides | |
| Aerial parts | Monocaffeoyl tartaric acid, chlorogenic acid, and chicoric acid were determined in all varieties studied. However differences in phenolic and flavanoidic compounds were also observed. | Innocenti et al. (2005) |
| Root and leaf | Sesquiterpene lactones are known from root and leaf extracts. | Kisiel and Zielińska (2001) |
| N/A: | Hydroxycinnamic acid, flavone, flavonol and anthocyanin | Tardugno et al. (2018) |
| N/A: | 28β-hydroxytaraxasterol, usnic acid, β-sitosterol, 1,3-dioleylglycerate, sitoindoside II, 11β-13-dihydrolactucin and β-sitosterol-3-O-glucoside | Satmbekova et al. (2018) |
| N/A: | Guaianolides, 6-methoxyflavone, eudesmanolides, germacranolides, polyacetylene, sterol, anthocyanin, delphinidin, 3,4-dihydroxyphenethyl | Imam et al. (2019) |
| N/A: | Sonchuside A, cichoriosides, eudesmanolides, inulin, ixerisosides, magnolialide | Faraji et al. (2020) |
| N/A: | 3,4-dihydroxyphenethyl, 6-methoxyflavone, delphinidin, germacranolides, polyacetylene, sterol | Imam et al. (2019) |

N/A: Not applicable

kg CI ethanolic extract as a single dose for its effectiveness in oral glucose tolerance test and also for 14 days to see its hypoglycemic activity. Oral glucose tolerance test showed a potent hypoglycemic activity and also 14 days of administration showed a lowering of blood glucose, triglyceride and cholesterol level (Pushparaj et al. 2007). Results show that ethnopharmacological use of the plant against diabetes mellitus is valid at least as its shown in rat studies.

Aqueous CI seed extract was tested on 150 type 2 diabetes mellitus patients in a double-blind randomized clinical study. The mean hemoglobin A1c (HbA1c) level which is an important clinical parameter to assess diabetes mellitus decreased at the end of 12 weeks of administration. In addition reduction in inflammation and oxidative stress was also observed due to CI aqueous seed treatment (Chandra et al. 2020).

### 10.5.2 In Vitro Activity

Many of the phytometabolites of CI exerted cytotoxic activities in vitro, as well as antitumor action in in vivo which questions the potential of CI metabolites as antitumoral drugs (Imam et al. 2019).

Anthocyanins from red chicory in aqueous solution were evaluated for their antioxidant and in vitro cytotoxic activity. Antioxidant activity assay performed with DPPH (2,2-diphenyl-1-picrylhydrazyl) test revealed potent chemical and biological antioxidant activity which was assessed with erythrocyte hemolysis test (Migliorini et al. 2019).

Cytotoxic effects of the methanolic extracts, evaluated as cell viability, showed that it is significantly higher than the aqueous extracts of CI. This finding brings caution to use of this plant since roots are more commonly used whereas this study shows that the aerial parts (stem, leaves and flowers) should also be investigated for their biological activities (ERAY et al. 2020).

### 10.5.3 Antibacterial Activity

Water, ethanol and ethyl acetate extracts of CI showed antibacterial activity. Among those extracts ethyl acetate was found to be the most active. In addition its aqueous extract showed inhibitory activity on *Agrobacterium radiobacter* sp. *tumefaciens*, *Erwinia carotovora*, *Pseudomonas fluorescens* and *P. aeruginosa* (Petrovic et al. 2004).

### 10.5.4 Antiparasitic Activity

CI plant synthesize various antiparasitic bioactive compounds and most of the research were

conducted on sesquiterpene lactones (Peña-Espinoza et al. 2018).

Sesquiterpene lactones which are defence compounds synthesized by plants against herbivores were tested on Cryptosporidium which is an important parasite for both humans and livestock. Leaf and root extracts of CI (Cichorium intybus cv. Spadona) which are rich for Sesquiterpene lactones were shown to exert significant growth inhibition on Cryptosporidium parvum oocysts infected colon adenocarcinoma (HCT-8) cells (Woolsey et al. 2019).

CI root and leaf extracts were tested for anti-helmintic activity against Caenorhabditis elegans and the pig nematode Ascaris suum. Results showed that chicory root pulp showed significant in vitro anthelmintic activity against C. elegans and A. suum, without exerting significant cytotoxicity to mammalian cells (Peña-Espinoza et al. 2020).

Extracts from root or aerial parts of CI against the early larvae of *Anopheles stephensi* (which transmits malaria), *Aedes aegypti* (which transmits dengue fever), and *Culex quinquefasciatus* (which transmits filariasis) showed that extracts of CI has a larvicidal activity against vectors of such diseases (Imtiyaz Ali et al. 2018).

### 10.5.5 Anticancer Activity

Anticancer features of silver nanoparticles (AgNPs) synthesized using water leaf extract of CI was shown to have a potential cancer treatment modelled in an in vitro cytotoxicity setup using human breast cancer MCF-7 cells (Behboodi et al. 2019).

Methanol extract of CI has cytotoxic effects on human breast cancer tumor cells (Rahimipour et al. 2017).

### 10.5.6 Anti-inflammatory Activity

Anti-inflammatory activity of roots of chicory (ethanolic and aqueous extracts) evaluated with paw edema model in Wistar albino rats show an attenuation of serum TNF-α, IL-6, and IL-1 levels which are important markers of inflammation. In addition, they decreased malonylaldehyde levels whereas increased Catalase and GPx enzyme levels in rat paw tissue (Rizvi et al. 2014).

Aqueous extract of CI seed exerted neuroprotective effects on spinal cord ischemia/reperfusion injury in rat and this activity was mediated by the anti-oxidative and anti-inflammatory activities of the plant (Ghaffari et al. 2018).

### 10.5.7 Antioxidant Activity

Ethanol extract of CI had an antioxidant activity against free radicals shown with diphenyl-1-picyryl-hydrazyl test (Sedighi et al. 2021a).

Aqueous-methanol extract of CI seeds showed an antioxidant activity during carbon tetrachloride (CCl4)-induced liver toxicity in albino Wistar rats (Khalid et al. 2018).

### 10.5.8 Cardiovascular Activity

Hydroalcoholic extract of CI significantly decreased blood pressure in male Wistar albino rats (Sedighi et al. 2021a).

### 10.5.9 Cholesterol Lowering Activity

Ethanolic CI extract was used in experimentally induced diabetic male Sprague-Dawley rats. CI extract resulted with a significant reduction in triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) levels and significant elevation high density lipoprotein cholesterol (HDL-C) compared to lone STZ treated rats (Samarghandian et al. 2013).

### 10.5.10 Endocrine

Hairy root cultures of CI was shown to uptake and degrade DDT (1,1,1-trichloro-2,2-bis-(4′-chlorophenyl)ethane) in cellular culture media

which suggests an efficient environmental cleaner against a potent endocrine disrupting chemical (DDT) (Suresh et al. 2005).

### 10.5.11 Gastro-Intestinal Activity

Antiulcer activity of CI hydroalcolic root extract was investigated on rats with oral administration of ethanol 99.5% (dose 1 ml/200gm b.w.) and ligation of pylorus. Results show a significant antiulcer activity probably mediated with the antioxidant properties of this extract (Saxena et al. 2011).

Another study to assess gastroprotective effect of CI root extract was modelled with H. Shay's experimental ulcer model in rats. Observed effect was explained with an antisecretory activity of the extract and also stimulation of protective layer of the gastric mucosa (Krylova et al. 2015).

### 10.5.12 Hepatoprotective Activity

Alcoholic extract and one phenolic compound AB-IV of seeds of CI was tested for its antihepatotoxic activity on carbon tetrachloride induced liver damage in albino rats. Methanolic fraction and compound AB-IV presented a potent antihepatotoxic activity which was also supported with histopathological findings (Ahmed et al. 2003).

Chicory Root polysaccharides fraction CP-1 showed hepatoprotective effect in a rat model of high-fat diet induced non-alcoholic fatty liver disease. Therefore, CP-1 significantly attenuated the high-fat diet-induced NAFLD in rats via AMPK activation (Wu et al. 2018).

Chicory supplementation was found as a potential treatment in the nonalcoholic fatty liver disease (Faraji et al. 2020).

CI hydroalcoholic extract protects the liver via altering parameters such as prothrombin time, albumin, alanine aminotransferase, aspartate aminotransferase and TNF-α against injury induced by obstructive cholestasis in rats (Moloudi et al. 2021).

### 10.5.13 Lung

Chicoric acid was found as a protective agent in LPS induced Acute lung injury (Ding et al. 2019).

### 10.5.14 Neuroprotective Activity

CE extract showed alleviation of pyridoxine-induced peripheral neuropathy in rats. This beneficial effect was shown with behavior tests such as hotplate and rotarod tests and this activity is suggested to be related with modulation of GABAergic thus exerting an anti-neurotoxic effect Hasannejad et al. 2019.

In a study in which the author of this book chapter is also involved (Okan Arihan) effects of Cichorium intybus on alcohol induced brain damage was studied. C. intybus treatment altered some of the apoptotic and antioxidant parameters to exert a partial amelioration (Erkec et al. 2018).

### 10.5.15 Sexual Function

CI ethanolic leaf extract was tested in male Wistar rats against lead treatment. Results showed that CI extract has a potential protective activity against lead-induced testicular toxicity (Dorostghoal et al. 2020).

Inulin rich CI roots were given to pigs in different administration schemes. Such an administration promise positive results without any apparent side effect (Hansen et al. 2006).

Administration of ethanolic CI leave extract on adult male Wistar rats improved reproductive parameters (testis and epididymis weight, serum testosterone level and also augmented testis antioxidant enzyme levels) (Dorostghoal et al. 2019).

CI root extract on diazinon toxin administered mice shows that sexual parameters (sperm parameters, testicular tissue and testosterone) are less affected by this toxin due to protective activity of CI extract (Ahmadi et al. 2021).

### 10.5.16 Anti-Gout Activity

Antigout effect of CI was tested on colchicine treated rats which presents an attenuation of IL-1β release via suppressing the NF-κB and NLRP3 signaling pathways which is an important pathway in gout. Such findings suggest a protective effect of CI extract on gout (Wang et al. 2019).

### 10.5.17 Kidney Protective

CI extract was found to protect male Wistar rats against hydroxyapatite nanoparticle induced kidney damage (El-Masry et al. 2020).

### 10.5.18 Other Activities/Usages

Chicory is considered as a plant which can reduce nitrate leaching and deep drainage. Therefore, it is suggested to be used in attenuating the soil acidification and salinity (Li and Kemp 2005).

A study by Baltacioğlu et al. (2020) shows that a substitution of CI root extract with wheat flour during cake production caused an increase in antioxidant activity and ascorbic acid levels.

**Environmental Cleaning Aspects**
CI seedlings growing under phytotoxic diclofenac exerted some biological activities on CI plant however this chemical does not accumulate in chicory leaves which suggests no threat to human health due to CI digestion (Podio et al. 2020). Such activity may also be tested in different environmental contaminants since this plant is an edible plant contributing to nutrition of different societies. Another study Suresh et al. (2005) shows that hairy root cultures of CI suggests a breakdown of DDT pesticide due to its enzymatic breakdown in the roots. These results suggest a promising possibility to use CI as an environmental clean up plant.

**Livestock**
CI plant is a valuable plant-based food source for livestock since it contains various different macro nutrients such as proteins, carbohydrates and micronutrients such as vitamins, minerals, trace elements as well as soluble fiber (Nwafor et al. 2017). In addition, its bioactive compounds show different health promoting activities which are listed in this chapter above. Therefore it is a promising livestock feed supplement which can become more common in future.

## 10.6 Side Effects

Since it is also used as a food, CI seems safe for adult consumption. However, when taken as a medication CI extracts still needs more scientific study since there is not enough scientific information on the subject. Gastrointestinal side effects such as gas, bloating and abdominal pain can be observed due to its inulin content (Micka et al. 2017).

## 10.7 Toxicity

In parallel with its few side effects toxicity concerning CI ingestion is not a common issue. On the contrary, CI extracts have been shown to exert protective activity against certain experimental models of toxicity such as carbon tetra chloride induced liver toxicity. One animal study on the CI toxicity shows no apparent toxicity at high dosage such as 1000 mg/kg/day to rats for 28 days (Schmidt et al. 2007).

## 10.8 Commercial Formulations

### 10.8.1 Commercial Preparations Related to Well-being

A study by El-Kholy et al. (2020) showed that low-fat synbiotic yoghurt containing 1% inulin was comparable in its performance features to the full-fat probiotic yoghurt control.

### 10.8.2 Cosmetic Preparations

A human trial shows that CI root extract exerted a vitamin D like active ingredient to use in cosmetic formulations to avoid skin dryness, whereas, another study presented an improvement in skin barrier function due to 28 days of CI root extract administration (Maia Campos et al. 2016, Paseto et al. 2017).

Some commercial formulations are presented below.

https://skinsort.com/ingredients/cichorium-intybus-root-extract

https://www.arifoglu.com/chicory-herb-70g

https://goteborgsaventyrscenter.se/product/no4j8w6dlgvv/organic-inulin-chicory-root-extract-powder-20-1-cichorium-intybus

## 10.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

Present literature on CI shows that certain aspects of ethnomedicinal knowledge is sound and valid shown by scientific trials especially on animal studies. However, human trials are not sufficient for its wider use in modern medicinal approaches. In this aspect CI should stimulate more research.

## 10.10 Challenges and Future Recommendation

Although CI has a wide distribution Europe and Asia as well as Southwest Asia including Iran there is no sufficient information about its seed germination and seedling growth under different environmental factors. Therefore, more studies like Vahabinia et al. (2019) are needed to evaluate effects of different environmental parameters such as pH, salinity, temperature and water stress on different aspects of germination such as percentage, rate and uniformity as well as root and shoot length.

Also impact of different soil characteristics on secondary metabolites is another important aspect since biosynthesis of secondary metabolites and their antioxidant potential are dependent on the stress factors exerted by soil characteristics and other environmental factors (Zlatic and Stankovic 2017).

Current literature studies present a wide range of biological activity for CI. Future studies may focus more on other diseases which are becoming more common such as degenerative diseases due to increased life span of humans.

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https://www.verywellhealth.com

# *Cistus laurifolius* L.

11

Damla Kırcı and Safa Gümüşok

**Abstract**

*Cistus* (Cistaceae) genus is considered the marker of the Mediterranean climate and region and has more than 20 species worldwide. *C. laurifolius* choose soils with silicium and high altitude of the Mediterranean region with mountains. *C. laurifolius* has various ethnomedicinal usages from rheumatic pain to diabetes. *C. laurifolius* are very rich for flavonoids and essential oils. *C. laurifolius* are investigated about biological activities such as antioxidant, hepatoprotective, analgesic, antiulcerogenic, antidiabetic activity, antimicrobial, anti-inflammatory, antinociceptive activity and prostaglandin inhibitory.

**Keywords**

*Cistus Laurifolius* L. · Cistaceae · Flavanoids · Essential oils · Diabetes

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## 11.1 Introduction

*Cistus* (Cistaceae) genus is considered the marker of the Mediterranean climate and region and has more than 20 species worldwide (Gurbuz et al. 2019). *Cistus* L. or rock rose, dicotyledonous genus, is perennial herbaceous plants which has hard leaves and can be grown naturally in open areas covered with stones and infertile soils. Their seeds have strength against power of fire; they have grown after forest fires. The genus is characterized by a number of hair styles on the leaves, stems, and calyxes, like non-glandular trichomes (Papaefthimiou et al. 2014).

The genus' plant type is shrub. Leaves are opposite, exstipulate and petiolate. The sepals are 3 or 5 members. The inner sepals are smaller than the outer. Petal colour are pink or white. Stamens are all fertile. Stigma can be subsessile or on a straight style. Carpel number can be 5 or 10 (Coode 1965).

*Cistus laurifolius* is longest member of the genus. *C. laurifolius* choose soils with silicium and high altitude of the Mediterranean region with mountains (Papaefthimiou et al. 2014).

*C. laurifolius* can be 1–3 meters. Leaf type is mostly ovate, but sometimes lanceolate and acute leaves can be observed. Petiole is long, connate. Upper surface is almost hairless and sticky. Lower face is grey and covered with tomentose hairs. Flowers are lateral cyme, 3–5 flowered with long peduncules. Flower is white and



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3–5 cm. Sepal number is 3, sometimes 4. End of sepal is not cordate. Style type is changeable from short to none. Flowers open in May and June (Coode 1965). Ankra University Herbarium sample of *Cistus laurifolius* is given in Fig. 11.1.

Plant has one synonym: *Ladanium laurifolium* Spach. *Cistus laurifolius* has many names in Turkish: Defne yapraklı laden, Domuzpamuklusu, Domuzpamukluğu, Pamukla, Fatmagül, Garahan, Tavşancıl, Karahan, Garahan otu, Tavşanak, Karahan otu, Tavşancık, Murt, Murtotu, Tavşanaki, Tavşan pıynarı, Yuvan, Süt püşüren, Yavşancıl, Tistüs, Karakan yaprağı, Karakan otu, Pinar, Davşanak, Tavşanak ağacı, Davşanak ağacı, Tavşancıl, Davşancıl, Yetgüm, Yavşanak and Karağan. The plant is named laurel-leaved cistus or laurel-leaved rock rose in English, hélianthème in French, jara o estepa de montaña in Spanish, esteva in Porteguese, ροκ τριαντάφυλλο in Greek and rosa di roccia in Italian. Additionally, in Morocco, the plant is known as ouchtobou (Nassif and Tanji 2013).

## 11.1.1 Distribution

*C. laurifolius* are naturally grown in Mediterranean climate and region. The following


**Fig. 11.1** Herbarium sample of *Cistus laurifolius* L. from AEF herbarium

countries are natural living habitat for *C. laurifolius*, France, Greece, Italy, Portugal, Spain and Turkey (Kewscience 2021), and distribution of *C. laurifolius* is given in Fig. 11.2. Sometimes it can be seen in Centre Europe (Coode 1965). But some ethnobotanical data says that *Citrus laurifolius* are naturally grown in Morocco.

*C. laurifolius* choose soils with silicium and high altitude of the Mediterranean region with mountains (Papaefthimiou et al. 2014).

**Ethnobotanical Knowledge**

Plant has very different range of treatment in ethnomedicine but limited locality because it is native to Mediterranean region. Traditional uses of *Cistus laurifolius* are summarized in Table 11.1.

## 11.1.2 Chemical Composition

The majority of *Cistus* species have a strong aromatic and sweet scent, and the source of these odours is essential oils, which is generally distinct amounts of a monoterpene, diterpene and sesquiterpene compounds. Some *Cistus* genus secretes "labdanum", and the secretion is found on stems and leaves in summer. Depending on the *Cistus* genus, monoterpenes (borneol, carvacrol, pinene and camphor), oxygenated sesquiterpenes (zingiberene and viridiflorol) and diterpenes (abietatriene and manoyl oxide) are the very common and abundant components of essential oils of *Cistus* (Barrajón-Catalán et al. 2016). The main compounds of *C. laurifolius* are comprised of terpenes such as nonacosane and borneol in Turkey (Öğütveren and Tetik 2004). Some terpenoids of *C. laurifolius* are given in Fig. 11.3.

Flavonoids are highly effective secondary compounds in terms of biological activity. In this context, there are many studies on *C. laurifolius* plant. Many flavonoid components are isolated from different sections of this plant using various solvent systems. Flavanoid structures of *C. laurifolius* are given in Fig. 11.4.

The resin of *C. laurifolius* leaves was found quercetin and quercetin 5,3′–dimethyl ether, 3,5,3′-trimethyl ether which is flavonol aglycones (Vogt et al. 1988). Water extract of *C. laurifolius* herba was identified flavonoids and polyphenolic compounds such as flavanol ((−)-(epi)gallocatechin), flavonol (quercitrin, myricitrin), uralenneoside, gentisoyl glucoside, myrciaphenone-B and *p*-coumaroylquinic acid (Barrajón-Catalán et al. 2011). Additionally *C. laurifolius* younger leaves are especially a very producer of tannins all the year (Ammar et al. 2004).

Ethanolic extract of *C. laurifolius* herba has found flavonoids such as quercetin-3-methyl

**Fig. 11.2** Distribution of *C. laurifolius*

**Table 11.1** Ethnomedicinal data of *Cistus laurifolius*

| Locality | Part of plant | Treatment | Usage | Source |
|---|---|---|---|---|
| Morocco | Seed<br>Mixture of *C. laurifolius* (0.93), *Citrus sinensis* (0.85), *Fraxinus dimorpha* (0.88), *Alpinia officinarum* (0.83), *Nasturtium officinale* (0.86), *Dysphania ambrosioides* (0.88), *Thymus maroccanus* and *T. willdenowii* | Cold treatment, general health and gastrointestinal diseases<br>General health | Oral ingestion<br>In mixture | Teixidor-Toneu et al. (2016) |
| Turkey | Heated leaves<br>Seeds | Rheumatic pain<br>Asthma | Wrapped around body part<br>Chewed | Kargıoğlu et al. (2008) |
| Morocco | Leaves | Diabetes | Oral decoction | Katiri et al. (2017) |
| Turkey | Flowering branches | Antidiarrhoea | Oral infusion | Bulut and Tuzlaci (2013) |
| Turkey | Dried leaves | Diabetes | 50 g of leaves boiled in 250 mL water. Decoction used twice a day before meal | Durmuskahya and Ozturk (2013) |
| Turkey | Branches | Diabetes | Infusion -O. ad. For a whole week, intake a teacup twice per day | Polat and Satıl (2012) |
| Turkey | Roots<br>Buds<br>Leaves | Hypercholesterolemia, diabetes, intestinal spasm and costiveness<br>Diaphoretic, antipyretic | Decoction, 2–3 weeks, drink a teacup 2 to 3 times per day<br>Mash | Sargın et al. (2013) |
| Spain | Aerial part | Antialgic, anti-inflammatory<br>Antiseptic<br>Antiulcerous | Lotion<br>Symptomatic<br>Oral<br>Curative | Agelet and Valles (2003) |
| Turkey | Leaves | Cancer | Its leaves are drunk like tea for cancer treatment by brewing | Nacakci and Dutkuner (2018) |
| Morocco | Seeds<br>Flowers | Diabetes | Oral powder | Idm'hand et al. (2020) |
| Turkey | Leaves | Rheumatismal diseases<br>Diabetes | Wrapped into the areas<br>İnfusion, daily taken | Kargıoğlu et al. (2010) |
| Turkey | – | Painkiller, peptic ulcer and rheumatic pain | – | Yeşilada (2009) |
| Turkey | Leaves | Ache treatment | Decoction | Albayrak and Daşkın (2018) |
| Turkey | Flower buds<br>Leaves | Asthma, cancer, high fever, lumbago, peptic ulcer, rheumatism, urinary inflammation, as diuretic, tension regulator | Decoction | Günbatan et al. (2016) |

(continued)

**Table 11.1** (continued)

| Locality | Part of plant | Treatment | Usage | Source |
|---|---|---|---|---|
| Turkey | Leaves | Hypertension | Decoction, infusion | Olcay and Kultur (2020) |
| Turkey | Roots<br>Flowers<br>Leaves | Navel displacement and abdominal pain<br>Dysentery treatment<br>Antitussive, expectorant | Wrapped to area<br>Oral | Deniz et al. (2010) |
| Turkey | Roots<br>Buds<br>Leaves | Diabetes, oedema | Decoction, for 2–3 weeks, drink one teacup 2–3 times per day | Sargin et al. (2015) |
| Turkey | Buds | Diabetes | Infusion, drink as tea | Ertuğ (2004) |
| Turkey | Flower<br>Flower buds | Ulcer treatment | Decoction, oral | Kültür et al. (2017) |
| Turkey | Flower buds<br>Leaves | Unspecified cancer | Decoction | Bozyel et al. (2019) |

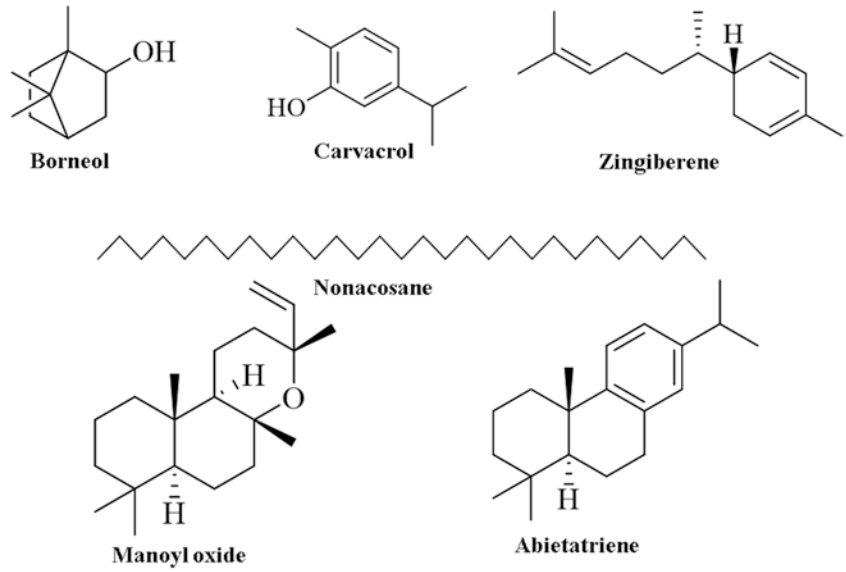


**Fig. 11.3** The terpenoids of *C. laurifolius*

derivative, naringenin, apigenin, quercetin, luteolin and kaempferol. Six flavanoids are isolated by Ustün et al. (2006) . One of the components, isorhamnetin (quercetin 3-methyl ether), has very high antiulcerogenic activity (Ustün et al. 2006). This plant has isolated three compounds 3,7-O-dimethylkaempferol, 3,7-O-dimethylquercetin and 3-O-methylquercetin (Küpeli and Yesilada 2007).

In addition, it contains sesquiterpenes, diterpenes laurifolic acid (6β,8-dihydroxy-ent-13E-labden-15-oic acid), salmantic acid, salmantidiol, lignan glycosides (berchemol 9-O-rhamnoside, olivil 9-O-β-d-xyloside) and phenolic acids (ellagic acid, gallic acid and chlorogenic acid), coumarin scopoletin and inositol (de Pascual Teresa et al. 1983, 1986; Sadhu et al. 2006; Küpeli et al. 2006; Orhan et al. 2013). The glucosides were purified in the form of the acetyl derivatives: 1,3-dihydroxy-5-β-D--glucopyranosiloxybenzene, 4-β-D-glucopyranosiloxyacetophenone, β-D-glucopyranosiloxyethane, and roseoside (de Pascual Teresa et al. 1986).

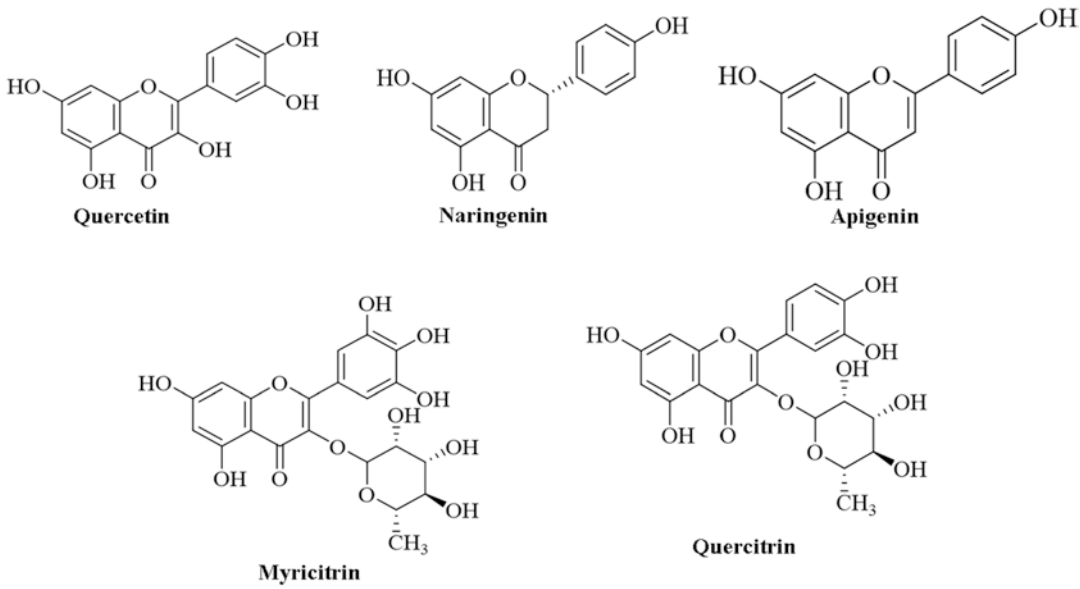


**Fig. 11.4** Flavanoid structures of *C. laurifolius*

### 11.1.3 Biological Activities

There are many studies on *Cistus laurifolius*. These studies have demonstrated biological activities such as antioxidant and hepatoprotective (Küpeli et al. 2006), analgesic (Ark et al. 2004), antiulcerogenic (Yeşilada et al. 1997, Ustün et al. 2006), antidiabetic (Orhan et al. 2013), antimicrobial (Barrajón-Catalán et al. 2016), antinociceptive and anti-inflammatory activities (Küpeli and Yesilada 2007) and prostaglandin inhibitory (Sadhu et al. 2006).

- ***Antimicrobial Activity***

Several research results have recorded important antimicrobial activity and antioxidant activity. Especially essential oils of *Cistus* species are affected against a broad variety of fungal and bacterial diseases. The reason for this effect is thought to be due to the terpenes in the essential oil (Barrajón-Catalán et al. 2016).

The methanol extract and its fractions *of C. laurifolius* leaf are used strains of *Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Proteus mirabilis, Acinetobacter baumannii, Enterococcus faecalis* and *Staphylococcus aureus* for antimicrobial activity and is used *Candida parapsilosis* and *C. albicans* for antifungal. Its fractions of *C. laurifolius* are found minimum inhibitory concentration (MIC) 32 µg/mL, so antimicrobial activity is strong against Gram-negative bacteria (Üstün et al. 2016).

Extracts of *C. laurifolius* fruits and leaves were prepared with different polarity solvents. The extracts and fractions were studied antimicrobial activity against six bacteria (*Escherichia coli*, *Bacillus subtilis*, *B. cereus*, *Streptococcus faecalis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*) and one fungus (*Candida albicans*). Against *E. coli*, butanol extract had a minor antibacterial activity, while all extract and fractions have high activity against *C. albicans* (Güvenç et al. 2005).

The other study done two different methods for antiviral activity. 50% ethanol extract of *C. laurifolius* leaves, the antiviral activities were researched both in dark and light, and the result shown low activity of antiviral photosensitizers (Hudson et al. 2000).

Moreover, the extract and its fractions were investigated *Herpes simplex* virus-1 (HSV-1) for

antiviral activity. The hexane extract of *C. laurifolius* has shown antiviral activity against PI-3 (Üstün et al. 2016).

- ***Antioxidant and Hepatoprotective***

In the previous research, the ethanol extract of *Cistus laurifolius* leaves and fractions were studied in the in vitro antioxidant activity and against acetaminophen-induced liver damage in mice. Quercetin-3,7-dimethyl-ether (oral dose 114 mg/kg) is determined to have strong antioxidative effect (Küpeli et al. 2006). Isolated compounds of the methanol extract leaves are analysed by DPPH method. The antioxidant activity of 8 of the 16 compounds isolated in this area was found to be very high (Sadhu et al. 2006).

In the study, *n*-butanol and ethyl acetate fractions of *C. laurifolius* exhibited the best effect against FRAP and DPPH methods (Akkol et al. 2012).

- ***Antiulcerogenic Activity***

An ulcer is a numerous common cause of human suffering nowadays. The disease is the source of an imbalance between the lumen and protective mechanisms within the gastroduodenal mucosa. Emotional stress, trauma, anxiety, burns and haemorrhagic surgical trauma are known to cause severe gastric irritation. But the disease mechanism is just not well-known (Nidavani et al. 2014). *C. laurifolius* is recognized to suppress *H. pylori* colonization to decrease gastric inflammation by chemokine release (Kuna et al. 2019).

Antiulcerogenic activity is investigated both in vivo which is used in immobilization-induced stress and water immersion ulcer model and in vitro is a method in anti-Helicobacter pylori activity (Yeşilada et al. 1997, Ustün et al. 2006). Six flavonoids are isolated by in vitro method. The number of compounds, isorhamnetin (quercetin 3-methyl ether), has the highest antiulcerogenic activity (Ustün et al. 2006). The flower buds and flower of *C. laurifolius* are prepared by the bioassay-guided fractionation of the material. Extracts are used for subcutaneous injection and per os administration. The aqueous extract is investigated as an effective antiacid activity (Yeşilada et al. 1997). In the other research, *C. laurifolius* chloroform extract showed great anti-*H. pylori* effect due to flavonoid compounds (3′-demethoxysudachitin and sudachitin) (Bovicelli et al. 2007).

Therefore, in these studies, purified flavonoids can be used as a supplement to treat *H. pylori* infection (Üstün et al. 2016).

- ***Antidiabetic Activity***

Diabetes mellitus is responsible for disturbing carbohydrates, protein and fat metabolism. The disease causes decreased sensibility of the tissue to insulin and a shortage of insulin secretion (Arulselvan et al. 2014).

In the study, it is shown that 250 and 500 mg ethanol extract doses are reduced glucose levels in the blood of the STZ-induced diabetic rats. The extract has the inhibitory effect on enzymes involved in carbohydrate digestion (α-amylase and α-glucosidase) and blood glucose level (Orhan et al. 2013).

The inhibition of enzymes responsible for the hydrolysis of carbohydrates (α-amylase and α-glucosidase) takes longer to digest times of all carbohydrate derivatives, in this case, causing a reduction in hyperglycaemia and in the glucose absorption ratio (Orhan et al. 2013).

In the other in vitro research, *C. laurifolius* (fruit) is investigated on haematological and aldose reductase (AR) inhibitory activities. Diabetes mellitus is a common situation with various complications. Polyol pathway is a very important aldose reductase (AR) enzyme. The study's results showed that the blood coagulation process was effectively inhibited. Ethyl acetate extract of *C. laurifolius* leaves was isolated three flavonoids. One of the compounds, quercetin-3-O-methyl ether, was found to be as strong as that of epalrestat, which is known to be a treatment associated with diabetes (Enomoto et al. 2004).

- ***Analgesic Activity***

Using acetic acid-induced tail immersion and tail-flick experiments in rats, the analgesic effect of *C. laurifolius* extracts prepared using the combined extract methods is evaluated. The number of writings induced with the acetic acid test is found in 500 mg/kg, i.p. (chloroform extract). This study observed that *C. laurifolius* leaves include antinociceptive components. So, the effect mechanism of chloroform extract is performed through a central mechanism (Ark et al. 2004).

- ***Anti-inflammatory and Antinociceptive Activity***

Prostaglandins are well-known mediators for their inflammatory effects, and the components affecting its receptors may cause a decrease such as inflammation, pain and fever. PGE2 receptors are an essential role in rheumatoid arthritis pathogenesis. Inflammatory disorders that persist over time were determined to increase vulnerability to cancer build-up, and long-time use of COX-2 and NSAIDs inhibitors of PGs is reported to reduce cancer incidence (de Visser et al. 2006; Sadhu et al. 2006). Sadhu et al. investigated that the *C. laurifolius* extract showed PG inhibitory effect by the Magnus method. Methanol extract and isolating 15 compounds have inhibitory efficacy of PG (30–95 μM). Furthermore, methanol extract is included as the main compound of 3-O-methyl quercetin (Sadhu et al. 2006).

Yeşilada and Küpeli (2007) isolated major compounds of ethanol extract of *C. laurifolius* leaves. The flavonoid structure compounds are 3,7-O-dimethylquercetin, 3-O-methylquercetin and 3,7-O-dimethylkaempferol and are shown to antinociceptive effects and in vivo anti-inflammatory (Küpeli and Yesilada 2007).

- ***Anticholinesterase***

Ethanolic extract, its fractions and purified flavonoids are tested anticholinesterase activity against acetyl- (AChE) and butyryl-(BChE) cholinesterase. The ethanolic extract has the strongest acetylcholinesterase inhibition activity (80.07 ± 1.06% at 200 μg/mL) (Akkol et al. 2012).

### 11.1.4 Toxicological Studies

Several secondary metabolites produced by *Cistus* genus have affected toxic in mammals. Consuming *Cistus* genus in cattle was determined some lethal toxicosis cases. Also, consuming *Cistus* in sheep was shown lipofuscinosis and convulsions in the central nervous system. The tannins and gallic acid, which are harmful to the kidneys and liver, are the most toxic components (Papaefthimiou et al. 2014).

Flavonoid-rich extract of *C. laurifolius* has a degenerative effect on the peripheral nervous system due to convulsive syndrome in mice. (Bregante et al. 1981).

*C. laurifolius* suppresses precancerous changes and inhibits cytokine. This mechanism is realized by suppressing nuclear factor-kappa B DNA binding, which produces apoptosis and suppresses mutagenesis (Kuna et al. 2019).

3,7-O-Dimethylquercetin, 3,7-O-dimethylkaempferol and 3-O-methyl quercetin, purified ethanolic extract of *C. laurifolius* leaves, are shown per os without inducing any possible gastric damage as well as acute toxicity (Küpeli and Yesilada 2007).

The Cistus genus has Oleoresin, called labdanum and is used for characterisation. But its oral consumption is restricted due to reported nephrotoxic, hepatotoxic and neurotoxic effects (Barrajón-Catalán et al. 2016).

Its fractions and methanol extract of *C. laurifolius* are investigated parainfluenza-3 (PI-3) using Vero cell lines and Madin-Darby bovine kidney. The hexane fraction has cytopathogenic activity of 8-32 μg/mL so it is very promising fraction regarding its cytotoxic effect (Üstün et al. 2016).

## 11.2 Conclusion

In conclusion, the marker of the Mediterranean climate and region is *Cistus* genus. *Cistus laurifolius* has medicinal importance.

*Cistus laurifolius* has very different local uses from rheumatic pain to diabetes. Biological studies about analgesic, antiulcerogenic and antidiabetic activities are matched up with the ethnobotanical uses.

Flavonoids, volatile components, resin and diterpenes are examples of secondary metabolites, which are *Cistus* species purified. The compounds display toxicological activity and can be consumed in lower amounts due to their biological activities.

While there are many antiviral effective products on the market with *Cistus canadensis*, *Cistus laurifolius* does not have any products. Additionally, the use of several *cistus* species resins, and the use of essential oils, is now permitted as flavouring agents in low amounts. Labdanum of *Cistus* spp. is approved by the Council of Europe, which is in list number COE No: 134 while by the US Food and Drug Administration (FDA 2014) also is included in using as flavouring agent or a food additive 21CFR172.510 (Barrajón-Catalán et al. 2016). The species are needed further studies on the way to become a medicine.

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# *Coriandrum sativum* L.

12

Zekiye Ceren Arituluk

**Abstract**

*Coriandrum sativum* L. (coriander, cilantro, Chinese parsley) belonging to Apiaceae (Umbelliferae) family is an annual herbaceous aromatic plant widely cultivated and distributed in Asia, Europe, and Northern Africa. Coriander is a well-known culinary herb around the world and has a long history of use as a medicinal plant that dates back to 1500 BC. Dried fruits (usually called seed) and fresh leaves are the most commonly used parts of the plant. Coriander, as well as its essential oil, has been traditionally used to treat various diseases by different civilizations. This chapter covers the botanical properties, traditional uses, chemical composition, pharmacological activities, and the safety profile of coriander.

**Keywords**

*Coriandrum sativum* · Coriander · Apiaceae · Ethnomedicine · Bioactive constituent · Pharmacological activity · Safety

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## 12.1 Introduction

*Coriandrum sativum* L. (coriander, cilantro, Chinese parsley), a member of the Apiaceae (synonymous with Umbelliferae) family, is an annual aromatic plant. Coriander is an ancient herb with a long history of use. The oldest coriander fruits were discovered in the Nahal Hemar Cave in Israel (6000 B.C.). Coriander was in the list of medicinal plants mentioned in an Egyptian papyrus (1500 B.C.). In traditional Greek medicine, coriander was used by Hippocrates and Dioscorides (Abascal and Yarnell 2012; Diederichsen 1996). The plant was also used as medicine and for flavoring wine by the Romans and introduced into the northern countries of Europe (Burdock and Carabin 2009; Diederichsen 1996).

Coriander is a well-known culinary herb all over the world. It has been widely cultivated for its aromatic fruits and leaves. The dried ripe fruits and the fresh leaves have a completely different flavor from each other because of their particular essential oil compositions (Fig. 12.1). Coriander fruits (mostly called seed in the literature) have been used as spice since ancient times by different civilizations. In India, coriander fruits are popularly used as a spice and for flavoring pastry and tobacco products (Diederichsen 1996). In addition, it is the main ingredient of curry powder (Laribi et al. 2015). Fresh leaves, commonly known as cilantro, are consumed in salads, soups,



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**Fig. 12.1** Coriander leaves and fruits (commonly called seed)

and dressings in many countries including India, China, Malaysia, Indonesia, Mexico, the USA, as well as South America and the Near East (Diederichsen 1996; Laribi et al. 2015). Besides its popular use as food, coriander is an important medicinal plant. In this chapter, botanical properties, traditional uses, chemical composition, pharmacological activities, and the safety profile of coriander are summarized.

## 12.2 General Information

The genus *Coriandrum* L. is represented by only two species: *C. tordylium* (Fenzl) Bornm. (wild) and *C. sativum* (cultivated). The position of *C. sativum* in taxonomic classification is presented in Table 12.1.

*C. sativum* is an annual herbaceous glabrous plant with a slender taproot. The stem is branched, and each branch ends with an inflorescence. While basal leaves are ternately lobed to ovate segments with toothed margin, upper leaves are pinnately dissected with linear segments. The inflorescence is compound umbel. Unequal rays are 2–6 (−8). The five unequal calyx teeth are prominent. The flowers have five petals. While the central flowers of the umbellets are circular with small curved petals, the peripheral flowers are asymmetric with larger bilobed outer petals. Petals are pale pink or white. Fruit is a schizocarp, and mericarps are united. Ripe fruits are pale gold-brown, 3–4 mm long, and sub-globose with longitudinal ridges on the surface. There are 0–2 vittae on the commissural face (Diederichsen 1996; Hedge and Lamond 1972).

*Bifora loureirii* Kostel., *Coriandropsis syriaca* H.Wolff, *Coriandrum diversifolium* Gilib., *C. globosum* Salisb., *C. majus* Gouan, *C. melphitense* Ten. et Guss., *C. testiculatum* Lour. and *Selinum coriandrum* E. H. L. Krause are some of

**Table 12.1** The taxonomic classification of *C. sativum* (Al-Snafi 2016)

| Kingdom | Plantae |
|---|---|
| Subkingdom | Tracheobionta |
| Superdivision | Spermatophyta |
| Division | Magnoliophyta |
| Class | Magnoliopsida |
| Subclass | Rosidae |
| Order | Apiales |
| Family | Apiaceae |
| Genus | *Coriandrum* L. |
| Species | *C. sativum* L. |

the synonyms of the species (Diederichsen 1996; www.theplantlist.org). The common local names of the plant in different languages are given in Table 12.2.

Coriander is a tropical crop that needs loamy to moderately heavy soils for growing, an optimum temperature between 20–25 °C for germination, as well as a cool, dry, frost-free climate, especially during the flowering and seed formation stages (Sharma and Sharma 2004).

## 12.3 Origin and Distribution

The plant was first described from Italy. The origin of the plant is still unknown, but it is most probably native of the eastern Mediterranean (Coşkuner and Karababa 2007; Hedge and Lamond 1972). On the other hand, the archeobotanical findings and ancient literature support the hypothesis that the plant originated in the Near East (Diederichsen 1996). Coriander has been widely cultivated since ancient times; thus it may have spread to India, China, and rest of the world. Today, it is naturalized throughout most regions of the world including Asia, Europe, and Northern Africa (Coşkuner and Karababa 2007; Hedge and Lamond 1972; Al-Snafi 2016). India plays a major role in the cultivation of coriander. Besides India, coriander is cultivated also in Morocco, France, the Netherlands, Spain, Italy, Turkey, Rumania, Pakistan, Myanmar, Mexico, Argentina, the UK, and the USA (Khan et al. 2014).

**Table 12.2** Common names of *C. sativum* in different languages (Diederichsen 1996)

| Language | Name |
|---|---|
| Arabic | Kuzbara, kuzbura |
| Armenia | Chamem |
| Chinese | Yuan siu, hu sui |
| Czech | Koriandr |
| Danish | Koriander |
| Dutch | Koriander |
| English | Coriander, collender, chinese parsley, cilantro |
| Ethiopian | Dembilal |
| French | Coriandre, persil arabe |
| Georgian | Kinza, kindza, kindz |
| German | Koriander, Wanzendill, Schwindelkorn |
| Greek | Koriannon, korion |
| Hindi | Dhania, dhanya |
| Hungarian | Coriander |
| Italian | Coriandolo |
| Japanese | Koendoro |
| Malay | Ketumbar |
| Persian | Geshnes |
| Polish | Kolendra |
| Rumanian | Coriándru |
| Russian | Koriandr, koljandra, kišnec, kinza |
| Portuguese | Coentro |
| Spanish | Coriandro, cilantro, cilandrio, cilantro |
| Spanish | Coriandro, cilantro, cilandrio |
| Swedish | Koriander |
| Swiss | Chrapfechörnli, Böbberli, Rügelikümmi |
| Turkish | Kişniş |

## 12.4 Traditional and Ethnomedicinal Uses

In India, coriander has been used traditionally to treat digestive, urinary, and respiratory systems disorders (Laribi et al. 2015). In southern India, in the Thanjavur district, a paste made by leaves has been used internally for body heat and vomiting of blood. Besides, the fruit decoction has been used to treat dysentery, and powdered fruits have been used for headaches with *Zingiber officinale* Roscoe (Rajalakshmi et al. 2019). In the northern areas (Gilgit) of Pakistan, the whole plant has been used traditionally for the treatment of cough, dysentery, diarrhea, flatulence, jaundice, stomach problems, and vomiting (Khan and Khatoon 2008). Fruits has been traded in the herbal markets of the Rawalpindi region, and powdered fruits have been used with almonds for

better eyesight, diabetes, anemia, liver diseases, rheumatism, dyspepsia, diarrhea, and digestion problems (Ahmad et al. 2018; Bibi et al. 2014). To treat rheumatism, the infusion of fruits has been used with almond (Malik et al. 2018). In northern Thailand, coriander has been grown as a home garden plant, and aerial parts have been eaten as a fresh vegetable to treat the common cold (Panyadee et al. 2019).

*C. sativum* has been found as one of the most popular Apiaceae species used as traditional medicine in different localities of Turkey (Bulut et al. 2014). In Turkey, decoction or infusion of fruits has been used traditionally to treat headache, dizziness, dyspepsia, and stomachache as well as to enhance appetite and as a carminative and digestive agent (Bulut et al. 2014; Fujita et al. 1995; Sargın et al. 2013; Ugulu et al. 2009). Fruits have been eaten as antihypertensive (Yeşilyurt et al. 2017). Externally, crushed fruits have been used as insect repellent (Bulut et al. 2014). In Aegean region, aerial parts of the plant have been used as carminative and to treat abdominal pain (Bulut et al. 2017; Sargin et al. 2015). Leaves, fruits, and roots have been used for stomach pain, gastritis, ulcer, and heart disorders in Antakya district hosting people from different ethnic and religious communities for centuries (Güzel et al. 2015). In Cappadocia, dried fruits have been sold by herbalists as a carminative and aphrodisiac agent as well as for headaches and rheumatism (Akgül et al. 2016). Coriander candies made from dried fruits have been eaten for headache (Ulutaş Deniz et al. 2018). In northern parts of Iran, among Turkmens, the decoction of coriander leaves has been used for gastralgia and sore throat (Ghorbani 2005). In Iranian folk medicine, coriander has been used for insomnia and anxiety (Emamghoreishi et al. 2005). In Saudi Arabia and Jordon, the infusion of fruits has been used for diabetes (Laribi et al. 2015). In Morocco, coriander has been documented to be used for diabetes indigestion, flatulence, insomnia, and renal disorders, to enhance appetite, and as a diuretic (Aissaoui et al. 2008). In Algeria, different parts of the plant are used to treat diabetes (Hamza et al. 2019). In Spain, the decoction of fruits has been drunk for epilepsy (Rivera et al. 2019). In the Northeast Brazilian region, fruit infusion and fresh leaves have been used for dysphonia, abdominal cramps, gastroenteritis, and convulsion and as an expectorant (Magalhães et al. 2019).

## 12.5 Nutritional and Bioactive Composition

All parts of *C. sativum* are edible; however, the most frequent parts used are dried fruits and fresh leaves. The main constituents of coriander fruits are the essential oil (between 0.03 and 2.6%) and fatty oil (between 9.9 and 28.4%). In addition, the coriander fruits contain water (11.37%), crude fiber (28.43%), crude protein (11.49%), starch (10.53%), pentosans (10.29%), sugar (1.92%), and mineral matter (4.98%) (Coşkuner and Karababa 2007; Diederichsen 1996; Ramadan and Mörsel 2002). The coriander fresh leaves contain moisture (87.9%), protein (3.3%), carbohydrates (6.5%), and mineral matter (1.7%), as well as vitamin A (up to 12 mg/100 g), vitamin $B_2$ (up to 60 mg/100 g), and vitamin C (up to 160 mg/100 g) (Sharma and Sharma 2004; Diederichsen 1996). Essential oil, phenolic compounds, and fatty acids are among the other bioactive constituents detected in the leaves (Sahib et al. 2013). In addition, aerial parts of the plant contain high percentages of calcium (10%), phosphorus (3%), magnesium (3%), sodium (1%), and especially potassium (30%) which plays an important role in the regulation of cardiovascular system functions (Oganesyan et al. 2007).

### 12.5.1 Essential Oils

Various parts of the coriander plant including fruits, leaves, stems, and flowers contain essential oil. The yields and major constituents of essential oils from various parts of *C. sativum* from different origins have been represented in Table 12.3.

The yield and profile of essential oil vary in different parts of *C. sativum* (Table 12.3). Besides, several factors such as genotypes, geo-

**Table 12.3** The extraction methods, yields, and major constituents of essential oils from various parts of *C. sativum* from different origins

| Origin | Plant part | [a]Method | Yield | Composition | Reference |
|---|---|---|---|---|---|
| Algeria | Fruits | H | – | Linalool (73.11%), *p*-mentha-1,4-dien-7-ol (6.51%), α-pinene (3.41%), neryl acetate (3.22%), camphor (1.85%), ρ-cymene (1.76%), limonene (1.23%) | (Zoubiri and Baaliouamer 2010) |
| Bangladesh | Fruits | H | 0.4% | Linalool (37.7%), geranyl acetate (17.6%), γ-terpinene (14.4%), geraniol (1.9%), citronellal (2%), β-pinene (1.8%), citral (1.4%), citronellyl acetate (1.4%), *m*-cymene (1.3%), citronellol (1.3%), curcumene (1.0%) | (Bhuiyan et al. 2009) |
| | Leaves | H | 0.1% | 2-Decenoic acid (30.8%), *E*-11-tetradecenoic acid (13.4%), capric acid (12.7%), undecyl alcohol (6.4%), undecanoic acid (7.1%) tridecanoic acid (5.5%), *E*-undecanoic acid (5%), 2-undecenal (3.9%), dodecanoic acid (2.6%), cyclododecane (2.5%), undecanoic acid (2.1%), decanal (1.4%), dodecanal (1.3%), 2-dodecanal (1.3%), nonanoic acid (1.2%), decamethylene glycol (1.2%), 2-tridecenal (1%) | (Bhuiyan et al. 2009) |
| Brazil | Fruits | H | – | Linalool (77.48%), γ-terpinene (4.64%), α-pinene (3.97%), camphor (2.6%), ρ-cymene (2.16%), heptanal (2.06%), limonene (1.28%), geranyl-acetate (1.06%) | (De Figueiredo et al. 2004) |
| Canada | Fruits | H | 0.8–2.2% | Linalool (64–84.6%), camphor (3.4–6.2%), α-pinene (1.2–3.2%), phellandrene (1.7–4.1%), linalyl acetate (2.4–3.3%), limonene (0.7–1.8%), geranyl acetate (0.9–1.6%), *Para*-cymene (0.5–1.3%) | (Zheljazkov et al. 2008) |
| Fiji | Leaves | SD | – | *E*-2-Decen-1-ol (26%), 1-decanol (19.6%), *E*-2- decenal (9.1%), *E*-2- tetradecenal (7%), decanal (6.6%), *E*-2-dodecenal (5.4%) | (Eyres et al. 2005) |
| India | Fruits | H | 0.6–2.2% | Linalool (55.42–75.3%), geranyl acetate (2.18–8.12%), geranial (6.33%), myrcene (5.53%), α-humulene (5.29%), 1,8-cineole (3.30%), α-pinene (2.87–4.09%), limonene (2.55%), linalyl acetate (1.30%), geraniol (1.11%), β- phellandrene (1.69%), decanal (1.44%) | (Padalia et al. 2011; Singh et al. 2006) |
| | Leaves | H | 0.15% | (*E*)-2-Decenal (18.02%), decanal (14.36%), dec-9-en-1-ol (11.66%), *E*-2-dodecenal (8.72%), *n*-tetradecanol (6.09%), dodecanal (5.81%), decanol (5.77%), 2-methyl undecanal (4.03%), undecanal (2.60%), n-octanal (1.74%), (*Z*)-4-decen-1-ol (1.73%), 3-decanone (1.48%), undecanol (1.49%), tetradecanal (1.40%), nonanal (1.15%) | (Padalia et al. 2011) |
| | Inflorescence | H | 0.3–0.4% | Linalool (4.5–60.5%), (2*E*)-decenal (0.2–28.7%), citronellol (0–23.2%), caryophyllene oxide (1.4–22.6%), fenchone (0–16.3%), α-pinene (1.6–4.1%) | (Punetha et al. 2018) |
| Iran | Fruit | H | 0.1–0.36% | Linalool (40.9–79.9%), γ-terpinene (5.8–13.6%), neryl acetate (2.3–14.2%), α-pinene (1.2–7.1%), ρ-cymene (1.1–4.2%), 2e-dodecanal (2.2–8.7%), n-tetradecane (0.7–1.7%), n-hexadecane (0.8–3.8%), nerol (1.8%), dodecanal (0.4–1%), β-pinene (1.2%), pentadecane (1.1%), limonene (1.0%), decanal (1.0%) | (Nejad Ebrahimi et al. 2010) |

(continued)

**Table 12.3** (continued)

| Origin | Plant part | [a]Method | Yield | Composition | Reference |
|---|---|---|---|---|---|
| Italy | Fruit | SCE | 0.19–0.58% | Linalool (65–79%), γ-terpinene (4–7%), camphor (3%), geranyl acetate (2–4%), limonene (1–2%), geraniol (1–3%), α-pinene (1–3%) | (Grosso et al. 2008) |
| | | H | 0.34% | Linalool (67–72%), γ-terpinene (5–7%), camphor (3%), limonene (3%), geraniol (3%) and α-pinene (2–3%), geranyl acetate (1–3%) | (Grosso et al. 2008) |
| Kenya | Leaves | H | – | 2*E*-Decenal (15.9%), decanal (14.3%), 2*E*-decen-1-ol (14.2%) and *n*-decanol (13.6%), 2*E*-tridecen-1-al (6.75%), 2*E*-dodecenal (6.23%), dodecanal (4.36%), undecanol (3.37%), undecanal (3.23%), *n*-undecanol (2.38%), *trans*-2-undecen-1-ol (2.12%), tridecanal (1.16%), nonane (1.21%) | (Matasyoh et al. 2009) |
| Korea | Leaves | H | 0.45% | Cyclododecanol (23.11%), tetradecanal (17.86%), 2-dodecenal (9.93%), 1-decanol (7.24%), 13-tetradecenal (6.85%), 1-dodecanol (6.54%), dodecanal (5.16%), 1-undecanol (2.28%), decanal (2.33%), 1-undecanol (2.28%), tridecanal (1.65%), (*Z*)6-pentadecen-1-ol (1.46%), 2-(4 methoxyphenyl)benzo[b]furan (1.4%), tetradecanal (1.35%), 2-hexadecen-1-ol, 3, 7, 11, 15-tetramethyl-, [R-[R*, R*-(*E*)]] (1.31%) | (Chung et al. 2012) |
| | Stem | H | 0.2% | Phytol (61.86%), 15-methyltricyclo[6.5.2(13,14),0(7,15)]-pentadeca- 1,3,5,7,9,11,13-heptene (7.01%), dodecanal (3.18%), 1-dodecanol (2.47%), 9H-pyrrolo[3′,4′:3,4]pyrrolo[2,1-a]phthalazine-9,11(10H)-dione, 10-ethyl-8-phenyl (1.9%), acrylic acid tetradecanyl ester (1.62%), hexadecanoic acid, ethyl ester (1.62%), tridecanal (1.59%), tetradecanal (1.56%), 1-methyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxyisochromene (1.19%), linoleic acid ethyl ester (1.10%), decanal (1.05%) | (Chung et al. 2012) |
| Pakistan | Fruits | H | 0.15% | Linalool (69.60%), geranyl acetate (4.99%), γ-terpinene (4.17%), α-pinene (1.63%), anethol (1.15%), ρ-cymene (1.12%) | (Anwar et al. 2011) |
| Romania | Fruits | SCE | 0.18–0.52% | Linalool (70.20%), α-pinene (6.17%), myrcene (5.39%), γ-terpinene (4.81%), camphor (3.23%), limonene (3.19%), ρ-cymene (1.14%), geraniol (1.09%), geranyl acetate (1.08%) | (Dima et al. 2016) |
| Serbia | Fruit | H | 0.89% | Linalool (74.6%), camphor (5.9%), geranyl acetate (4.6%), ρ-cymene (4%), *trans*-geraniol (2.8%) and limonene (10.1%), γ-terpinene (1.2%), borneol (1.2%), *trans*-anethole (1.8%) | (Samojlik et al. 2010) |

(continued)

**Table 12.3** (continued)

| Origin | Plant part | [a]Method | Yield | Composition | Reference |
|---|---|---|---|---|---|
| Tunisia | Fruits | H | 0.3–0.35% | Linalool (72.35–87.54%), *cis*-dihydrocarvone (2.36%), geranyl acetate (1.49%), thymol (1.85%), α-pinene (1.65%), γ-terpinene (2.15%), camphor (2.57%), geraniol (1.63%) | (Msaada et al. 2007; Msaada et al. 2009; Sriti et al. 2009) |
| | Pericarp | H | 0.04% | Linalool (24.65%), α-pinene (14.7%), tricyclene (2.95%), heptanal (1.33%), limonene (2.04%), (*z*)-3-hexanol (2.35%), camphor (7.22%), terpinene-4-ol (1.8%), β-caryphyllene (3.12%), geranyl acetate (1.67%), nerol (1.18%), geraniol (2.93%), *p*-cymene-8-ol (3.47%), *cis*-dihydrocarvone (1.32%), thymol (1.83%) | (Sriti et al. 2009) |
| | Seed | H | 0.68% | Linalool (91.19%), camphor (2.31%), geraniol (2.22%) | (Sriti et al. 2009) |
| | Leaves | H | 0.12–0.18% | (*E*)-2-Decenal (52%), decanal, dodecanal, (*E*)-2-tridecenal, (*E*)-2-dodecenal | (Neffati and Marzouk 2008) |
| Turkey | Fruits | H | 0.32–0.4% | Linalool (42.1–95.56%), geranyl acetate (1.7–3.2%), α-pinene (2.1–2.6%), γ-terpinene (1–4.8%), hexadecanoic acid (1.9–15.9%), ρ-cymene (1–3.5%), geraniol (0.9–2.5%), tetradecanoic acid (3.4–10.5%), (*Z*)-isoapiole + dillapiole (1.2–2.7%), camphor (0.5–1.7%) | (Kosar et al. 2005; Şanlı et al. 2012; Telci et al. 2006) |
| | | M | 0.4–0.5% | Linalool (75.5–81.2%), geranyl acetate (1.5–4.1%), hexadecanoic acid (1.3–6%), dodecanoic acid (1.5%), α-pinene (0.1–1%), γ-terpinene (0.5–3%), ρ-cymene (0.3–1%), geraniol (1–1.1%) | (Kosar et al. 2005) |

[a] *H* hydrodistillation; *SD* steam distillation; *SCE* supercritical $CO_2$ extraction; *M* microwave-assisted hydrodistillation

graphic region, cultivating environments, collecting time, and extraction process can influence the yields and compositions of essential oils from the same parts of the plant (Wei et al. 2019).

The essential oils extracted by hydrodistillation from fruits and leaves of coriander were investigated in different countries including India (Padalia et al. 2011), Bangladesh (Bhuiyan et al. 2009), and Tunisia (Msaada et al. 2009; Neffati and Marzouk 2008). The yields of essential oils were found higher in fruits (0.3–0.6%) compared to leaves (0.1–0.15%). In Atlantic Canada, different cultivars of coriander were grown, and the yield of fruit essential oil was found between 0.8 and 2.2% (Zheljazkov et al. 2008). The fruit essential oils of two varieties of *C. sativum* (var. *vulgare* Alef. and var. *microcarpum* DC.) from Turkey were investigated, and the oil yields were found to vary significantly between varieties. The essential oil contents were ranging from 0.15 to 0.25% in var. *vulgare* and from 0.31 to 0.43% in var. *microcarpum* (Telci et al. 2006). The aerial parts of coriander from Iran were harvested, and essential oils were obtained by hydrodistillation in different stages including vegetative, full flowering, green fruits (immature), and brown fruits (mature). The yields of essential oils at different stages were found as 0.14, 0.23, 0.37, and 0.31%, respectively (Ramezani et al. 2009). On the other hand, the yields of essential oils obtained by hydrodistillation from coriander fruits showed a significant increase during the maturation process. Fruits collected in the initial, middle, and final stages of maturity gave essential oils with a yield of 0.01, 0.12, and 0.35%, respectively (Msaada et al. 2007).

Many reports from various regions stated that the chemical profiles of essential oils of coriander fruit and leaves showed significant difference (Table 12.3). A comparative study on fruit and leaf essential oils from India showed that the fruit oil was dominated by monoterpenoids (90.18%) comprised of oxygenated monoterpenoids (74.01%) and monoterpene hydrocarbons (16.17%), while the leaf oil possessed aliphatic compounds (90.2%) mainly comprised of $C_{10}$-$C_{16}$

aldehydes and alcohol. The major volatile compound in fruit oil was linalool (55.42%), followed by geranial (6.33%), myrcene (5.53%), α-humulene (5.29%), 1,8-cineole (3.30%), α-pinene (2.87%), and geranyl acetate (2.18%). In contrast, leaf essential oil was found to contain (*E*)-2- decenal (18.02%), dec-9-en-1-ol (11.66%), (*E*)-2-dodecenal (8.72%), *n*-tetradecanol (6.09%), dodecanal (5.81%), decanol (5.77%), 2-methyl undecanal (4.03%), and undecanal (2.60%) as major compounds (Padalia et al. 2011). Another phytochemical study conducted on coriander essential oil from Bangladesh reported that the major compounds were linalool (37.7%), geranyl acetate (17.6%), and γ-terpinene (14.4%) in fruit oil and 2-decenoic acid (30.8%), E-11-tetradecenoic acid (13.4%), capric acid (12.7%), undecyl alcohol (6.4%), and tridecanoic acid (5.5%) in leaf oil (Bhuiyan et al. 2009). Because of the difference in chemical compositions, the essential oils of mature fruits and fresh leaves have a completely different odor and flavor. While fruit essential oil with high linalool content has a characteristic odor and mild, sweet, warm, and aromatic flavor, the aliphatic aldehydes mainly comprised of $C_8$-$C_{16}$ aldehydes are responsible for the peculiar, fetid-like aroma of leaf essential oil (Mandal and Mandal 2015; Padalia et al. 2011). On the other hand, at the seedling stage, the composition of volatile compounds with an oily, sweet, and grassy odor in the leaves was found to be quite similar to that in stems. This property makes the seedling coriander a highly desirable culinary herb (Kohara et al. 2006).

Many other studies on the chemical composition of the essential oil of coriander showed that linalool was the major compound of the mature fruit oil regardless of origins with different concentrations ranging between 37.7 and 95.56% (Table 12.3). The major compound of the essential oils obtained from the whole fruit, seed, and pericarp was also found to be linalool with 86.1, 91.1, and 24.6% of the oils, respectively (Sriti et al. 2009). On the other hand, phytochemical analysis of the essential oil of coriander fruits conducted in different stages of maturity process revealed the great differences of linalool content of essential oils occurring during the maturation process (Msaada et al. 2007; Msaada et al. 2009). While geranyl acetate (46.27%) and linalool (10.96%) were the main compounds of the essential oil obtained from immature fruits, the essential oil of the mature fruits was composed mainly of linalool (87.54%) (Msaada et al. 2007).

Hydrodistillation is one of the classical techniques of extraction which is widely used for the extraction of essential oils from different parts of coriander (Table 12.3). In a comparative study, hydrodistillation, Soxhlet extraction, supercritical fluid extraction, and subcritical water extraction techniques were used to obtain essential oil from coriander fruits. While the essential oil obtained by hydrodistillation had the highest content of linalool (835.2 mg/g extract), Soxhlet extract showed the lowest linalool content (52.2 mg/g extract). Besides, supercritical fluid and subcritical water extraction techniques were suggested as suitable alternatives (Pavlić et al. 2015). The essential oils obtained from Italian coriander fruits by supercritical $CO_2$ fluid extraction were evaluated under different conditions of temperature, particle size, pressure, and $CO_2$ flow rate. The best supercritical fluid extraction conditions were found to be a pressure of 90 bar, a flow rate of 1.10 kg/h, a particle size of 0.6 mm, and a temperature of 40 °C (Grosso et al. 2008). In another study, it was suggested that supercritical fluid extraction at 35 °C, 8 MPa, 2 h might be the optimal method to get the maximum of essential oil from the aerial parts of coriander (Chen et al. 2009). The essential oils of the whole and ground fruits of coriander obtained by microwave-assisted hydrodistillation and classical hydrodistillation techniques were investigated. While the distillation time decreased significantly in microwave-assisted hydrodistillation (1 h) compared to classical hydrodistillation technique (3 h), no significant difference in yields and chemical profiles of the essential oils were detected in both techniques (Kosar et al. 2005).

### 12.5.2 Lipids

Besides essential oil composition, the presence of fatty acids, sterols, and tocols in coriander fruit accounts for its medicinal properties and nutritional value (Laribi et al. 2015; Sriti et al. 2009). The fatty oil content of coriander fruit has been found in the range between 9.9 and 28.4% (Diederichsen 1996; Ramadan and Mörsel 2002). A phytochemical study from Tunisia reported that the oil content changed significantly during the maturation of fruits. While the oil content of fruits harvested 5 days after flowering (unripe and fully green) detected in a quite low level (2.7%), at full maturity stage, 22 days after flowering (fully ripe and brown), the oil content reached the maximum level (25.8%) (Msaada et al. 2009). In mature fruit, the major fatty acid was found to be petroselinic acid (65.7–80.9%), followed by linoleic acid (13.05–16.7%) (Msaada et al. 2009; Ramadan and Mörsel 2002). The fruit oils from two Turkish varieties of *C. sativum* (var. *vulgare* and var. *microcarpum*) cultivated under the same field conditions were analyzed, and the main fatty acid, petroselinic acid, was found to be higher in var. *vulgare* (76.31%) compared to var. *microcarpum* (72.32%) (Kiralan et al. 2009). Different parts of Tunisian coriander fruit were investigated, and the oil yields in whole fruit, seed, and pericarp were found to be 19.24%, 22.65%, and 9.3% of the dry weight (dw). Petroselinic acid was identified as the principal fatty acid in different fruit parts which was 76.37% in seed, 75.07% in whole fruit, and 42.2% in pericarp. Other main fatty acids were found to be linoleic, oleic, and palmitic acids, all of which were detected in higher amounts in pericarp (18.02, 9.88, and 18.45%, respectively) compared to seed (13.5, 5.45, and 3.48, respectively) and whole fruit (13.41, 5.91, and 3.96%, respectively) (Sriti et al. 2009).

Sterol content of coriander fruit from Germany was estimated to be 5.19 g/kg oil wherein stigmasterol (1.55 g/kg oil), $\beta$-sitosterol (1.46 g/kg oil), $\Delta$5-avenasterol (1.24 g/kg oil), and campesterol (0.51 g/kg oil) were found to be the sterol markers (Ramadan and Mörsel 2002). Sterol contents of different parts of coriander fruit were also determined by Sriti et al. (2009). The highest level of sterols was found in seed oil (36.92 g/kg oil) followed by fruit oil (6.29 g/kg oil) and pericarp oil (4.31 g/kg oil). In all parts of the coriander fruit, $\beta$-sitosterol, campesterol, stigmasterol, and $\Delta^7$ -stigmasterol were among the major components. The main sterol in fruit and pericarp oils was $\beta$-sitosterol, which represented 36.7 and 49.4% of the total sterols, respectively, while the sterol composition of the seed oil was dominated by stigmasterol with 29.5% of the total sterols, followed by $\beta$-sitosterol with 24.8% (Sriti et al. 2009).

Total tocol content in coriander fruit oil was found as 327.47 μg/g fruit. The major tocopherol was found to be $\gamma$-tocopherol (26.40 μg/g fruit), followed by $\delta$-tocopherol (13.50 μg/g fruit) and $\alpha$-tocopherol (11.70 μg/g fruit). In addition, total tocotrienol content was higher than tocopherol content. The main tocotrienol was $\gamma$-tocotrienol (238.40 μg/g fruit), followed by $\alpha$-tocotrienol (24.90 μg/g fruit) and $\delta$-tocotrienol (12.57 μg/g fruit) (Sriti et al. 2010).

The fatty acid contents of basal and upper leaves of coriander were also investigated. The total fatty acid content of basal leaves was found to be higher (61.21 mg/g dw) than upper leaves (41.8 mg/g dw). In both basal and upper leaves, $\alpha$-linolenic acid was the main fatty acid, with percentages of 39.4 and 41.1% (24.1 and 17.1 mg/g dw), respectively, followed by linoleic (9.85 and 8.22 mg/g dw), heptadecenoic (9.77 and 6.05 mg/g dw) and palmitic acids (7.8 and 5.73 mg/g dw). However, basal and upper leaves possessed oleic, stearic, stearidonic, and *cis*- and *trans*-palmitoleic acids in trace amounts which were accounted for 9.6 and 4.7% of the total fatty acid, respectively (Neffati and Marzouk 2008).

### 12.5.3 Phenolic Compounds

The vegetative parts and fruits of coriander were analyzed by HPLC-DAD–ESI/MS, and different phenolic profiles were obtained in each part of the plant. While five phenolic acids and four flavonoids were detected in vegetative parts, fruits revealed only phenolic acid derivatives. In vege-

tative parts, total flavonoid content was determined as 5259.52 mg/kg dw which included quercetin-3-*O*-rutinoside (3296.16 mg/kg dw), quercetin 3-*O*-glucuronide (1237.13 mg/kg dw), quercetin-3-*O*-glucoside (405.36 mg/kg dw), and kaempferol-3-*O*-rutinoside (320.86 mg/kg dw), and total phenolic acid content was determined as 1013.95 mg/kg dw which included dimethoxycinnamoyl hexoside (406.39 mg/kg dw), *p*-coumaroylquinic acid (303.83 mg/kg dw), 5-*O*-caffeoylquinic acid (173.51 mg/kg dw), ferulic acid glucoside (122.29 mg/kg dw), and caffeoylquinic acid (7.92 mg/kg dw). In fruits, total phenolic acid content was found to be 129.94 mg/kg dw which included caffeoyl *N*-tryptophan hexoside (45.33 mg/kg dw) and *p*-coumaric acid (23.81 mg/kg dw) as the main phenolic derivates (Barros et al. 2012). On the other hand, in the vegetative parts of in vitro grown coriander samples, apigenin-8-*C*-hexoside-7-*O*-pentoside was found to be the main phenolic compound in a range between 2982.87 and 3404.07 mg/kg dw. In addition, it was shown that the in vitro grown coriander samples showing a purple pigmentation on vegetative parts contained anthocyanins, and among them, peonidin-3-*O*-feruloylglucoside-5-*O*-glucoside was detected as the major anthocyanin (1.70 mg/kg dw) (Barros et al. 2012).

The fruits of Tunisian, Syrian, and Egyptian corianders were analyzed by RP-HPLC, and 21 phenolic compounds were identified in 3 different varieties including 8 flavonoids (apigenin, kaempferol, luteolin, quercetin dihydrate, quercetin-3-rhamnoside, naringin, rutin trihydrate, resorcinol) and 11 phenolic acids (cafeic, chlorogenic, gallic, *p*-coumaric, ferulic, *o*-coumaric, *trans*-cinnamic, *trans*-hydroxycinnamic, rosmarinic, salicylic, and vanillic acids). Tunisian variety was dominated by phenolic acids with a percentage of 81.47% and represented mainly by chlorogenic (15.09%), ferulic (11.07%), and *o*-coumaric (9.18%) acids, whereas, in the Syrian variety, flavonoids were predominant with a percentage of 61.34% due to the high content of luteolin (18.13%) and rutin trihydrate (13.06%). On the other hand, in the Egyptian variety, phenolic acids (49.17%) and flavonoids (50.83%) were approximately distributed equally, and apigenin was the main compound (12.99%) followed by quercetin-3-rhamnoside (9.19%) and rosmarinic acid (8.94%) (Msaada et al. 2017).

In a qualitative phytochemical study, flavonoids (acacetin, kaempferol, quercetin, 3′- OMe quercetin, 4′- OMe-quercetin) and phenolic acids (p-coumaric acid, cis-ferulic acid, and trans-ferulic acid, vanillic acid) were identified in coriander leaves (Nambiar et al. 2010).

In the aerial parts of coriander collected in the flowering stage, 24 phenolic compounds were identified and represented mainly flavonoids (apigenin, arbutin, catechin, diosmin, hyperoside, hesperidin, orientine, chrysoeriol, luteolin, quercetin, dihydroquercetin, rutin, vicenin, vitexin), phenolcarboxylic acids (caffeic, ferulic, gallic, and salicylic acids), and coumarins (esculetin, esculin, scopoletin, 4-hydroxycoumarin, umbelliferone, dicoumarin) (Oganesyan et al. 2007).

From various parts of coriander, seven isocoumarin were isolated in different times. First, from coriander leaves, two photoactive furoisocoumarins named coriandrin and dihydrocoriandrin were isolated (Ceska et al. 1988). Afterward, from the aerial parts of the plant, together with that known isocoumarins, two new isocoumarins named coriandrone A and B were isolated (Baba et al. 1991). Then, three new isocoumarins named coriandrones C, D, and E were isolated from whole plants (Taniguchi et al. 1996).

### 12.5.4 Carotenoids

Ten commercial varieties of coriander cultivated at identical conditions were analyzed by HPLC-MS to determine total carotenoids and $\beta$-carotene contents in different parts of the plant and at different stages of plant growth. In all varieties, $\beta$-carotene content was found to be higher in foliage at the mature stage, than in seedlings and fruits. Among varieties, the highest produced total carotenoids and $\beta$-carotene were detected at the pre-flowering stage with amounts of 217.5

and 73.64 mg/100 g dw, respectively (Divya et al. 2012).

Five carotenoid fractions including $\beta$-carotene, $\beta$-cryptoxanthin epoxide, lutein- 5,6-epoxide, violaxanthin, and neoxanthin were isolated from ether extract of coriander leaves and shoots. While total carotenoid content was determined as 536.7 μg/g dw, $\beta$-carotene was found to be 61.14% of the carotenoids detected in the total extract (Guerra et al. 2005).

### 12.5.5 Water-Soluble Constituents

Coriander fruits were investigated for their water-soluble constituents, and 33 compounds, including 2 new monoterpenoids, 4 new monoterpenoid glycosides, 2 new monoterpenoid glucoside sulfates, and 2 new aromatic compound glycosides, were obtained from the water-soluble portion of the methanol extract of the fruits (Ishikawa et al. 2003).

## 12.6 Pharmacological Activities

### 12.6.1 Analgesic Activity

The aqueous extract of coriander fruits produced significant analgesic activity against the hot plate method in mice. The fruit extract showed an analgesic effect at 200 mg/kg dose with a reaction time of 5.281 seconds, while the reaction time of morphine (5 mg/kg i.p.) was 6.282 seconds. The pain inhibition percentage of the extract was more than that of control. It was reported that the analgesic effect of the coriander fruit extract was probably mediated by the inhibition of central pain receptors (Pathan et al. 2011). The analgesic activities of aqueous, ethanol, and chloroform extracts of aerial parts of *C. sativum* were also investigated using the hot plate test in mice. The aqueous, ethanol, and chloroform extracts at three doses (20, 100, and 500 mg/kg) showed significant analgesic activity with a high maximal percent effect (MPE) which was comparable to the effect of morphine. Besides, ethanol and chloroform extracts were found more effective than aqueous extract. It was suggested that these effects of the extracts might be mediated by the opioid system (Kazempor et al. 2015).

### 12.6.2 Anticonvulsant Activity

Coriander fruits were investigated for their anticonvulsant effect in mice. The aqueous extract, hydroalcoholic extract, and the essential oil of coriander fruits were administered at different doses (200, 400, 600, and 800 mg/kg) 30 minutes before the injection of pentylenetetrazole (90 mg/kg). Both of the extract, as well as the essential oil, showed anticonvulsant effect at doses of 600 and 800 mg/kg by increasing the latency of myoclonic and clonic convulsions (Emamghoreishi and Heidari-Hamedani 2004). In another study, the coriander fruit extracts at 5 g/kg showed anticonvulsant activity in mice similar to that of phenobarbital at a dose of 20 mg/kg in the pentylenetetrazole seizure test. In addition, in the maximal electroshock test, it was demonstrated that the duration of tonic seizures was decreased by the aqueous extracts prepared by decoction and maceration at a dose of 0.5 g/kg and the ethanolic extracts at doses of 3.5 and 5 g/kg (Hosseinzadeh and Madanifard 2000).

### 12.6.3 Antidiabetic Activity

*C. sativum* has been used as a folk medicine for the treatment of diabetes in different countries (Ahmad et al. 2018; Aissaoui et al. 2008; Hamza et al. 2019; Laribi et al. 2015). The traditional use of coriander in diabetes has been validated by many pharmacological studies (Aissaoui et al. 2008; Chithra and Leelamma 1999b; Eidi et al. 2009; Gray and Flatt 1999; Mechchate et al. 2021; Sreelatha and Inbavalli 2012; Swanston-Flatt et al. 1990).

The effects of *C. sativum* fruits on glucose homeostasis were investigated in normal and streptozotocin-induced diabetic mice. The fruits were added to the diet (6.25% by weight of the diet), and fruit infusion (2.5 g/L) was supplied in place of drinking water. It was observed no

change in food and fluid intake, body weight gain, plasma glucose, and insulin concentrations in normal mice treated with fruits by 12 days. After streptozotocin (200 mg/kg i.p.) treatment on day 12, in coriander-treated mice, the level of hyperglycemia decreased during the development of streptozotocin-induced diabetes (Swanston-Flatt et al. 1990).

In another study, administration of coriander fruit in the diet (62.5 g/kg) and drinking water (2.5 g/L, prepared by decoction) decreased the hyperglycemia of streptozotocin-diabetic mice by day 20. To understand mechanisms, in vitro actions of the aqueous extract of coriander fruits on glucose metabolism and insulin secretion were also investigated. Results of the study showed that the antihyperglycemic activity of coriander is associated with stimulation of insulin secretion and enhancement of glucose uptake and metabolism by muscle, reflecting the effects of more than one active constituent (Gray and Flatt 1999).

The supplementation of 10% powdered coriander fruits resulted in a significant decrease in fasting blood glucose level and increase hepatic glycogen level in rats fed with a high-fat and cholesterol-containing (2% cholesterol and 15% coconut oil) diet. The mechanism of the hypoglycemic action of the coriander fruits was attributed to the decreased rates of glycogenolysis and gluconeogenesis and the increased rates of glycogenesis and glycolysis (Chithra and Leelamma 1999b).

In a sub-chronic study, daily administration of the aqueous extract of coriander fruits (20 mg/kg) for 30 days in obese-hyperglycemic-hyperlipidemic *Meriones shawi* rats resulted in a remarkable decrease in plasma glucose level (58%; $p < 0.001$), plasma insulin level (54%; $p < 0.001$), and insulin resistance (80%; $p < 0.001$). The results of the study suggest that regular consumption of coriander fruit could reduce hyperglycemia (Aissaoui et al. 2011).

The ethanol extract of the coriander fruits was investigated for the effects on insulin release from the beta cells of the pancreas in streptozotocin-induced diabetic rats. The results of the study demonstrated that administration of the ethanol extract (200 and 250 mg/kg, i.p.) significantly reduced the serum glucose in streptozotocin-induced diabetic rats. Treatment with extract (200 mg/kg) increased insulin release from pancreatic beta cells compared to the diabetic control rats (Eidi et al. 2009).

The antihyperglycemic effect of coriander leaf and stem extracts was also studied on alloxan-induced diabetic rats. Increased blood glucose levels after administration of alloxan (150 mg/kg, i.p.) for 2 weeks were significantly reduced through ethyl acetate extracts of coriander leaf and stem. The antidiabetic activity was attributed to the regeneration of destroyed beta cells caused by alloxan (Sreelatha and Inbavalli 2012).

The polyphenol fraction of *C. sativum* fruits containing vanillic acid, chlorogenic acid, catechin, epicatechin, oleuropein, epicatechin gallate, rutin, gallocatechin, and epigallocatechin was administered to the alloxan-induced diabetic mice at two doses (25 and 50 mg/kg/day) for 4 weeks to observe the long-term effect on the diabetic state of the animals. After 4 weeks, the polyphenol fraction, as well as the positive control, caused a significant decrease (57, 65, and 73% for doses 25, 50, and glibenclamide at 2 mg/kg/day, respectively; $p > 0.001$) in fasting blood glucose of diabetic mice compared to the negative control (Mechchate et al. 2021).

Even though coriander extract has been studied several times for its efficacy on diabetes, little information is available on in vivo antidiabetic effect of coriander essential oil. It has been shown that administration of coriander essential oil (40 mg/kg b.w. orally) for 21 days reduced serum glucose level from 162.5 ± 3.19 (mg/dL) to 72.96 ± 1.73 (mg/dL) in diabetic male albino rats. In addition, it improved the diabetic pathological changes on the kidney and pancreas of the diabetic rats. The hypoglycemic activity of coriander essential oil could be contributed to the synergistic action of its bioactive compounds including linalool, geranyl acetate, and γ -terpinene (El-Soud et al. 2012).

These results suggest that coriander is a potential source of useful dietary supplements and new bioactive agent(s) for diabetes therapy.

### 12.6.4 Antihypertensive Activity

The intravenous administration of the aqueous-methanolic extract of coriander fruit produced a dose-dependent (1–30 mg/kg) decrease in both systolic and diastolic blood pressure in normotensive rats. The cholinergic and $Ca^{2+}$ antagonist actions of coriander fruit were shown as the possible mechanisms mediating its hypotensive effect (Jabeen et al. 2009).

To explore the mechanism of action of bioactive compounds in coriander leaves as angiotensin-converting enzyme (ACE) inhibitors, four bioactive fractions including alkaloids, flavonoids, steroids, and tannins extracted from coriander leaves were investigated for their ACE inhibition potential. Among the studied fractions, the high ACE inhibition was shown by the only flavonoid-rich fraction with an $IC_{50}$ value of 28.91 ± 13.42 μg/ mL. The results of the study indicated that the flavonoids with ACE inhibitory potentials in coriander leaves could help to manage blood pressure effectively (Hussain et al. 2018).

### 12.6.5 Antimicrobial Activity

The antibacterial activity of commercial coriander essential oil against Gram-positive and Gram-negative bacteria and its mechanism of action were evaluated. Coriander oil was reported to show effective antibacterial activity against all bacteria tested by causing membrane damage which leads to cell death. It was also reported that the lower susceptibility of the Gram-positive bacteria than the Gram-negative bacteria seems to be related to membrane permeability. In addition, linalool, the major component in coriander essential oil and mostly found as *S* (+) enantiomer form which increases the permeability of negatively charged membranes, could disrupt the outer membrane of the Gram-negative bacteria. On the other hand, alcohol could lead to increased resistance in Gram-positive bacteria (Silva et al. 2011). The essential oils of fruits obtained from two varieties of *C. sativum* containing high levels of linalool (78.8% and 90.6%) exerted higher antibacterial activity than linalool alone (Duman et al. 2010).

A novel antimicrobial peptide isolated from coriander leaf extract demonstrated a wide range antimicrobial activity while no hemolytic activity against human red blood cells unlike most of the antimicrobial peptides. This new peptide named "Plantaricin CS" showed the greatest antimicrobial effect on resistant *Staphylococcus aureus* strain with a MIC value of 1.3 mg/mL. It has been also observed that Plantaricin CS was less effective on Gram-negative bacteria which could be probably due to the presence of cell wall polysaccharides, preventing active compounds from reaching the cytoplasmic membrane of these bacteria (Zare-Shehneh et al. 2014).

The essential oil and ethanol extract of coriander leaves were tested for their antimicrobial activity against 28 foodborne microorganisms including 19 bacteria, 7 fungi, and 2 yeasts. While the ethanol extract showed antimicrobial activity with a MIC value of 500 μg/mL against *Enterococcus faecalis*, *Flavobacterium indologenes*, *Klebsiella pneumoniae ozaenae*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Providencia alcalifaciens*, *Pseudomonas pseudoalcaligenes*, *Streptococcus pyogenes*, *Yersinia enterocolitica*, and *Candida albicans*, the essential oil of leaves exhibited some degree of antimicrobial activity against all microorganisms tested. The essential oil showed the highest antimicrobial activity against *C. albicans* with a MIC value of 7.8 μg/mL and against *Listeria monocytogenes* and *Staphylococcus aureus* with a MIC value of 31.3 μg/mL (Yildiz 2016). In another study, the essential oil of coriander fresh leaves containing high concentrations of alcohols and aldehydes exhibited antifungal activity with MIC values varying from 125 to 500 μg/mL against *C. albicans*, *C. krusei*, *C. parapsilosis*, and *C. dubliniensis*. On the other hand, the fractions of the essential oil obtained by dry-column chromatography containing a higher concentration of alcohols showed stronger antifungal activity against *C. albicans*, *C. parapsilosis*, *C. dubliniensis*, and *C. tropicalis* with lower MIC values ranging from 7 to 63 μg/mL (Begnami et al. 2010). The essential oil of coriander fruits with a high content of

linalool (58.65%) exhibited also good antifungal activity against *Candida* species (Soares et al. 2012). The essential oil of *C. sativum* may be a potential source for drug discovery in treatment or prevention of the infections caused by candida yeast (Laribi et al. 2015; Soares et al. 2012).

### 12.6.6 Antioxidant Activity

In a comparative study, the antioxidant activity of coriander leaf and fruit extracts in different polarities was evaluated using three different bioassays. Coriander leaf extracts (i.e., aqueous ethanol, dichloromethane, ethyl acetate, *n*-butanol, and aqueous extracts) showed stronger antioxidant activity than fruit extracts (i.e., aqueous ethanol, diethyl ether, ethyl acetate, *n*-butanol, and aqueous extracts). The strongest activity was shown by ethyl acetate extracts containing the highest amounts of phenolic compounds in both plant parts, while dichloromethane extract of fruit containing only fat was found to be inactive (Wangensteen et al. 2004).

The antioxidant activities of essential oils obtained from fruit and whole plant of *C. sativum* were determined using DPPH and Fenton's assays. The whole plant oil was more effective than fruit oil in both assays. The whole plant and fruit oil at 50 μg/mL inhibited 73.59 and 54.58% of DPPH radical and 75.20 and 58.58% of hydroxyl radicals, respectively. The DPPH free radical scavenging activity of the essential oils was found to be higher than methanolic, diethyl ether, and aqueous extracts reported in previous studies (Singh et al. 2015).

In another study, it was shown that the polyphenol fraction of coriander fruits had a stronger antioxidant activity against the DPPH radical with an $IC_{50}$ value of 0.0005 μg/mL compared to BHT ($IC_{50}$ = 0.14 μg/mL) (Mechchate et al. 2021).

Antioxidant profiles of vegetative parts (stem and leaves) of in vivo (commercial) and in vitro grown coriander samples were investigated. The highest antioxidant activity was shown by the in vivo sample, possibly due to its high concentration of hydrophilic compounds such as sugars, phenolics, flavonols, and anthocyanins (Dias et al. 2011).

The fruit methanolic extracts of Tunisian, Syrian, and Egyptian varieties of coriander were studied for their antioxidant activities. The Syrian variety possessed the highest level of total polyphenol, total flavonoid, and total condensed tannin contents. However, the Tunisian variety showed the strongest DPPH scavenging activity with an $IC_{50}$ value of 27 ± 6.57 μg/mL compared to Syrian and Egyptian varieties with $IC_{50}$ values of 36 ± 3.22 and 32 ± 2.87 μg/mL, respectively. The ability to prevent the bleaching of β-carotene was also higher in Tunisian variety ($IC_{50}$ = 160 ± 18.63 μg/mL) than both Syrian and Egyptian varieties ($IC_{50}$ = 240 ± 26.35 and 240 ± 25.84 μg/mL). On the other hand, the Syrian variety showed the higher reducing capacity ($EC_{50}$ = 54.20 ± 6.22 μg/mL) than Egyptian ($EC_{50}$ = 56.11 ± 7.45 μg/mL) and Tunisian ($EC_{50}$ = 122.01 ± 13.25 μg/mL) ones. Besides, comparing the phenolic profiles of three varieties, while the Tunisian variety was rich in phenolic acids (81.47%), Syrian was rich in flavonoids (61.34%). In the Egyptian variety, the flavonoid (50.83%) and phenolic acid (49.17%) contents were approximately equal (Msaada et al. 2017).

In an in vivo study, it was shown that feeding with coriander fruit powder supplemented (10%) high-fat and cholesterol-containing diet for 90 days decreased the level of lipid peroxides, free fatty acids, and glutathione levels and increased the activity of antioxidant enzymes in different organs of female albino rats resulting in protection of the tissues from the damage caused by unwanted free radicals (Chithra and Leelamma 1999a). Coriander fruit extract was investigated for their protective effects against lead nitrate-induced oxidative stress in mice. Oxidative stress was induced in male Swiss albino mice by treating lead nitrate (40 mg/kg body weight) for 7 days. From day 8, two different doses of aqueous (300 and 600 mg/kg body weight) and ethanolic (250 and 500 mg/kg body weight) extracts were administered by oral gavage once daily for 33 days. The results of the study showed that treatment with plant extracts along with lead nitrate decreased the lipid peroxidation level and

increased the SOD and CAT activities, as well as GSH concentration, in the liver and kidney of experimental animals compared to lead-induced group (Kansal et al. 2011).

### 12.6.7 Antiparasitic Activity

The anthelmintic activities of aqueous and hydroalcoholic extracts of coriander fruits were investigated on nematode parasite *Haemonchus contortus.* While hatching of eggs was inhibited by both extracts without a significant difference at a concentration less than 0.5 mg/mL, the hydroalcoholic extract was more effective against adult parasites than the aqueous extract. However, the efficacy of extracts was not of the required therapeutic level (Eguale et al. 2007).

The ethyl acetate, chloroform, and methanol fractions obtained from *C. sativum* fruit extract were tested on *Leishmania infantum*, a protozoan species causing visceral leishmaniasis. All fractions were found to inhibit *L. infantum* promastigotes. However, the methanol fraction of *C. sativum* was the most effective on amastigotes (Rondon et al. 2011).

### 12.6.8 Anxiolytic Activity

In Iranian folk medicine, *C. sativum* has been used for insomnia and anxiety. To validate its traditional use, the aqueous extract of coriander fruits was investigated for its anxiolytic activity using an elevated plus-maze model in male albino mice. The aqueous extract (100 mg/kg, i.p.) increased the amount of time on open arms and the percentage of open arm entries, compared to the control group, and showed an anxiolytic activity (Emamghoreishi et al. 2005).

### 12.6.9 Diuretic Activity

Coriander fruits have been used as a diuretic plant in traditional medicine (Aissaoui et al. 2008). To confirm its traditional use, the aqueous extract of coriander fruits was tested in Wistar rats. The crude extract was administered intravenously at 40 and 100 mg/kg doses, and furosemide (10 mg/kg) was used as a reference drug. The aqueous extract of coriander fruits possessed diuretic and saluretic activity by increasing diuresis, excretion of electrolytes, and glomerular filtration rate in a dose-dependent way with a similar mechanism of action of furosemide even if at a lower potency. The results of the study confirm the traditional use of *C. sativum* as a diuretic agent (Aissaoui et al. 2008).

### 12.6.10 Hepatoprotective Activity

The hepatoprotective effect of coriander has been proved by many in vivo studies showing biochemical and histopathological evidences, and this effect has been associated with its antioxidant potential (Donia 2019; Kansal et al. 2011; Moustafa et al. 2014; Pandey et al. 2011; Sreelatha et al. 2009).

The studies aimed to investigate the protective effect of Coriander fruit against lead toxicity in experimental animals showed that the oral administration of aqueous and ethanolic extracts of coriander fruits reduced the adverse effect related to hepatic oxidative stress and diminished the histopathological changes in liver tissue in animals treated with lead (Donia 2019; Kansal et al. 2011).

Feeding with standardized diets containing coriander leaves and fruits attenuated thioacetamide-induced hepatotoxicity in rats. In the study, adult male Sprague Dawley rats were fed with standardized diets containing coriander leaves or fruits and at the same time treated intraperitoneally with thioacetamide (200 mg/kg body weight, twice/week) for 12 weeks. Coriander feeding decreased the alanine aminotransferase (ALT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST) activities in the serum, and nitric oxide (NO) and thiobarbituric acid reactive substance (TBARS) levels in the liver of thioacetamide-induced rats. The hepatoprotective effect of coriander was also confirmed by histopathological studies. In addition, coriander leaves were found more effective than fruits

which could be due to the presence of higher phenolic and antioxidant contents in the leaves of coriander (Moustafa et al. 2014).

Coriander was also reported to show a protective effect against $CCl_4$-induced liver injury (Pandey et al. 2011; Sreelatha et al. 2009). Pretreatment of Wistar albino rats with hydroalcoholic extracts of coriander stem and leaf at doses of 100 and 200 mg/kg body weight provided a significant decrease in the levels of serum transaminases (SGOT, SGPT) and TBARs while a significant increase of hepatic antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) against $CCl_4$-treated rats. The increase in the activity of antioxidant enzymes mediated by pretreatment of coriander extract indicated that coriander extract potentially played a role as an antioxidant by preventing the peroxidative damage induced by $CCl_4$. Furthermore, oral administration of the leaf extract at the dose of 200 mg/kg significantly reduced the hepatotoxic effect of $CCl_4$, which was comparable with the standard drug, silymarin (Sreelatha et al. 2009). Another study stated that oral administration of the ethanolic extract of coriander leaves at a dose of 300 mg/kg resulted in the disappearance of fatty deposits, ballooning degeneration, and necrosis, indicating antihepatotoxic activity (Pandey et al. 2011).

### 12.6.11 Hypolipidemic Activity

Coriander fruit has been reported to possess hypolipidemic action in experimental animals (Aissaoui et al. 2011; Chithra and Leelamma 1997; Lal et al. 2004; Sreelatha and Inbavalli 2012). The supplementation of 10% coriander fruits resulted in a significant decrease in cholesterol and triglyceride levels in rats fed with a cholesterol-containing (2% cholesterol and 15% coconut oil) diet. Furthermore, the concentration of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol decreased, while that of high-density lipoprotein (HDL) cholesterol, as well as activity of hepatic β-hydroxy-β-methyl-glutaryl CoA reductase (HMGCoA) and plasma lecithin cholesterol acyl transferase (LCAT), increased in animals administered with coriander fruits (Chithra and Leelamma 1997). In another study, the administration of 10% powdered coriander fruits counteracted the increase of the concentration of lipids and the decrease of excretion of bile acids caused by 1,2-dimethylhydrazine-induced colon cancer in rats. In addition, the results of the study indicated that consumption of coriander fruit in the daily diet plays a protective role against chemical carcinogenesis in the colon (Chithra and Leelamma 2000).

The sub-chronic administration of aqueous extract of coriander fruits (20 mg/kg) in obese-hyperglycemic-hyperlipidemic *Meriones shawi* rats resulted in a remarkable decrease in the elevated levels of total cholesterol (48%; $p < 0.001$), LDL cholesterol (55%; $p < 0.001$), and triglyceride (55%; $p < 0.001$) (Aissaoui et al. 2011).

In addition to the hypoglycemic effect, ethyl acetate extracts of coriander leaf and stem showed a significant hypolipidemic effect by altering the levels of lipid metabolites in alloxan-induced diabetic rats. In the extract-treated group, the levels of total cholesterol, triglycerides, and LDL cholesterol decreased in serum, while that of HDL cholesterol increased compared to the diabetic control rats (Sreelatha and Inbavalli 2012).

### 12.6.12 Neuroprotective Effect

Coriander essential oil and its main active constituent, linalool, were investigated for their protective effect against the neurotoxicity induced by amyloid-$\beta_{1-42}$ oligomers, the main molecular trigger of neurodegeneration in Alzheimer's disease. It was shown that both coriander essential oil and linalool at the concentration of 10 μg/mL improved viability and reduced nuclear morphological abnormalities in nerve growth factor (NGF)-differentiated rat pheochromocytoma (PC12) cells exposed to $A\beta_{1-42}$ oligomers (5 μM, 24 h). On the other hand, coriander essential oil was found more effective than linalool in reduc-

ing nuclear morphological abnormalities (Caputo et al. 2021).

## 12.7 Clinical Studies

There is some evidence suggesting that the consumption of polyphenol-rich foods can improve markers of postprandial oxidative stress (Umeno et al. 2016). To investigate the effect of polyphenol-rich curry consumption on postprandial plasma concentrations of allantoin, a randomized controlled crossover trial was carried out. Mixed spice preparations containing turmeric, coriander fruits, cumin fruits, dried Indian gooseberry (amla), cayenne pepper, cinnamon, and clove in the ratio of 8:4:4:4:2:1:1 were consumed at three doses (0, 6, and 12 g) by 17 nonsmoking, healthy, Chinese men volunteers aged 23.7 ± 2.4 years (BMI 23.1 ± 2.3 kg/m$^2$) at breakfast, after overnight fasting. All volunteers completed all three doses with at least 1 week washout period between each treatment. The results of the study showed that postprandial plasma allantoin concentrations as well as allantoin to uric acid ratio decreased significantly (both $p < 0.001$) at 2 h and 3 h test meal consumption with increasing doses of curry intake (Haldar et al. 2019).

The antioxidant and antiarthritic activities of coriander leaves were investigated in osteoarthritis patients. Selected osteoarthritis patients between 40 and 60 years old were administered coriander leaf powder (5 g/day) for 60 days. At the initial and final stages of the experiment, essential biochemical and clinical parameters were evaluated and compared with that of the untreated group. Coriander treatment resulted in a decrease in lipid peroxidation level in erythrocytes (42%, $p < 0.01$) and plasma (20%, $p < 0.01$), as well as the serum uric acid (60%, $p < 0.05$) and ceruloplasmin (30%, $p < 0.01$) levels, whereas an increase in erythrocyte-reduced glutathione level (43%, $p < 0.01$) and erythrocyte glutathione-S-transferase (GST) activity (62%, $p < 0.01$) in arthritis patients. The results of the study showed that coriander leaf treatment controlled oxidative stress in arthritis patients (Rajeshwari et al. 2012).

A commercial preparation (Carmint®) containing total extracts of *Melissa officinalis*, *Mentha spicata*, and *C. sativum* were investigated for its effectiveness in relieving abdominal pain and bloating symptoms in irritable bowel syndrome (IBS) patients. A double-blind, randomized, placebo-controlled, multicenter clinical trial was conducted on 28 IBS patients. Patients were randomized to receive 30 drops of either Carmint® or placebo three times a day after each meal for 8 weeks. At the end of the treatment, the severity and frequency of abdominal pain and bloating decreased significantly in the Carmint® group compared to the placebo group (Vejdani et al. 2006).

## 12.8 Toxicological Studies

Coriander fruit has been categorized as Class 1 (herbs that can be safely consumed when used appropriately) by the American Herbal Products Association (AHPA) (Burdock and Carabin 2009). The hydro-methanolic extract of coriander fruit were investigated for its acute and subchronic toxicity in mice using OECD guidelines. In both acute and sub-chronic toxicity studies, the fruit extract was administered orally at 1000, 3000, and 5000 mg/kg body weight. The coriander fruit extract was found to be nontoxic up to 3000 mg/kg body weight and could be considered as safe for consumption (Patel et al. 2012). Acute oral toxicity of the ethanolic extract of coriander leaves was also determined according to OECD guidelines. Coriander leaves extract did not show any mortality or toxicity up to 2000 mg/kg dose, except centrally induced depression (Pandey et al. 2011). Coriander juice showed antimutagenic activity on three tested aromatic amines including 4-nitro-o-phenylenediamine, m-phenylenediamine, and 2-aminofluorene by decreasing their mutagenic activity (83.21, 87.14, and 92.43% in mutagenesis reductions, respectively). Coriander juice was found to be nor mutagenic neither toxic in the range of concentration tested (50–1000 μL/coincubation flask) (Cortés-Eslava et al. 2004).

Coriander oil has been approved by the Food and Drug Administration (FDA) and the Flavor and Extract Manufacturers' Association (FEMA) as generally recognized as safe (GRAS) for use in food as flavoring agent and adjuvant (Burdock and Carabin 2009). The median lethal dose ($LD_{50}$) of fruit essential oil of coriander was determined as 2.257 mL/kg in mice (Özbek et al. 2006).

## 12.9 Conclusion

Coriander has been traditionally used as food and medicine since ancient times. The bioactive constituents of the plant, especially essential oil, fatty acids, and phenolic compounds, account for the numerous pharmacological activities including analgesic, anticonvulsant, antidiabetic, antihypertensive, antimicrobial, antioxidant, antiparasitic, anxiolytic, diuretic, hepatoprotective, hypolipidemic, and neuroprotective. Coriander fruit and its essential oil have been approved as safe for use as food ingredients; however, further safety studies are needed for its long-term use at therapeutic doses. Coriander and its precious bioactive constituents are great potential sources for the food and pharmaceutical industries.

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# *Cornus mas* L.

13

Büşra Cumhur

**Abstract**

*Cornus mas* L. (cornelian cherry) is a member of the Cornaceae family. It is widely used in traditional cuisine and folk medicine in numerous countries of Europe and Asia. Anthocyanins, flavonoids, iridoids, vitamin C and minerals are the major bioactive components of this plant. In folk medicines, different parts of the plant have been used for the treatment or prevention of multifarious diseases (for instance; diabetes, diarrhoea, gastrointestinal disorders, rheumatic pain, kidney and liver diseases, sunstroke, etc.). Moreover, antioxidant, antimicrobial, anti-hyperlipidaemic, anti-diabetic, anti-obesity, cardio-protective, liver-protective and renal-protective activities of *C. mas* have been confirmed by various studies. Regrettably, clinical trials are very few. This chapter aims to contribute an overview of ethnomedicinal uses, chemical ingredients, pharmacological properties and usefulness as a nutritional supplement of *C. mas*.

**Keywords**

*Cornus mas* L. · Diabetes · Diarrhoea · Multifunctional food · Cornelian cherry · Anthocyanin

## 13.1 Introduction

The genus *Cornus* L described by Linneaus in 1753 (Wilson 1964) belongs to the Cornaceae family. It is represented by approximately 65 species (Dinda et al. 2016; Czerwinska and Melzig 2018). This genus had four subgroups (cornelian cherries and dwarf, big-bracted, white- or blue-fruited dogwoods) (Fan and Xiang 2001; Zhang et al. 2008), previously with problematic phylogenetic relationships (Gawrońska et al. 2019). However, its complex taxonomies have been analysed by a series of phylogenetic analyses based on molecular (using rbcL and matK, 26S rDNA and ITS 1-5.8S rDNA regions (Czerwinska and Melzig 2018)) and morphological data (Gawrońska et al. 2019; Fan and Xiang 2001; Zhang et al. 2008).

*Cornus g*enus in Turkey is represented by two species and three subspecies (Güner et al. 2012). *Cornus mas* L. is one of the members of the *Cornus* genus which is the most interesting in terms of pharmacy and food industry (Kucharska et al. 2015) and has a deep-rooted history of traditional medicine (Czerwinska and Melzig 2018).

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The *Cornus* name stems from the Latin vocable *Cornu* meaning horn, probably because of the strength and density of wood, and the epithet name "mas" originates from the Latin vocable *maschile* which means immensely hardwood (Dinda et al. 2016). The accepted binominal name *C. mas* has 1 homotypic and 15 heterotypic synonyms (The Plant List 2021). The synonyms of the plant are given in Table 13.1.

*C. mas*, generally known as "kızılcık" in Turkish (Aykut and Konuklugil 2018), is called "Cornelian cherry, European cornel" in English (Czerwinska and Melzig 2018). Different regions in Turkey also use the following names: eyren (Gerçekcioğlu 1998), eğren, eyir, kevren, kiren, zoğal (Baytop 2007; Gerçekcioğlu 1998), küren (Özdemir-Nath and Kültür 2016), beyaz kızılcık, çalı kızılcığı, çum, güren, kevren, kıran, kıren, şefit, zağal, zanğal, zavrak, zonğal, zoval, zuğal, zuhal and zuval (Baytop 2007). The local names of the *C. mas* in the countries where it is distributed to are presented in 1.1.2 Ethnomedicinal and Other Usages topic.

*C. mas* is a small tree growing 2–6 m tall (as an exception reaching 8–9 m) or deciduous shrub (Da Ronch et al. 2016) is the European-Siberian Element (Güner et al. 2012), which. The crown is bushy, regular and hemispherical and may extend more horizontally up to 5 m (Da Ronch et al. 2016). Yellow (Aykut and Konuklugil 2018), small hermaphrodite flowers are grouped in umbels (Popovic et al. 2018). They bloom before they produce the leaves (Czerwinska and Melzig 2018). The fruit which ripens in midsummer is a bright cherry-like, single-stone drupe. Olive-shaped, long (12–15 mm), smooth-surfaced fruit can be eaten when dropped (Da Ronch et al. 2016). It inhabits dry meadows, pastures and rocky-limestone areas, the edges of sparse oaks forest up to 1300 m and over the sea level in Asia and Europe (Stankovic et al. 2014). Figure 13.1 shows the general view of the plant.

In this chapter, the purpose and methods of use of *C. mas* where it is naturally distributed such as Asia, Europe and the Caucasus in terms of ethnopharmacology are compared, and its local names are compiled. Besides this, it is aimed to compile pharmacological, phytochemical, pharmacokinetic, bioactivity study data on this plant, which has a very old history in both curative, nutrition and tool making in traditional use, and to examine the overlap of traditional use and scientific data.

**Table 13.1** Synonyms of *Cornus mas* L. (The Plant List 2021)

| | | |
|---|---|---|
| *C. erythrocarpa* St.-Lag. | *C. homerica* Bubani | *C. mas* f. *conica* Jovan. |
| *C. vernalis* Salisb. | *C. nudiflora* Dumort. | *Macrocarpium mas* (L.) Nakai. |
| *C. flava* Steud. | *C. mas* var. *oblongifolia* Jovan. | *C. mas* f. *oxycarpa* Jovan. |
| *C. mascula* L. | *C. praecox* Stokes | *Eukrania mascula* (L.) Merr. |
| *C. mas* f. *pyriformis* Sanadze | *C. mas* f. *microcarpa* Sanadze | *C. mas* f. *macrocarpa* Dippel |

## 13.1.1 Geographical Distribution and Status

Coming from the foothills of the Caucasus, it has been distributed to Romania, Turkey, Bulgaria and Italy (Dinda et al. 2016). *C. mas* grow naturally in Southern Europe and some of South-West Asia regions (Bakirtzi et al. 2013; Czerwinska and Melzig 2018), and in Turkey, it is especially seen in the wild in the forests of the North Anatolian (Yılmaz et al. 2020). For centuries, since it has been exported first as a pharmaceutical plant and fruit, then as an ornamental plant, and nowadays, it has been naturalized in some countries; the plant can distribute widely outside its natural area (Da Ronch et al. 2016). Figure 13.2 shows the distribution of *C. mas* in the world.

*C. mas* has a high adaptation potential (Bakirtzi et al. 2013) and is rarely affected by pests and diseases (Bakirtzi et al. 2013; Da Ronch et al. 2016). Hence, *C. mas* is a unique species that is protected in natural form in various varieties without applying chemicals under reasonable agrotechnical conditions (Dinda et al. 2016).

**Fig 13.1** *Cornus mas* L.

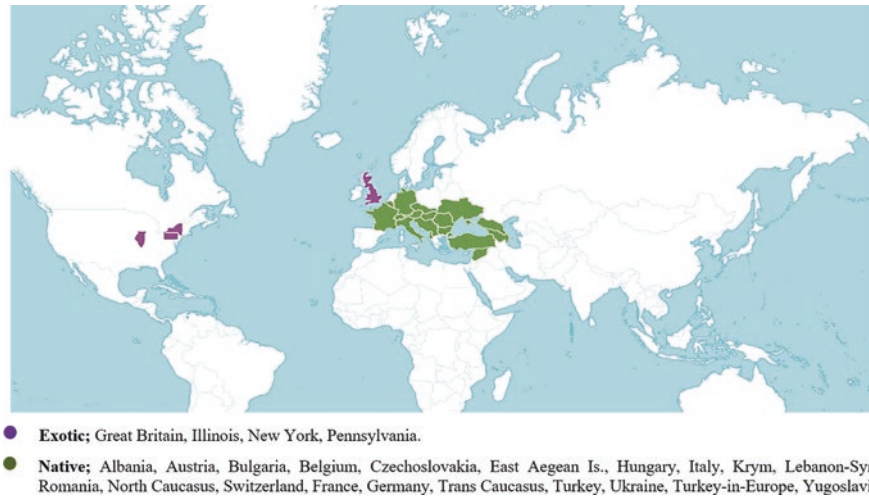


**Fig 13.2** The distribution of *Cornus mas* L. in the world (PoWO 2021)

### 13.1.2 Ethnomedicinal and Other Traditional Usages

In the archaeobotanical study conducted in six Late Neolithic (3600–2800 B.C) excavations sites, *C. mas* seeds were found in the inner (bone and stone tool manufacturing area) and outer (forecourt) areas of a burnt house (Kohler-Schneider and Caneppele 2009). In another archaeobotanical study conducted in the Kerkenes Mountain (middle Phrygian period region (540 B.C)), *C. mas* endocarps were found in the Palatial complex (Smith and Branting 2014). Data are showing that the bark and leaves of the

plant were used therapeutically in ancient and Neolithic ages (Aykut and Konuklugil 2018). These data show us how long the use of the plant goes back to the past.

It is known that traditional medicine usage of *C. mas* in Central Asia and the Caucasus (treatment of digestion problems, sore throats, chickenpox, measles, anaemia, rickets, kidney (pyelonephritis) and liver (hepatitis A) diseases (Dinda et al. 2016)) is for more than 1000 years (Asgary et al. 2013; Aykut and Konuklugil 2018; Dinda et al. 2016; Hosseinpour-Jaghdani et al. 2017). In Ancient Asia (in particular China) and Europe, traditional medicines, which have different medicinal approaches, were found similar uses of the plant to better kidney and liver functions (Czerwinska and Melzig 2018). *C. mas* matter in Traditional Chinese Medicine (TCM) with its analgesic and diuretic impact (Aykut and Konuklugil 2018).

The fruits of *C. mas* and *Cornus officinalis* L. have a long history of use in TCM. Known as "shānzhūyú", it is used to retain the jing (essence), in cases of spermatorrhoea, and to tonify the kidneys (Lietava et al. 2019). In countries of the Caucasus region (Dinda et al. 2016), pulp and seed oil have been used in the treatment of difficult healing wounds, stomach ulcer and colitis (Dinda et al. 2016; Hosseinpour-Jaghdani et al. 2017). Powders prepared from flowers, leaves and aerial part have also been used therapeutically in traditional medicine. Also, galenic prepared from the *C. mas* bark have been used in traditional medicine to cure skin wounds and boils. It is known that the famous Physician Avicenna (A.D 980–1037) used the cornelian cherry juice to wash wounds and the root to prepare wound and burn ointment (Aykut and Konuklugil 2018).

*C. mas* has not been used only therapeutically from past to present. For instance, cornelian cherry fruit is consumed fresh or as a food product in many processed forms such as jam, marmalade (Aykut and Konuklugil 2018; Yiğit 2018), syrup (Yiğit 2018), jelly (Işık et al. 2014; Petkova and Ognyanov 2018), tarhana (Bayram and Özturkcan 2020; Işık et al. 2014; Petkova and Ognyanov 2018), fruit juice, alcoholic (Petkova and Ognyanov 2018) and soft drinks (Işık et al. 2014), compote, molass (Aykut and Konuklugil 2018), slatko (thin fruit preserve), rice soup and fruit yoghurt (Dinda et al. 2016). It is known that the strong wood of *C. mas* has been used by Greek craftsmen in making spears, javelins and bows since the seventh century BC (Dinda et al. 2016). Table 13.2 gives information about the fields of usage and used parts of *C. mas* among the people.

In Table 13.3, traditional medicine uses of *C. mas* around the world, used parts of the plant, use methods and local names are presented. Finally, I would like to add that the *C. mas* is a symbol of

**Table 13.2** Other traditional usages of *Cornus mas* L. among people

| Regions | Plant part | Usages | References |
|---|---|---|---|
| Eastern-Albania | FW | Honey plant | Pieroni et al. (2014) |
| | FR | Compote | |
| | | Syrup/soft jam (molass) | |
| | | Beverage | |
| Balıkesir-Turkey | Seed | Natural dye (red colour) | Özdemir-Nath and Kültür (2016) |
| Karst-Slovenia | FR | Jam, syrup, infusion, raw fruit | Lumpert and Kreft (2017) |
| Czech Republic | FR | Eaten raw, marmalade, compote, syrup | Pawera et al. (2017) |
| | | Wine, liqueur, brandy | |
| | | Recreational tea | |
| Central Italy | FR | To flavour grappa or eaten raw | Lucchetti et al. (2019) |
| | FW | Decoction to heal oily skins | |
| | Wood | To build boats | |
| Düzce-Turkey | – | For fishing | Gürbüz et al. (2019) |
| Armenia | FR, Wood, pips of FR | Buttons, bijouterie, chaplets | Nanagulyan et al. (2020) |
| | | Dry molass, jam, compote, juice, liqueur | |
| Anadrini-Kosova | FR | Jam, compote, beverage | Mullalija et al. (2021) |

*FW* flowers, *FR* fruits

**Table 13.3** Ethnobotanical field study results about traditional medicinal usage of *Cornus mas* L., around the world

| Regions | Local names | Plant part | Disease | Preparation | Administration | References |
|---|---|---|---|---|---|---|
| Zonguldak, Bartın, Karabük,Kocaeli-Turkey | Kiren | LV | Hypoglycaemia | Inf | Drunk | Yeşilada et al. (1999) |
| | | FR | DRH | Stewed | Eaten | |
| | | | Hypoglycaemia | Dec | Int | |
| | | | Cold, bronchitis | Soup | | |
| | | | Sunstroke | Stewed with sugar | | |
| West Azerbaijan-Iran | Derakhe zogal akhte | FR, BK | General tonic, astringent, antipyretic (BK), flavouring (FR) | Dec of fruits and bark<br>Fresh or dried fruits | – | Miraldi et al. (2001) |
| Zejane-Croatia | Corn | FR | Nutraceutical | Syrup | Drunk | Pieroni et al. (2003) |
| | | | Anti-obesity | Fermented to produce (vinegar) | | |
| Çatalca-Turkey | Kızılcık | Seed, FR | Diabetes | Swallowed | 1 × 1, used cold, before breakfast | Genç and Özhatay (2006) |
| | | | | Dec. | Int | |
| | | | Cough, DRH | – | Eaten | |
| Kırklareli-Turkey | | FR | DRH (for dogs) | Jam + water | Int (three teacups twice a day-4 days) | Kültür (2007) |
| | | | DRH, cardiac diseases, nephritis | Boiled in water + sugar(compote) | Int, eaten two times a day-8 days | |
| | | | Cough, cold, flu | | Int; eaten twice a day-10 days | |
| | | BK | Antifungal | Ash | Ext | |
| | | | Antipyretic | Dec | Drink one teacup twice a day-4 days | |
| South-West-Romania | – | FR, LV, BK | Astringent, vermifuge, febrifuge, DRH, dysentery, fever | Inf/dec | – | Tita et al. (2009) |
| North-Eastern-Bosnia and Herzegovina | Dren | BK, FR | DRH and intense menstrual bleeding | – | Int | Saric-Kundalic et al. (2011) |
| | | | İntestinal ailments, DRH and paludism | – | Mix | |
| Kosovar side – Albanian Alps | Thana | FR | Anti-diabetic | Dec | – | Mustafa et al. (2012) |
| | | | Stomach disorders, anti-rheumatic | Tincture | | |
| | | | Anti-anaemic | Decoction | | |
| Republic of Macedonia | Dreni, Thana | FR | DRH (in children), increase appetite | Inf: Juice (hoshaf) | – | Rexhepi et al. (2013) |
| Bingöl-Turkey | Kızılcık | FR, LV | Colds, flu and urinary inflammations | Inf | Dot | Polat et al. (2013) |
| Manisa-Turkey | Güren, Kizilcik | FR | DRH | – | Eaten | Bulut and Tuzlacı (2013) |
| Central Anatolia | Kızılcık | FR | Acute diarrhoea | Molass (dried fruits paste) | | Rose et al. (2013) |

(continued)

**Table 13.3** (continued)

| Regions | Local names | Plant part | Disease | Preparation | Administration | References |
|---|---|---|---|---|---|---|
| Eastern-Serbia | Dren | Flos FR | Against DRH, intestinal diseases, against anaemia, stimulant, immune system strengthening | Inf, ptisane | – | Zlatkovic et al. (2014) |
| Eastern-Albania | Thana | FR | Strengthening the heart | – | Snack | Pieroni et al. (2014) |
| Gorjanci-Slovenia | Dren | FR | Abdominal cramps | Maceration in schnapps | Int | Lumpert and Kreft (2017) |
| Czech Republic | Dřín, Drín, Dríenky, Drínky, Dřínky | – | – | – | – | Pawera et al. (2017) |
| Edirne-Turkey | Kızılcık | – | Diabetes | Pickled, fruits juice, jam | – | Güneş (2017) |
| Central Italy | Grugnale | Shoots | Febrifuge | Inf | – | Lucchetti et al. (2019) |
| Düzce-Turkey | Kızılcık, Kiren, Yabani kiren | FR | Diabetes, untreated disease | Compote sugar free | Int | Gürbüz et al. (2019) |
| | | | Abdominal pain and diarrhoea | Fruit juice | | |
| | | | Abdominal pain | Dried fruit Dec. | | |
| | | | Facilitating birth, relieving pain | Dried fruit compote | | |
| | | Twig | Toothache | The water coming out of the twig, which is kept on fire for a short time, is rubbed into the tooth | Ext | |
| Armenia | Hon | FR | DRH, cold, digestive disorders | Jam with tea | Int | Nanagulyan et al. (2020) |
| Romania | Corn | FR | Digestive, psychological, typhoid fever | – | – | Petran et al. (2020) |
| Anadrini-Kosova | Thana, Drenina Tërnine | FR | Fever, hypertension, improve immunity | Tea | – | Mullalija et al. (2021) |
| | | LV | Diabetes | Eaten raw | | |

*BK* bark, *Dec* decoction, *Dot* drink one tea cup after meals, *DRH* diarrhoea, *Ext* external use, *FR* fruits, *LV* leaves, *Inf* infusion, *Int* internal use, *UV* use volume

longevity, spiritual strength and endurance among the people, and even the phrase "healthy as cornelian cherry" in Serbia is used (Bilejic et al. 2011).

## 13.2 Chemical Compositions

*C. mas* is a rich resource of many bioactive substances such as vitamins, anthocyanins (Asgary et al. 2013; Yiğit 2018), ursolic acids (Asgary et al. 2013), oxalic acids (Badalica-Petrescu et al. 2014), minerals and fibres (Yiğit 2018). In addition to them, also *C. mas* comprises volatile oils (De Biaggi et al. 2018; Krivoruchko et al. 2011). Table 13.4 lists the volatile oil components of the plant. Some similar volatile oils were obtained from fruits (Italy (De Biaggi et al. 2018)), fruits/pulps (Greece (Bakirtzi et al. 2013)) and flowers (Serbia (Stevanović et al. 2014) and Ukraine (Krivoruchko et al. 2011)) of *C. mas*, which are collected from different regions. Similar

**Table 13.4** Volatile oils in *Cornus mas* L.

| Systematic name | Plant part | References |
|---|---|---|
| Limonene, borneol, verbenone, carvacrol, camphor, benzylacetate, dodecane, 2-methoxy-4-vinylphenol, pentadecane, tricosane | Flower | Krivoruchko et al. (2011) |
| Octen-3-ol, 2-(4-methylcyclohex-3-en-1-yl) propan-2-ol, furan-2-carbaldehyde 6,10,14-trimethylpentadecan-2-one, ethyl tetradecanoate, Kaur-16-ene, 2-(4-methylcyclohex-3-en-1-yl) propan-2-ol | Fruit | Bakirtzi et al. (2013) |
| 2-Methoxy-4-methylphenol, 2-phenylethanol, methyl hexadecanoate, methyl (9Z,12Z)-octadeca-9,12-dienoate | Pulp | |
| Heneicosane, tricosane, pentacosane, heptacosane, nonacosane, sesquiterpenoids, diterpenoids | Flower | Stevanović et al. (2014) |
| Phellandrene, γ-terpinene, terpinolene, limonene | Totally ripe fruit | De Biaggi et al. (2018) |

compounds found in parts of *C. mas* are given in Table 13.5.

Kucharska et al. (2015) in their study with *C. mas* fruit which are collected from five different regions (26 cultivars and 2 ecotypes) reported that "ligonic acid", which is rare in the fruits of other botanical families, was found predominantly, and compared to other anthocyanins analysed in this research, the amount of pelargonidin 3-O-galactoside reached 91%. And, they suggested that the presence of such rare anthocyanin would provide validation in the identification of cornelian cherry products. Cosmulescu et al. (2017), in their study with fruits belonging to seven different species (*Prunus spinosa* L., *C. mas*, *Crataegus monogyna* Jacq., *Rubus fruticosus* L., *Hippophaë rhamnoides* L., *Prunus padus* L., *Rosa canina* L.), reported that the highest concentrations of caffeic acid (1.26 ± 0.06) and myricetin (30.54 ± 1.23) were in the *C. mas* fruit. In the analysis conducted by Popovic et al. (2018), querciturone was the highest presence phenolic compound in methanolic fruit extracts (982.5 ± 342.62 μg/g of *Cornus sanguinea* and 81.13 ± 94.96 μg/g of *C. mas*). Chemical characterization of *C. mas* is given in Table 13.6.

Figure 13.3 shows the chemical structure depiction of pelargonidin 3-galactoside and ascorbic acid (vitamin C).

## 13.3 Pharmacological Activities

*C. mas* has high nutritional value and also has therapeutic properties (Yılmaz et al. 2020). *C. mas'* anti-diabetic, antioxidant, anti-inflammatory, antimicrobial, anti-hyperlipidaemic, hepatoprotective, renal-protective (Aykut and Konuklugil 2018; Hosseinpour-Jaghdani et al. 2017), anti-obesity, anti-epileptic, anti-atherosclerotic, anti-hypercholesterolemic, cytotoxic, cardioprotective, neuroprotective and memory-enhancing activities have been demonstrated by modern pharmacological studies (Aykut and Konuklugil 2018).

### 13.3.1 Antioxidant and Antimicrobial Activity

The plant is known to increase the death rate of some tumour cells and stop them from dividing. Accordingly, studies have reported that *C. mas* has antioxidant potential and anti-carcinogenic effect (Yılmaz et al. 2020). The results of the research with fruit stones have been reported a strong correlation between antioxidant activities and total phenolic. At the same time, some studies have revealed the antioxidant activities of leaves and flowers (Yiğit 2018).

Şengül et al. (2014) have reported supportive results on the antioxidant effect and nutraceutical potential of *C. mas*. Badalica-Petrescu et al. (2014) found antioxidant capacity (1.5–1.7 times) and total phenolic content (around three times, $p < 0.005$) of aqueous extract of *C. mas* leaf were higher than *C. monogyna*. Natic et al. (2019) found that the most effective ferric ion

**Table 13.5** Identified compounds from flowers, fruits and pulps of *Cornus mas*

| | Flowers | | Fruits | | Pulps |
|---|---|---|---|---|---|
| Compounds | Stevanović et al. (2014) | Krivoruchko et al. (2011) | De Biaggi et al. (2018) | Bakirtzi et al. (2013) | Bakirtzi et al. (2013) |
| 1-Octen-3-ol | – | + | – | + | + |
| 2-Phenylacetaldehyde | – | + | – | + | |
| 2-Methyldecane | – | + | – | – | + |
| 3,7-Dimethylocta-1,6-dien-3-ol | – | + | – | + | – |
| Limonene | – | + | + | – | – |
| Borneol | – | + | – | – | + |
| 2-(4-Methylcyclohex-3-en-1-yl)propan-2-ol | – | + | – | + | + |
| Dodecane | – | + | – | – | + |
| 5-Butylnonane | – | + | – | – | + |
| Pentadecene-1 | – | + | – | + | – |
| Pentadecane | – | + | – | – | + |
| Heptacosane | + | + | – | – | – |
| Heptadecene-1 | – | + | – | + | + |
| Heneicosane | + | + | – | + | – |
| Tricosane | + | + | – | + | – |
| Pentacosane | + | + | – | + | – |
| Sesquiterpenes | + | – | – | + | – |

chelating (81.37–90.66%) and anti-tyrosinase inhibition capacities (21.75–74.23%) of methanolic extract of *C. mas* fruits compare to 2 different species. In the same study, it was reported that *P. spinosa* extract had the highest activity in the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical test and the richest in polyphenols. Yılmaz et al. (2020) recorded the significant antioxidant effect of aqueous and methanolic extracts of the fruit of *C. mas* on brain, testis, liver, lung, kidney tumour development in Balb/C type male mice injected with Ehrirch Ascites Tumour model.

Yiğit (2018) showed the antimicrobial (aqueous and methanolic extracts showed the strongest effect against *Staphylococcus aureus*; the only methanolic extract was effective against the fungus) and antioxidant effect of the extract of *C. mas* fruit (DPPH scavenging activity is higher in aqueous than methanolic extract). Efenberger-Szmechtyk et al. (2020b) reported that the results of their study with the leaf extract of the *C. mas* did not agree with the literature data stating that gram(+) bacteria are more sensible to phenols than a gram(−). In Table 13.7, information on antioxidant and antimicrobial activity studies performed on *C. mas* plant parts collected from different regions are given.

### 13.3.2 Anti-diabetic and Anti-obesity Activities

Diabetes, which causes damage and dysfunction of different organs in the long term, leads to a decrease in quality of life and an increase in mortality. *Cornus* fruits are one of the major elements of many herbal anti-diabetic preparations in Asian countries (Jayaprakasam et al. 2005). For instance, *C. mas* is used in the treatment of diabetes-related diseases in Asia (Jayaprakasam et al. 2006). *C. mas* is known to be 1 of 17 species used in Chinese herbal formulations for diabetes management (Shi et al. 2019). Anti-diabetic medicinal herbs are low-cost and have fewer critical side effects compared to synthetic medicines, leading people to use these types of herbs (Jayaprakasam et al. 2005).

Dzydzan et al. (2019) stated that the results obtained by feeding type 1 diabetic rats with two cultivars of *C. mas* fruit extracts assume that "*C.*

**Table 13.6** Chemical characterizations of *Cornus mas* L.

| Phytochemical groups | Compounds | Plant parts | References |
|---|---|---|---|
| Anthocyanins | Cyanidin-3-O-rutinoside, peonidin 3-O-glucoside, delphinidin | FR | Şengül et al. (2014) |
| | Pelargonidin 3-galactoside, delphinidin 3-galactoside, cyanidin 3-galactoside | | Kucharska (2012); Jayaprakasam et al. (2006) |
| | Cyanidin 3-robinobioside, pelargonidin 3-robinobioside | | Kucharska (2012) |
| Carotenoids | (9Z) + (9′Z)-Lutein, (13Z) + (13′Z)-lutein, (9′Z)-neoxanthin, lutein-5,6-epoxide, (E)-neoxanthin, luteoxanthin (epimers), neochrome (epimers), β-cryptoxanthin, β-carotene-5,6-monoepoxide, β-carotene | FR | Horváth et al. (2007) |
| Carbohydrates | Fructose, glucose | FR | Perova et al. (2014) |
| | Calcium pectate | | Bilejic et al. (2011) |
| Coumarins | Aesculin | FR | Natic et al. (2019) |
| Fatty acids | Palmitic, stearic, oleic, Linoleic, linolenic acid | FR | Kucharska et al. (2007); Kucharska (2012) |
| | Behenic, pentadecanoic, palmitic, palmitoleic, stearic | FR, LV | Krivoruchko (2014) |
| | Hex-4-enoic acid | Pulp | Bakirtzi et al. (2013) |
| | Octanoic acid, nonanoic acid, decanoic acid | FR | |
| Phenolic acids | Vanilic, sinapic, salicylic acid | FR | Cosmulescu et al. (2017) |
| | p-Hydroxybenzoic acid, syringic acid | | Cosmulescu et al. (2017); Natic et al. (2019) |
| | 5 O-Caffeoylquinic acid (chlorogenic acid) | | Badalica-Petrescu et al. (2014); Natic et al. (2019) |
| | p-Coumaric acid | | Natic et al. (2019) |
| | Caftaric acid isomer, p-coumaroylhexoside isomer | LV | Efenberger-Szmechtyk et al. (2020b) |
| | Protocatequic acid, ellagic acid, gentisic acid, trans-cinnamic acid, sinapic acid, ferulic acid, caffeic acid hexoside I, o-coumaric acid hexoside, p-coumaric acid derivative | | Badalica-Petrescu et al. (2014) |
| | Caffeic acid derivative | | Badalica-Petrescu et al. (2014); Efenberger-Szmechtyk et al. (2020b) |
| | Ellagic acid | | Efenberger-Szmechtyk et al. (2020b) |
| | Gallic acid | FR | Cosmulescu et al. (2017); De Biaggi et al. (2018); Natic et al. (2019) |
| | | LV | Efenberger-Szmechtyk et al. (2020b); Badalica-Petrescu et al. (2014) |
| | Protocatechuic acid | FR | Natic et al. (2019) |
| | Cinnamic acids (coumaric acid, caffeic acid, ferulic acid, chlorogenic acid) | | De Biaggi et al. (2018) |

(continued)

**Table 13.6** (continued)

| Phytochemical groups | Compounds | Plant parts | References |
|---|---|---|---|
| Flavonols | Quercetin 3-O-galactoside | FR | Natic et al. (2019) |
| | Quercetin-3-O-rutinoside, quercetin-3-O-glucuronylpentoside Quercetin-3-O-glucoside | LV | Efenberger-Szmechtyk et al. (2020b) |
| | Kaempferol 3-glucuronide, quercetin 3-glucuronide | | Efenberger-Szmechtyk et al. (2020b); Badalica-Petrescu et al. (2014) |
| | Isorhamnetin 7-rhamnoside, quercetin-3-O'galactoside, 7-O'Rhamnoside, caffeic acid hexoside II, myricetin | | Badalica-Petrescu et al. (2014) |
| | Rutin | FR | De Biaggi et al. (2018); Natic et al. (2019); Popovic et al. (2018) |
| | Hyperoside, quercitrin | | De Biaggi et al. (2018) |
| Flavonoids | Catechin | FR | De Biaggi et al. (2018) |
| | Epicatechin | LV | Badalica-Petrescu et al. (2014) |
| | Naringin, apigenin, phlorizin | FR | Natic et al. (2019) |
| | Myricetin | | Cosmulescu et al. (2017) |
| Iridoids | Loganic acid | FR | Kucharska et al. (2015) |
| | Loganic acid isomer 1, secoxyloganin, loganic acid isomer 2, loganic acid isomer 3, cornuside | LV | Efenberger-Szmechtyk et al. (2020b) |
| | Catalposide | FR | Sochor et al. (2014) |
| | Sweroside | | Perova et al. (2014) |
| Minerals | Ca, Mg, Zn, Fe, | FR | Cosmulescu et al. (2017); Gozlekci et al. (2017); Karaaslan et al. (2018) |
| | Cr, Na, Mn, B, Cu | | Cosmulescu et al. (2017) |
| | K | | Gozlekci et al. (2017); Karaaslan et al. (2018) |
| | P | | Gozlekci et al. (2017) |
| Organic acids | Citric acid, succinic acid, malic acid, oxalic acid, tartaric acid | FR | De Biaggi et al. (2018) |
| Tannins | Ellagitannins (camptothin A isomer 1, camptothin A isomer 2, camptothin A isomer 3, cornusin F isomer 1, cornusin F isomer 2, cornusiin A isomer 1, Camptothin A isomer 4) | LV | Efenberger-Szmechtyk et al. (2020b) |
| | Vescalagin | FR | De Biaggi et al. (2018) |
| | Prosiyanidin $B_1$, prosiyanidin $B_2$ | | Drkenda et al. (2014) |
| Triterpenoid | Ursolic acid | FR | Jayaprakasam et al. (2006); Rudrapaul et al. (2015) |
| | | FW | Savikin et al. (2009) |
| Vitamins | Dehydroascorbic acid | FR | De Biaggi et al. (2018) |
| | Vitamin C | | De Biaggi et al. (2018); Kucharska et al. (2009) |
| Others | Resveratrol | FR | Sochor et al. (2014) |

*FR* fruits, *FW* flowers, *LV* leaves

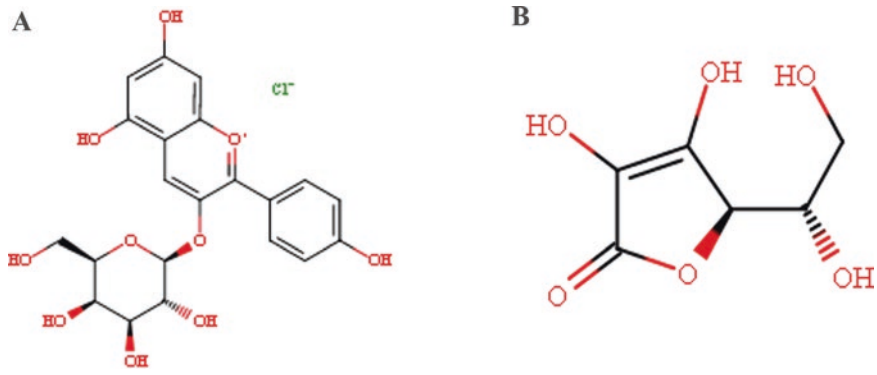


**Fig. 13.3** Chemical structure depiction of A: pelargonidin 3-galactoside B: vitamin C

**Table 13.7** Pharmacological activities of *C. mas* L. in vitro and in vivo experimentations

| Plant part | Region | Activities | Method/standard | Used materials | Extract | References |
|---|---|---|---|---|---|---|
| LV | Transylvania-Romania | OX | DPPH/Trolox | – | Water | Badalica-Petrescu et al. (2014) |
| LV, Flower, FR | Serbia | | DPPH/gallic acid, rutin hydrate, standardize *Gingko biloba* extract | In vitro | Methanol, water, ethyl acetate, acetone, petroleum ether | Stankovic et al. (2014) |
| FR (25 different genotypes) | Oltenia-Romania | | DPPH/ Trolox | – | Methanol | Cosmulescu et al. (2017) |
| FR | Erzincan-Turkey | OX | DPPH, thiocyanate (LPI) | | Water, methanol | Yiğit (2018) |
| | | MIC | Disk diffusion | 93 human pathogenic clinical strains isolates | | |
| FR (10 different genotypes) | Serbia | OX | DPPH, FCC, FRC, NO, Tyr | – | Methanol | Natic et al. (2019) |
| FR | Italy | | FRAP | | | De Biaggi et al. (2018) |
| FR | Erzurum-Turkey | | B-carotene bleaching | | Ethanol | Şengül et al. (2014) |
| LV | Central Poland | BAC | Micro-culture | Gram +/− bacteria found in meat and meat products | – | Efenberger-Szmechtyk et al. (2020b) |
| | | OX | DPPH, ABTS | – | | |
| FR | Turkey | | GSH, GST, SOD, CAT, LPI | Balb/C type, 32 male mice | Methanol, water | Yılmaz et al. (2020) |

*ABTS* 2,2-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid), *BAC* antibacterial, *CAT* catalase, *FCC* ferrous ion-chelating capacity, *FRC* ferric ion-reducing capacity, *GSH* glutathione, *GST* glutathione S-transferase, *LPI* lipid peroxidase inhibition, *MIC* antimicrobial, *NO* nitric oxide scavenging activity, *OX* antioxidant, *SOD* superoxide dismutase, *Tyr* anti-tyrosinase activity test

*mas* can be considered as a food supplement to alleviate diabetes mellitus and its complications". In the study conducted on the stimulation of insulin secretion on rodent pancreatic β-cells of anthocyanins isolated from *C. officinalis* and *C. mas*, at a concentration of 4 and 10 mM glucose, the most active insulin secretagogues were delphinidin-3-glucoside (isolated from *C. officinalis*) (1.8 time increase (49 ng/mg of protein); 1.4-fold (113 ng) respectively). However, cyanidin-3-galactoside (ısolated from *C. mas*) increased 17 ng/mg of protein of insulin (1.2-time) at 10 mM glucose (Jayaprakasam et al. 2005). Consequently, these results register that *Cornus* fruits can be used in the avoidance of type 2 diabetes. I would like to point out that little is known about the activities on diabetes of extracts of *C. mas* fruit compared to *C. officinalis* (Dzydzan et al. 2019). Addedly, the relationship of the aldose reductase enzyme in the development of chronic diabetic complications is known (Forman et al. 2020). In this sense, Forman et al. (2020) have been confirmed that potent inhibition effect on aldose reductase enzyme of *C. mas* and *Cornus kousa* Burg. flowers ($IC_{50}$ 3.06 ± 0.06 and 2.49 ± 0.07 μg/mL, respectively).

It is known that insulin resistance is generally associated with obesity. Consideration has been centred on food that may help prevent diet-induced body fat accumulation and probably decrease the risk of diabetes (Jayaprakasam et al. 2006). Jayaprakasam et al. (2006) obtained that the dietary anthocyanins (*C. mas* fruits) have been led to a 24% decline in body weight in mice. Table 13.8 includes the studies and results in this field.

### 13.3.3 Epilepsy

An epileptic seizure is caused by transient abnormal synchronization of neurons in the brain that disrupts normal neuronal communication patterns and causes increased and decreased

**Table 13.8** Anti-diabetic and anti-obesity effects list of *C. mas* L. in vivo and in vitro studies

| *C. mas* | Study group(s) | Duration | Dose | Administration | Variable and results | Authors |
|---|---|---|---|---|---|---|
| FRE | Wistar male Rats (type-1 diabetes mellitus) | 14 days | 20 mg $kg^{-1}$ of body weight | Oral | ↑ Erythrocyte resistance to acid haemolysis, Reduced glutathione, ↓Blood glucose, Glycated haemoglobin (by 25%), Decline in body weight | Dzydzan et al. (2019) |
| FR Dried powdered | Alloxan-induced diabetic rats | 4w | 2 g/d | | ↓ G, TCH, ALT, ALP, LDL-CH, AST | Asgary et al. (2014) |
| FR-Anthocyanins and Ursolic Acid | High-Fat-Fed C57BL/6 Mice | 8 weeks | 1 g of pure anthocyanin mix and 500 mg of ursolic acid per kg | | Anthocyanin-treated mice ↓ TG ↓ lipid liver accumulation Both ↑↑ insulin | Jayaprakasam et al. (2006) |
| Cyanidin-3-galactoside | Rodent pancreatic *β*-cells | – | 50 μg/mL | In vitro | ↑ Insulin secretion | Jayaprakasam et al. (2005) |

*FR* fruit, *FRE* fruit extract

electrical discharges on the EEG (Moshé et al. 2015). It is known that oxidative stress plays a role in the pathophysiology of epilepsy (Tubaş et al. 2017).

Tubaş et al. (2017) using Wistar rats (60 males; 8–12 weeks old) noted that the frequency of penicillin-induced epileptic activity decreased effectively by intraperitoneal injection of 10 mg/kg (effective dose) *Morus rubra* L. and *C. mas* extracts of fruits. Meanwhile, positive results on malondialdehyde in both extracts made the research team think that the anticonvulsive effect occurred through malondialdehyde.

### 13.3.4 Protective Properties

Dragan et al. (2014) found that the polyphenol extract of *C. mas* leaf (0.01 mg/mL) showed a cardioprotective activity on rats cardiomyocytes in both normoxic and hypoxic situations via rising the cell viability by 11% and 19%, sequentially (and *C. monogyna* increasing viability by 11% and 17%, respectively). However, *Prunella vulgaris* L. had no meaningful impact on cell viability. Table 13.9 shows cardioprotective and hepatoprotective effect studies.

Additionally, Zarei et al. (2014) demonstrated that ethanolic extract of *C. mas* fruits and vitamin E showed a protective effect against methotrexate-induced cytotoxicity in sperms of mice (48 young adults).

### 13.3.5 Cosmetic Accordance

In Europe, extracts of *C. mas* fruits are used for cosmetic aims, used instead of synthetic astringents, and are claimed to positively affect the skin (Şengül et al. 2014). Nizioł-Łukaszewska et al. (2018) stated that the addition of *C. mas* fruits extracts (solvents: water + glycerol and sunflower oil) to emulsion formulations plays an important role in increasing emulsion stability and has positive effects on the rheological particulars of the product. Besides, the results of the study have shown that the water-glycerin *C. mas* extracted formulation caused irritation on human skin fibroblasts (BJCRL-2522 cell line), while the oily extracts did not cause irritation.

### 13.3.6 Cytotoxic Activities

The aqueous extract of *C. mas* leaf exhibited more cytotoxic effect ($IC_{50=}$0.60%) against human colon adenocarcinoma cell line than extracts of *Aronia melanocarpa* (Michx.) Elliott and *Chaenomeles superba* Lindl. in MTT assay. Besides, extracts showed genotoxicity in a concentration-dependent manner in the alkaline comet assay (Efenberger-Szmechtyk et al. 2020a). However, *C. mas* fruit puree and *C. officinalis* juice were non-genotoxic in *Salmonella typhimurium* in reverse mutation tests (West et al. 2012).

**Table 13.9** Cardioprotective and hepatoprotective activities of *Cornus mas* L.

| Extract/compound-plant part | Model | Dosage | Effect | References |
|---|---|---|---|---|
| Polyphenol-leaf | Neonatal Wistar rats (270n.) cardiomyocytes | 0.01 mg to 0.0001 μg/mL (72 h) | ↑ Cell viability | Dragan et al. (2014) |
| Hydromethanolic-fruits | $CCl_4$-induced cardiotoxic rats | 300 and 700 mg/kg bw/d (16 days) pre- and post-treatments | Ameliorating myocardial injury and enhancing myocardial endogenous antioxidant enzymes and reducing the raised levels of myocardial lipid peroxides, serum LDH and CK | Es'Haghi et al. (2012) |
| Methanol: water-fruits | $CC_{l4}$-induced hepatotoxicity Wistar strain male albino rats (30n.) | 200 and 500 mg/kg orally (14 days) | ↓ TBARS production, MDA | Alavian et al. (2014) |

*TBARS* Thiobarbituric acid reactive substance, *bw* bodyweight

**Table 13.10** Review of clinical trials about *Cornus mas* L.

| *C. mas* | Study group(s) | Duration | Dose | S. design | Variable and results | Authors |
|---|---|---|---|---|---|---|
| Ethanol 80% and HCL 0.1% FRE | 80 NAFLD patients | 12 weeks | 320 $mg.d^{-1}$ anthocyanins per day | RDBPCT | – | Sangsefidi et al. (2019) |
| Hydro alcoholic FRE | 84 post-menopause women (45–60 years old) | 8 weeks | 3 capsules per day (total 900-mg) | RDBPCT | ↑ HDL, ApoA1 ↓ LDL/HDL, TC/HDL, Fibrinogen, BMI, FI, IRI | Gholamrezayi et al. (2019) |
| FREs | 12 healthy people (7 women, 5men; 12–48 years old) | 5 days | 30 µL | Patch test | No allergic or irritation reactions | Nizioł-Łukaszewska et al. (2018) |
| Standardized ethanolic FRE | 60 type 2 diabetic adults (41–65 years old) | 6 weeks | 2 capsules twice a day (equivalent to 600-mg of anthocyanins) | RDBPCT | ↑ Insulin ↓ BMI, TG, 2Hpp, $HbA_{1C}$, FPG | Soltani et al. (2015) |
| FR | 40 dyslipidaemic children (9–16 years old) | | 100 g fruits per day | RCT | ↓ TC, LDL, TG, ApoB, ICAM-1, VCAM-1 ↑ HDL, ApoA1 | Asgary et al. (2013) |

*BMI* body mass index, *FI* fasting insulin, *FPG* fasting plasma glucose, *FR* fruit, *FRE* fruit extract, *HDL* high-density lipoprotein, *ICAM-1* intracellular adhesion molecule-1, *IR*, insulin resistance index, *2Hpp* 2-hour postprandial glucose, *LDL* low-density lipoprotein, *NAFLD* nonalcoholic fatty liver disease, *RCT* randomized-clinical-trial, *RDBPCT* randomized double-blind placebo-controlled trial, *TC* total cholesterol, *TG* triglyceride, *VCAM-1* vascular cell adhesion molecule-1

## 13.4 Clinical Studies

Asgary et al. (2013) have reported a trend towards improvement in apolipoprotein status, lipid profile and vascular inflammation biomarkers in dyslipidaemic children. Soltani et al. (2015) found that daily consumption extract of *C. mas* fruit (equivalent to 600 mg anthocyanin) decreased triglyceride serum level in diabetic patients (type 2) and improved glycaemic control by rising insulin level. Nizioł-Łukaszewska et al. (2018) observed no-allergic or no-irritation reactions during patch testing of extracts in human subjects. Table 13.10 shows clinical studies of *C. mas*.

## 13.5 Toxicity Studies

*C. mas* fruit puree was non-toxic (lethal dose (LD) >5200-mg $kg^{-1}$ body weight) in acute oral toxicity assay (in three 9-week-old female rats) (West et al. 2012). Any adverse effects were not recorded in the oral consumption (for 6 weeks) anthocyanin extract of *C. mas* fruit (600-mg per day) in diabetic adult patients (Soltani et al. 2015). Asgary et al. (2013) reported that fresh *C. mas* fruit consumption (100 g per day for 6 weeks) on dyslipidaemic children and adolescents were not toxic. Gholamrezayi et al. (2019) showed that the consumption of 900 mg hydro alcoholic extract of *C. mas* fruit per day for 8 weeks had no side effects in postmenopausal women.

## 13.6 Available Products

A commercial drug with antimicrobial, antihyperglycaemic and antiviral properties, rich with Corni mas cortex (*C. mas*), which enhances regulating the activity of abdominal functions, has been produced (Pavlova et al. 2020). Pavlova et al. (2020) suggested that this product can be

considered as a drug with curative features as it has been discussed in the literature. The other product is consisted of noni fruit puree and is join in *C. officinalis* and *C. mas* juices and olive (*Olea europaea*) leaf extract (West et al. 2018). Cornelian cherry is present in this beverage due to their anti-inflammatory talent and antioxidant capacity (Tahitian Noni® 1996).

Tea, jam, syrup, fruit juice, liqueur, marmalade and tarhana were commercially produced products from fruits of *C. mas*. Cornelian cherry wine and chocolate were also produced.

### 13.6.1 Pharmacokinetics

Radbeh et al. (2020) showed that encapsulated into enteric-coated nanocarriers water: ethanol extract of *C. mas* fruit (CME) could increase $IC_{50}$ value (1.33 and 1.47 times) more than free CME. The science team indicated that encapsulated CME could stop cell proliferation at the G1 phase and induce apoptosis in the human colorectal cancer cell line.

## 13.7 Comparison of Ethnobotanical Data and Scientific Studies

The traditional uses of the plant for obesity and diabetes therapy and cardioprotective and antifungal purposes are consistent with the scientific evidence, but not all parts of the plant used ethnomedically have been examined. In other words, studies have focused on fruits in general. Likewise, also in clinical trials, the fruit has been used. However, according to the ethnobotanical data, parts of *C. mas* such as bark, twig, flower and seed are also known to be used in the treatment of many diseases.

## 13.8 Conclusions

Although varied parts of *C. mas* have been used in traditional medicine since ancient times, researches have mostly focused on the fruit. Certain traditional uses of the plant for therapeutic purposes in many diseases have been confirmed by in vivo and in vitro experiments. Nonetheless, clinical researches are very few. *C. mas*, which is a multifunctional food, also has the potential to be a medicine. More long-term multiparticipant clinical trials will support the pharmacological capacity of *C. mas*.

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# *Curcuma longa* L.

14

Tuğba Günbatan

**Abstract**

*Curcuma longa* L. (turmeric) is one of the oldest plants, which used as spice and medicine since ancient times. Powder obtained from its rhizome is a broadly used and well-known spice, food stabilizer, and coloring material in India, China, and Southeast Asia. *C. longa* rhizome is also included in the pharmacopoeias of India, China, Japan, and other Asian countries. Recently, its popularity has increased worldwide owing to miscellaneous scientific studies, especially those showing its antiinflammatory, anticarcinogenic, antioxidant, and choleretic effect. In this review, general information about *C. longa* and curcumin (its main component) is given, and their pharmacological properties and effects on health are summarized.

**Keywords**

*Curcuma longa* · Turmeric · Curcumin · Curcuminoids

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## 14.1 Introduction

*Curcuma longa* L. (turmeric) is widely used as a spice, food preservative, and coloring material especially in Indian subcontinent (Balaji and Chempakam 2010). Besides, it also has a religious and cultural significance in India due to its usages in rituals such as marriage ceremonies (Haldi ceremony), drawing "Tilaka" (a mark created by the application of powder or paste prepared with turmeric on the forehead). More importantly, it has long history as traditional medicine in China, India (Ayurvedic medicine), and Iran (Jacob and Toloue 2013; Noorafshan and Ashkani-Esfahani 2013). It was introduced to the Western world in the fourteenth century and recently still retains its importance (Noorafshan and Ashkani-Esfahani 2013). India is the largest producer, consumer, and exporter of *C. longa* (Jacob and Toloue 2013).

There are many scientific investigations on *C. longa* that globally used spice. According to these in vivo, in vitro, and clinical research, *C. longa* and its ingredients may have potential therapeutic activity against inflammatory disease, cancer, and digestive system disorders. Extensive research has proven that the majority of the actions of the turmeric are due to curcumin (Balaji and Chempakam 2010). Therefore, in this review, general scientific information about *C. longa* and curcumin, its major component, has been summarized.



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### 14.1.1 Botanical Aspects

*Curcuma longa* L. [Zingiberaceae, synonyms: *C. longa* L. var. *vanaharidra* Velay., Pandrav., J. K. George & Varapr., *C. domestica* Valeton, *C. rotunda* L., *C. xanthorrhiza* Naves, *Amomum curcuma* Jacq.] is a perennial, ascending, rhizomatous plant, up to 1.0 m in height. The main rhizome forms a tuber (about 3 cm in diameter and 4 cm long, orange inside) with numerous roots, while the digitate secondary rhizomes are unrooted. Rhizomes are yellowish-brown with stipules and become transversely ringed after death. Green leaves are up to 1.2 m long and 7–25 cm wide. Ovate-lanceolate leaves are thin, with acute apex, entire lamina margin, and narrows to a long sheath-like petiole at caudate lamina base. Petiole and sheath are sparsely to densely pubescent. Spike is 10 to 15 cm long, 5–7 cm in diameter, and attached to stem in a sheathing petiole. The flower has two pale green, 5 to 6 cm long bracts. The covering bracts are whitish, often red-tinged. Bracteoles are up to 3.5 cm long. Calyx is tubular, unilaterally split, and unequally three-lobed, while the corolla is funnel-shaped, three-lobed, yellowish-white or yellow. Stamens are lateral, petaloid, widely elliptical; filaments are united to anther about the middle of the pollen sac and spurred at base. Ovary is trilocular; style is glabrous. The fruit is globular capsule (PDR 2000; The-Plant-List 2012; WHO 1999).

### 14.1.2 Local Names

Acafrao, chiang-huang, curcum, dilau, gelbwurzel, haku halu, haladi, haridra, huang chiang, jiânghuang, khamin chan, koening, kunyit, kurkum, kurkumawurzelstock, luyang, manjal, nisha, rajani, rame, skyer-rtsa, tumeric, turmeric, ukon, ul gum, wong keong, yii-chin, zardchob (PDR 2000; WHO 1999)

### 14.1.3 Used Parts

Whole, cured (by boiling or steaming), dried rhizome with roots and outer surface removed (Curcuma longae rhizoma) (EMA 2018; PDR 2000)

## 14.2 Distribution and Status of Species

It is indigenous to India, Cambodia, China, Indonesia, Lao People's Democratic Republic, Madagascar, Malaysia, the Philippines, and Vietnam, but cultivated in India, Indonesia, Thailand, and other tropical regions of Southeast Asia and Africa (PDR 2000; WHO 1999).

## 14.3 Comparison of Traditional/Ethnomedicinal/Local Uses: In Turkey and Throughout the World (Asia and Europe)

Ethnobotanical usages of *C. longa* are dating back to 4000 years ago in the Vedic culture in India, where it was used as a culinary spice and for religious practices (Salehi et al. 2019). It is official in the Ayurvedic Pharmacopoeia of India and used extensively in the Indian traditional medicine systems (Ayurvedha, Siddha). It is well-known as antiinflammatory drug for arthritis. The paste prepared from turmeric is used topically for ulcers and scabies in Ayurvedha and Siddha systems. Additionally, its usages for stomach complaints, flatulence, conjunctivitis, constipation, ringworm infestation, colic, urticaria and skin allergy, viral hepatitis, and sore throat take part in Indian traditional medicine systems (EMA 2018; PDR 2000).

As in India, turmeric is official in the Pharmacopoeia of the People's Republic of China as well as in the Japanese Herbal Medicines Codex and is used for abdominal fullness, kidney pain, amenorrhea, nose bleeding, vomiting with bleeding, heat stroke, pains in the chest, ribs, abdomen, liver, and stomach (EMA 2018; PDR 2000).

In Europe, it is generally used for dyspeptic complaints, stomach, gall, and liver complaints (hepatitis), as cholagogue and choleretic (EMA 2018).

## 14.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques

Rhizome of turmeric contains volatile oil (5.8%, α- and β-tumerone, α-phellandrene, borneol, cineol, sabinene, artumerone, α- and γ-atlantone, curlone, zingiberene, curcumol, curcumene), curcuminoids (3–5%, curcumin, demethoxycurcumin and bisdemethoxycurcumin) (Fig. 14.1), 1,5-diaryl-penta-1,4-dien-3-one derivatives, carbohydrates (69.4%), mineral matter (3.5%), protein (6.3%), and fatty oil (EMA 2018; PDR 2000; WHO 1999).

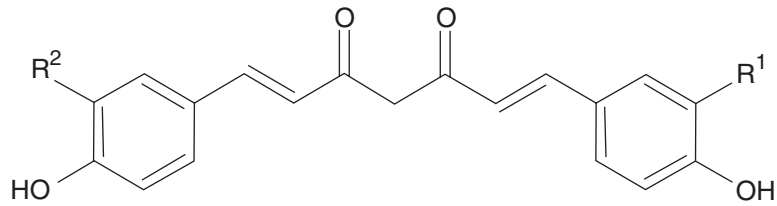
## 14.5 Scientific Evidences: Pharmacological Activities

The choleretic, antiinflammatory, antitumoral, hepatoprotective, antihyperlipidemic, antioxidant, and antimicrobial actions of *C. longa* are experimentally well documented. After the isolation of curcumin and other curcuminoids, which are the major components of turmeric, recently biological activity researches were mostly carried out on curcumin and other curcuminoids. Studies on *C. longa* and curcuminoids are summarized below under related titles.

### 14.5.1 Antiinflammatory Activity

Cytokines, which has important role in immune competent cell signaling, are important mediators of inflammatory pain. In a study that focused on immune-stimulatory and antiinflammatory activities of *C. longa*, NR-INF-02 (an aqueous based extract of *C. longa*) was determined to increase splenocytes number in presence and absence of mitogens (lipopolysaccharide or concanavalin A), and it showed potent inhibitory effect toward release of prostaglandin $E_2$ and interleukin-12 in lipopolysaccharide-stimulated mouse splenocytes. Besides, a significant increase on nitric oxide, interleukins (IL-2, IL-6, IL-10, IL-12), interferon-γ, tumor necrosis factor-α, and monocyte chemotactic protein-1 production in unstimulated mouse splenocytes and mouse macrophages were observed with NR-INF-02 treatment. On the other hand, immune-modulatory effects of polysaccharide fraction and mother liquor of NR-INF-02 were also studied. Polysaccharide fraction represented more potent inhibitory activity than mother liquor of NR-INF-02 on prostaglandin $E_2$ and interleukin-12 in lipopolysaccharide-stimulated splenocytes. These obtained data showed the antiinflammatory property of NR-INF-02, and its polysaccharide fraction occurs via inhibition of interleukin-12 and prostaglandin $E_2$ secretion (Chandrasekaran et al. 2013).

Shakibaei et al. (2007) investigated the effects of curcumin in human articular chondrocyte culture treated with interleukin 1β and tumor necrosis factor-α for up to 72 h. Curcumin was determined to suppress interleukin-1β-induced nuclear factor-κB activation and inhibited the interleukin-1β-induced stimulation of upstream protein kinase B. Similar results were observed in tumor necrosis factor-α-stimulated chondrocytes. On the other hand, it prevented the interleukin-1β-induced downregulation of




| Compound | $R^1$ | $R^2$ |
|---|---|---|
| Curcumin | OMe | OMe |
| Demethoxycurcumin | H | OMe |
| Bisdemethoxycurcumin | H | H |

**Fig. 14.1** Major curcuminoids of *C. longa*

collagen type 2 and β1-integrin receptor expression. According to these results, curcumin was thought to be potential inflammatory agent for osteoarthritis by suppressing nuclear factor-κB-mediated interleukin-1β/tumor necrosis factor-α signaling pathways in chondrocytes (Shakibaei et al. 2007).

In a study focused on antiinflammatory effect of free curcuminoids and nanoencapsulated curcuminoid preparations of poly(vinyl pyrrolidone), male Swiss mice received orally a single dose of nanoencapsulated and free curcuminoids 1 h before croton oil application or topical treatment immediately after croton oil application (200 μg diluted in 70% acetone). Topical application of free curcuminoids and nanoencapsulated curcuminoids (0.25 mg/ear) reduced ear edema by 71% and 91%, respectively, while the oral treatment with free curcuminoids (400 mg/kg) and nanoencapsulated curcuminoids (50 mg/kg) reduced edema formation by 47% and 38%, respectively. Reduction up to 76% and 67% at myeloperoxidase activity were also observed with topical and oral administration of curcuminoids. Finally, the topical and oral treatment with curcuminoids prevented the increase in carbonylated protein levels and decrease in GSH (Glutathione) levels. Although antiinflammatory activity of curcuminoids was demonstrated with this study, it was revealed that curcuminoids can penetrate when applied topically, but nanoencapsulation of curcuminoids is important to prevent biodegradation when taken orally (Lima et al. 2020).

### 14.5.2 Anticancer Activity

Anticancer properties of curcumin have been extensively investigated, and a lot of articles were published in this field. One of these researches performed by Mohammad et al. (2010), *n*-hexane extract of *C. longa*, showed dose-dependent telomerase inhibitory activity and cytotoxic effect on A549 lung cancer cell line with 0.28, 0.27, and 0.23 mg/ml $IC_{50}$ values (half maximal inhibitory concentration) for 24, 48, and 72 h MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assays, respectively (Mohammad et al. 2010).

Fractions (CF-1, CF-2, CF-3, and CF-5) obtained by fractional distillation and chromatographic separation of turmeric oil demonstrated significant biological activity against the PANC-1 pancreatic cancer cell line, at concentrations below 110.52 μg/ml, equivalent to 300 μM curcumin. But according to obtained data, cytotoxic activity of CF-2 and CF-3 does not appear to be associated with caspase activation (Yan et al. 2013).

The oil fractions of *C. longa* purified by repeated high vacuum distillations to constant boiling points and column chromatography (DF-5 and CF-3) and combination with paclitaxel [paclitaxel (1 mg) and DF-5 (10 mg)] had growth inhibitory activity against SKBR-3 ($IC_{50} = 2.33 \times 10^{-4}$, $3.18 \times 10^{-4}$, and $3.9 \times 10^{-7}$, respectively), PANC-1 ($IC_{50} = 3.22 \times 10^{-4}$, $4.02 \times 10^{-4}$, and $4.60 \times 10^{-9}$, respectively), and PC-3 cancer cell lines ($IC_{50} = 4.98 \times 10^{-4}$, $3.34 \times 10^{-4}$, and $1.76 \times 10^{-8}$, respectively) and reduced activity against a non-cancerous cell line, WI-38 ($IC_{50} = 2.98 \times 10^{-3}$, $3.28 \times 10^{-4}$ and $8 \times 10^{-4}$, respectively). These results revealed that turmeric oil fractions obtained by selective distillation have anticancer activity against breast, pancreatic, and prostate cancers and display synergistic effect with paclitaxel (Jacob and Toloue 2013).

Li et al. (2018) reported that 95% ethanol extract of turmeric exhibited cytotoxic effect, inhibited colony formation, and decreased cell motility, migration, and epithelial-mesenchymal transitions via pathways including cofilin, focal adhesion kinase/phospho-steroid receptor coactivator, AKT (Protein kinase B), extracellular-regulated kinase, and Signal transducer and activator of transcription 3 signaling pathways in murine colorectal cancer cell lines (murine colon 26, colon 26-M01, and human HT-29, HCT 116). $IC_{50}$ values of turmeric extract and curcumin on colorectal cancer cells were in the range of 2.77 and 20.1 μg/ml after 48 h treatment. On the other hand, decrease in colon tumor burden and inhibition of liver and

lung metastasis were observed at a dose of 200 mg/kg, in vivo. In the orthotopic xenografts bearing immune-competent mice, tumor microenvironment elements, including T cell (cytotoxic and T helper cells) and cytokines (interleukin-6 and 12), were also regulated by turmeric extract treatment (Li et al. 2018).

Narayanankutty et al. (2020) analyzed the chemopreventive potential of curcumin-enriched virgin coconut oil (4 and 8 ml/kg, orally) in 7,12-dimethyl benz[a]anthracene (DMBA;470 nmoles/200 ml/week for 2 weeks topical)/croton oil (3% v/v in 200 ml acetone twice a week for 6 weeks topical)-induced skin papilloma. 60% inhibition of tumor index and an increased latency period (12.5 ± 0.9 weeks) were observed by curcumin-enriched virgin coconut oil pretreatment. In addition, it caused improvement in DMBA/croton oil-induced reduction in glutathione levels (increase to 49.63 ± 1.86 nmoles/mg protein) and increase in thiobarbituric acid reactive substance (decrease to 2.78 ± 0.52 nmoles/mg protein) in the skin microenvironment (Narayanankutty et al. 2020).

Borges et al. (2020) reported that curcumin reduced cell viability, induced cell death (necrosis/late apoptosis: 44% curcumin vs. 16.4% vehicle), and arrested cell cycle at phase G2/M on SCC-9 and FaDu cell lines. Besides, it downregulated the phosphatidylinositol-3-kinase-AKT-mammalian target of rapamycin signaling pathway by modifying the expression of key genes and proteins. Hence, curcumin may be considered as a promising therapeutic agent for head and neck cancer (Borges et al. 2020).

### 14.5.3 Activity Against Peptic Ulcer and Reflux Esophagitis

Activity of ethanol extract of turmeric against peptic ulcers caused by pyloric ligation, hypothermic-restraint stress, indomethacin, reserpine, cysteamine, and cystodestructive agents (80% ethanol, 0.6 M HCl, 0.2 M NaOH, and 25% NaCl) was evaluated. At a dose of 500 mg/kg, it exhibited significant antiulcerogenic activity on hypothermic-restraint stress, pyloric ligation, indomethacin, and reserpine-induced ulcer methods and protective effect against cystodestructive agents. But turmeric extract treatment could not significantly prevent cysteamine-induced duodenal ulcers (Rafatullah et al. 1990).

To investigate the mechanism underlying its antiulcerogenic activity, *C. longa* 80% ethanol extract was tested whether it inhibits gastric ulcers by blocking the $H_2$ histamine receptor. *C. longa* extract showed preventive effect against dimaprit (a $H_2$ histamine receptor agonist)-induced cyclic adenosine monophosphate production in a dose-dependent manner, while it showed no effect on the elevation of cyclic adenosine monophosphate levels triggered by isoproterenol-induced $\beta_2$-adrenoceptor activation in U937 cells. To identify the active component(s), activities of ethyl acetate, *n*-butanol, and water fractions were also investigated. The most potent $H_2$ histamine receptor antagonistic effect against dimaprit-induced cyclic adenosine monophosphate production was observed with the ethyl acetate fraction. Interestingly, curcumin did not show $H_2$ histamine receptor blocking effect. Furthermore, *C. longa* ethanol extract and ethylacetate fraction prevented the binding of [$^3$H]-tiotidine to membrane receptors on HL-60 cells. Based on these results, *C. longa* extract was thought to reduce gastric ulcer by providing selective and competitive $H_2$ histamine receptor antagonistic effects (Kim et al. 2005).

Curcumin pre-treatment (200 mg/kg) caused reduction in increased leukocyte adherence to post capillary venule by indomethacin. In addition, curcumin pre-treatment significantly decreased the elevated intercellular adhesion molecule-1 and tumor necrosis factor-α levels. The rats treated with indomethacin and curcumin showed improved stomach histopathology and only a mild neutrophil infiltration score and fewer erosive lesions in the gastric mucosa (Thong-Ngam et al. 2012). In another antiulcerogenic activity research, curcumin (50 mg/kg, p.o.) administration showed decrease in ulcer index, total acid output, pepsin activity in gastric juice, and gastric mucosal malondialdehyde concentra-

tion by indomethacin-induced ulcer method in rats, while it caused increase in gastric juice mucin concentration, gastric mucosal nitric oxide level, catalase, and superoxide dismutase activities. These findings were supported by immunohistochemical investigations that demonstrated expression of inducible nitric oxide synthase, nuclear factor-κB, and caspase-3 markedly decreased by curcumin treatment (Morsy and El-Moselhy 2013).

Kim et al. (2016) pre-treated the rats with curcumin (10, 50, and 100 mg/kg) for 3 days and formed gastric mucosal lesions by 80 mg/kg naproxen application twice daily for 3 days. As a result, curcumin was determined to inhibit naproxen-induced gastric antral ulcer formation and lipid peroxidation in a dose-dependent manner. Furthermore, curcumin caused increase in activities of radical scavenging enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase in a dose-dependent manner (Kim et al. 2016).

Curcumin was also evaluated on experimental reflux esophagitis in rats. Results showed that curcumin (20 mg/kg, i.d.) inhibited the formation of acute acid reflux esophagitis by 52.5%. Curcumin alone was found ineffective in preventing chronic acid reflux esophagitis, while the combination of curcumin and dimethyl sulfoxide determined to reduce the mortality rate and the severity of the esophagitis ulcer index (56.5%). On the other hand, intraduodenal administration of curcumin also prevented the formation of acute mixed reflux esophagitis, together with reducing the incidence or the severity of neutrophil infiltration (Mahattanadul et al. 2006).

### 14.5.4 Choleretic Effect

It was reported that 30 min after intravenous injection of curcumin and bisdemetoxycurcumin at a dose of 25 mg/kg, 100%, 180%, and 220% increases in bile flow were observed with the bile fistula model in rats. On the other hand, following cyclosporin injection, which caused 40% reduction in bile flow, bile acid concentration, and excretion, curcumin and bisdemethoxycurcumin administration transiently increased bile flow to 100% and to 125% of the starting value, respectively (Deters et al. 1999). In the further study of the same research group, curcumin (25 and 50 mg/kg, i.v. injection) determined to increase basal bile flow (up to 200%), biliary bilirubin excretion (up to 150%), and biliary cholesterol excretion (up to 113%) with the bile fistula model in rats. Curcumin injection (25 and 50 mg/kg) 30 min after cyclosporine application also caused increase in reduced bile flow and biliary excretion of cholesterol and of bilirubin by cyclosporine. Injection of curcumin 15 min before cyclosporine prevented the cyclosporine-induced drop of bile flow and reduction in biliary bilirubin excretion until 180 min (Deters et al. 2000).

Aqueous suspension of *C. longa* (600 mg powder of *C. longa* was suspended in 10 ml distilled water) was determined to significantly increase the accumulation of bile in gallbladder in mice at a dose of 20 mg/10 g body weight, similarly to verapamil (at a dose of 0.24 mg/10 g body weight). The mean of bile weight was determined as 14.33 ± 0.792 and 14.17 ± 1.641 mg for *C. longa* and verapamil groups, respectively. Therefore, it was concluded that *C. longa* may show similar action with verapamil on bile secretion via p-glycoprotein (Najafzadeh et al. 2011).

### 14.5.5 Hepatoprotective Effect

Hepatoprotective activity of *C. longa* rhizome ethanolic extract was evaluated in rats by thioacetamide-induced liver cirrhosis method. According to obtained results, histopathological, immunohistochemical, and liver biochemical indicators [hepatic cytochrome P450 2E1, transforming growth factor-β1, tumor necrosis factor-α, malondialdehyde, urinary 8-hydroxyguanosine and nitrotyrosine levels, protein expression of pro-apoptotic Bax (B-cell lymphoma 2-associated X-protein) and antiapoptotic Bcl-2 (B-cell lymphoma 2) proteins] were significantly lower in the *C. longa*-treated group compared to control. Besides, *C. longa* was determined to induce

apoptosis, inhibiting hepatocytes proliferation but had no effect on hepatic cytochrome 2E1 levels (Salama et al. 2013). In another research, hepatoprotective effect of *C. longa* against lead-induced toxicity was investigated in Wistar albino rats. Washed, dried, and powdered *C. longa* rhizomes were used along with acacia gum. *C. longa* treatment (500 mg/kg, daily along with 1000 mg/kg lead acetate) was determined to significantly decrease alkaline phosphatase (from 182.44 to 166.58 IU/L), aspartate amino transferase (from 225.18 to 199.29 IU/L), alanine amino transferase (from 73.90 to 52.89 IU/L), and lipid peroxidation levels (from 4.11 to 3.90 nM. malondialdehyde $g^{-1}$) elevated by lead acetate (1000 mg/kg daily orally, for 28 days), while the reduced glutathione levels were increased by *C. longa* treatment (from 2.64 to 4.86 nM/g). But no significant difference was found in superoxide dismutase level and lead concentration in the liver (Baxla et al. 2013).

### 14.5.6 Antidepressant Effect

14-day oral administration of aqueous extract of *C. longa* showed more potent antidepressant effect than fluoxetine in mice, by the tail suspension test and the forced swimming test, at a dose of 560 mg/kg. Monoamine oxidase A activity in whole brain were significantly inhibited with *C. longa* administration at 140 mg/kg or higher doses, while monoamine oxidase B inhibitory activity was observed only at a dose of 560 mg/kg. Obtained data demonstrated that *C. longa* have specifically antidepressant activity via inhibition of monoamine oxidase A (Yu et al. 2002).

### 14.5.7 Antifungal, Antibacterial, Antiviral Effect

Antiviral activity of curcumin was evaluated against antisevere acute respiratory syndrome-associated coronavirus using Vero E6 cells and determined as a potent inhibitor ([Half maximal effective concentration (EC50): >10 μM] (Wen et al. 2007).

Dai et al. (2018) evaluated the effect of curcumin against influenza A virus infection in vitro and in vivo. According to obtained results, curcumin could directly inactivate influenza A virus, blocked its adsorption, and inhibited its proliferation. The mechanisms underlying these activities are inhibiting influenza A virus-induced oxidative stress; stimulating nuclear factor erythroid 2-related factor 2, heme oxygenase-1, nicotinamide adenine dinucleotide phosphate quinone dehydrogenase 1, glutathione S-transferase A3, and interferon-β production; and suppressing influenza A virus-induced activation of toll-like receptors2/4/7, Akt, p38/Jun N-terminal kinase mitogen-activated protein kinase, and nuclear factor-κB pathways. Besides, survival rate of mice was significantly increased, and lung index, inflammatory cytokines, and lung influenza A virus titer were reduced by curcumin (Dai et al. 2018).

Curcumin was also found to be effective against other viruses such as human immunodeficiency virus, enterovirus 71, herpes simplex virus, hepatitis C virus, and human papillomavirus (Babaei et al. 2020).

De et al. (2009) examined the effect of curcumin against 65 clinical isolates of *Helicobacter pylori* in vitro and in vivo. Minimal inhibitory concentrations (MIC) were determined to range from 5 μg/ml to 50 μg/ml. According to histological examination of the gastric damage due to infection in *H. pylori*-infected C57BL/6 mice, orally curcumin administration (25 mg/kg, for 7 days) was found to be highly effective in eradication of *H. pylori* as well as in restoration of *H. pylori*-induced gastric damage (De et al. 2009).

In another research, *C. longa* essential oil determined to show good antifungal activity against *Trichophyton mentagrophytes* and *Microsporum audouinii* at 100 μl per disc concentration (inhibition zones, 55 mm and 57 mm, respectively) (Saxena and Sharma 2017).

Curcumin showed antibacterial effect with 128 mg/l MIC value against *Mycobacterium abscessus* and was synergic with amikacin, clarithromycin, ciprofloxacin, and linezolid (Marini et al. 2018). MIC and Minimum bactericidal concentration values of curcumin deter-

mined as 12.5 μg/ml against *Porphyromonas gingivalis*, and it has been concluded that curcumin has significant antibacterial activity against this bacterium (Sha and Garib 2019).

Methanolic extract of *C. longa* was determined to be active against *Bacillus* spp., *Enterococcus faecalis*, *Micrococcus varians*, *Streptococcus agalactiae*, *Staphylococcus aureus*, *Staphylococcus saprophyticus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Providencia stuartii, Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Serratia marcescens*, and Shigella dysenteriae with high inhibition zones (10.0–24.0 mm) (Zaccchaeus et al. 2020).

### 14.5.8 Anthelmintic Activity

70% ethanol extracts of *C. longa* rhizome and its combination with *Zingiber officinale* Roscoe rhizome (1:1) were determined to have significant anthelmintic activity against *Pheretima posthuma* with maximum vermifuge activity at 50 mg/ml concentration. At this concentration, required times for paralysis and for death were 4.6 and 16.1 min, respectively, with only *C. longa* extract, while required time for paralysis and death was 4.8 min and 16.3 min, respectively, with *C. longa*. and *Z. officinale* combination (Dora babu et al. 2020).

### 14.5.9 Antioxidant Activity

Curcumin, demethoxycurcumin, and bisdemethoxycurcumin were determined to have a strong scavenging effect on superoxide radicals ($IC_{50}$ = 33.63 and 198 μM, respectively) and DPPH (2,2-diphenyl-1-picrylhydrazyl) ($IC_{50}$ = 22.63 and 98 μM, respectively) (Sreejayan and Rao 1996). In another research, curcumin, demethoxycurcumin, bisdemethoxycurcumin, and diacetylcurcumin were determined to nitric oxide scavenging activity with $IC_{50}$ values between 17.9 and 20.4 μM (Sreejayan and Rao 1997).

Methanolic extract of *C. longa* represented high antioxidant activity in galvinoxyl free radical scavenging activity and DPPH free radical scavenging activity test ($IC_{50}$ values were 25 and 5 μg/ml, respectively), and its total antioxidant capacity was found as 1173.08 μg/mg ascorbic acid equivalent (Zaccchaeus et al. 2020).

Antioxidant activity of the methanol, ethanol, and ethyl acetate extracts of turmeric rhizome was evaluated with $H_2O_2$ scavenging activity test, FRAP (ferric reducing antioxidant power), and DPPH assays. Highest antioxidant activity obtained with ethanol extract in FRAP assay (463.25 ± 36.15 μM Fe(II)/g of extract). Similarly, lowest inhibitory concentrations determined with ethanol extract in DPPH assay and $H_2O_2$ scavenging activity test ($EC_{50}$ = 30 and 42 μg/ml, respectively) (Maithilikarpagaselvi et al. 2020).

### 14.5.10 Cardiovascular Diseases

It was reported that rats supplemented with 1% cholesterol and 0.1%, 0.25, and 0.5% curcumin to their diets for 7 weeks showed a decrease in serum total cholesterol levels (125, 122, and 128 mg/ml, respectively) and liver cholesterol levels (720, 957, and 596 mg/100 g) compared to the control group that supplemented with only cholesterol (Rao et al. 1970). In another investigation, serum triglyceride, total cholesterol, and LDL cholesterol values of rats receiving a high-fat diet enriched with curcumin for 8 weeks were found to be 27%, 33.8%, and 56% lower, respectively, compared to the control group which received a standard high-fat diet. In addition, the hepatic triglyceride level was found to be 41% lower in the group receiving curcumin compared to the control group (Kim and Kim 2010).

Subsequent to ischemia and reperfusion injury, aqueous extract of *C. longa* (100 mg/kg, for 1 month) significantly reduced terminal deoxyribonucleotidyl transferase-mediated dUTP Nick end labeling positivity ($p < 0.05$), Bax protein ($p < 0.001$), and upregulated Bcl-2

($p < 0.001$) expression and demonstrated mitigating effects on myocardial injury-induced hemodynamic and histopathological perturbations in Wistar albino rats. Observed significant cardioprotection and functional recovery with *C. longa* were associated with its antiapoptotic property (Mohanty et al. 2006).

Ethylacetate, methanol, and water extracts of *C. longa* were shown to be more potent angiotensin-converting enzyme inhibitors than the reference drug captopril ($IC_{50}$ = 6.28 μg/ml) with $IC_{50}$ values 0.06 μg/ml, 0.19 μg/ml, and 0.38 μg/ml, respectively (Lekshmi et al. 2014).

### 14.5.11 Diabetes

Aqueous extract of *C. longa* was determined to stimulate insulin secretion from mouse pancreatic tissues under both basal and hyperglycemic conditions, but maximum stimulatory effect was only 68% of that of tolbutamide. It also induced glucose uptake from abdominal muscle tissues. The peak glucose uptake activities observed with a dose of 5 μL (− insulin; 27.3%) and 2.5 μL (+ insulin; 44.76%) were significantly different from the controls which means that *C. longa* extract significantly potentiated the effect of insulin. In this study, it was concluded that water-soluble compounds of *C. longa* have insulin-releasing and mimicking actions (Mohankumar and McFarlane 2011).

Ethylacetate, methanol, and water extracts of *C. longa* have been shown to inhibit α-glucosidase with $IC_{50}$ values 0.4, 3.1, and 12.6 μg/ml, respectively, while the obtained $IC_{50}$ values for α-amylase inhibitory activity were 71.6, 90.3, and 498.3 μg/ml, respectively. Acarbose, the standard glucosidase-inhibiting drug, inhibited α-amylase and α-glucosidase with $IC_{50}$ values 290.6 μg/ml and 17.1 μg/ml, respectively (Lekshmi et al. 2014).

Isopropanol extracts of *C. longa* rhizome exhibited strong concentration-dependent human pancreatic amylase inhibitory activity ($IC_{50}$ = 0.16 $\mu g ml^{-1}$) (Ponnusamy et al. 2011). With further investigation performed by the same research group, curcumin, demethoxycurcumin, and bisdemetoxycurcumin were isolated from *C. longa* rhizomes, and they determined to cause 6.8, 0, and 72.4% porcine pancreatic α-amylase inhibition (at a dose of 15 $\mu g ml^{-1}$). Bisdemetoxycurcumin has also been shown to inactivate human pancreatic α-amylase ($IC_{50}$ = 0.025 mM) (Ponnusamy et al. 2012).

### 14.5.12 Neurodegenerative Diseases

Dohare et al. (2008) subjected the rats to occlusion of the middle cerebral artery by a thrombus and treated them with different doses of curcumin (100, 200, and 300 mg/kg) or the vehicle after 4-h ischemia. Reduction in ischemia-induced cerebral infarct and edema volume were observed after 24 h by curcumin treatment. Reduction on neurological deficit score up to 1.6 ± 0.09 ($p < 0.001$) was observed by curcumin treatment (2.9 ± 0.09 for vehicle). Curcumin was determined to reduce post-ischemic brain neutrophil infiltration, nitrate, and nitrite levels and improve the loss of GSH-Px (plasma glutathione peroxidase) and tends to increase the GSH levels. Decrease in neuronal levels of reactive oxygen species, peroxynitrite, nitric oxide, and inhibition at inducible nitric oxide synthase expression were also observed after curcumin treatment (Dohare et al. 2008).

In Mongolian gerbils with global cerebral ischemia induced by transient occlusion of the common carotid arteries, administration of curcumin by i.p. injections (30 mg/kg body) or by supplementation to the AIN76 diet (2.0 g/kg diet) for 2 months significantly decreased ischemia-induced neuronal death, glial activation, lipid peroxidation, mitochondrial dysfunction, and the apoptotic indices. According to these findings, researchers suggest that curcumin supplementation might offer health benefits in preventing or delaying age-related neurodegenerative disorders (Wang et al. 2005).

## 14.6 Clinical Studies

### 14.6.1 Antiinflammatory Activity

Turmeric and curcumin are well-known for its antiinflammatory activity, and their effects in various inflammatory diseases were evaluated extensively with many clinical studies. One of the most investigated inflammatory diseases is arthritis and osteoarthritis. One of these clinical research, effects of a formulation, containing *C. longa* and *Boswellia serrata* Roxb. ex Colebr. extracts [containing 350 mg *C. longa* extract (70% curcumin, 17% demethoxycurcumin, 3.5% bis-demethoxycurcumin and 7.5% turmeric essential oil) and 150 mg *B. serrata* extract (75% boswellic acids and 10% 3-O-acetyl-11-keto--boswellic acid), twice a day] and celecoxib (100 mg, twice a day) was compared in 28 osteoarthritic patients. After the treatment for 12 weeks, the *C. longa* and *B. serrata* formulation provided more improvement than celecoxib for the pain, walking distance, and joint line tenderness scores. Only 21.43% of subjects who used *C. longa* and *B. serrata* formulation remained in the moderate/severe category, whereas 50% of celecoxib users remained in the moderate/severe category. 92.86% of subjects used *C. longa* and *B. serrata* formulation, and 85.71% in celecoxib group could walk more than 1000 m. Additionally, the *C. longa* and *B. serrata* formulation was well tolerated; any adverse effect and dose-related toxicity was found (Kizhakkedath 2013).

In a different clinical research, effects of Mixodin [a dietary supplement consists of turmeric extract (300 mg curcumin), ginger (7.5 mg gingerols) and black pepper (3.75 mg piperine), twice a day] and naproxen (250 mg, twice a day) on prostaglandin $E_2$ levels on 60 patients with two different levels of knee osteoarthritis (grade 2 and 3) were compared. After 4 weeks of treatment, significantly decrease on prostaglandin $E_2$ levels was determined in both groups ($p < 0.001$), and no significant difference between the two groups was observed (Heidari-Beni et al. 2020).

In a randomized, non-inferiority, controlled clinical study conduct on 144 knee osteoarthritis patients, subjects received bioavailable turmeric extract (BCM-95®, 500 mg capsule) two times daily or paracetamol (650 mg tablet) three times daily for 6 weeks. Results revealed that turmeric extract caused significant improvement in Western Ontario and McMaster Universities Osteoarthritis Index total score, pain, stiffness, and function scores (23.59, 32.09, 28.5, and 20.25%, respectively). Significantly reduced C-reactive protein and tumor necrosis factor-α levels (37.21 and 74.81%, respectively) were also observed in the turmeric group. In addition, fewer side effects were reported in the turmeric group (5.48%) compared to the paracetamol group (12.68%) (Singhal et al. 2021).

Daily et al. (2016) evaluated the randomized clinical trials which focused on turmeric extracts and curcumin for treating arthritis symptoms. According the results obtained from eight suitable articles, reduction of pain visual analogue score [mean difference: −2.04 (−2.85, −1.24)] by turmeric or curcumin supplementation in comparison with placebo ($p < 0.00001$) was reported in three clinical trials. Besides, decrease in Western Ontario and McMaster Universities Osteoarthritis Index was determined by meta-analysis of four studies [mean difference, −15.36 (−26.9, −3.77); $p = 0.009$]. Meta-analysis of five studies showed no significant mean difference in pain visual analogue score between turmeric/curcumin and analgesic drugs. Consequently, these data could be accepted as scientific evidence that supports the efficacy of turmeric extract (about 1000 mg/day of curcumin) in the treatment of arthritis (Daily et al. 2016).

Results of a meta-analysis of nine randomized controlled trials showed that curcuminoid supplementation caused significant reduction of circulating interleukin-6 concentrations (weighted mean difference, −0.60 pg/ml; 95% confidence interval, −1.06, −0.14, $p = 0.011$), and there was significant association between the interleukin-6 lowering activity of curcumin and baseline interleukin-6 concentration (slope, −0.51; 95% confidence interval, −0.80, −0.23; $p = 0.005$). But meta-regression did not suggest any significant association between the circulating interleukin-6

lowering effects of curcuminoids with either dose or duration of treatment. Significant effect of curcumin in lowering circulating interleukin-6 concentrations was revealed by this meta-analysis (Derosa et al. 2016). Supporting this data, in another meta-analysis, curcumin supplementation caused significant reduction of circulating tumor necrosis factor-α concentrations (weighed mean difference, −4.69 pg/ml; 95% confidence interval, −7.10, −2.28, $p < 0.001$). But there was not any significant association between the circulating tumor necrosis factor-α lowering effects of curcumin with either dose or duration of treatment (slope, 0.197; 95% confidence interval, −1.73, 2.12; $p = 0.841$) (Sahebkar et al. 2016).

### 14.6.2 Effects on Gallbladder

In a randomized, double-blind, and crossover design study on 12 healthy volunteers, 11.8, 16.8, 22.0, and 29.3% reduction in gallbladder volume were observed at 0.5, 1.0, 1.5, and 2.0 h after 20 mg curcumin administration, respectively. These findings suggest that curcumin induces contraction of the gallbladder (Rasyid and Lelo 1999).

### 14.6.3 Anticancer Effect

Five familial adenomatous polyposis patients with prior colectomy were treated with 480 mg curcumin and 20 mg quercetin orally 3 times a day, for 6 months. After the treatment, polyp number [60.4% ($p < 0.05$)] and size from baseline [50.9% ($p < 0.05$)] decreased in all patients. The potential use of curcumin and quercetin against colorectal neoplasia was supported by this clinical study (Cruz-Correa et al. 2006). In the sequel of this research, 44 patients with familial adenomatous polyposis (18–85 years old), who had at least 5 intestinal adenomatous polyps, received 100% pure curcumin (1500 mg orally, twice per day) or placebo capsules for 12 months. After 12 weeks, there was no significant difference in the mean number of polyps and in mean polyp size between the placebo group and the curcumin group. But rate of compliance was 83% in the curcumin group and 91% in the placebo group, after 1 year of treatment. Contrary to the work mentioned above, obtained results did not support the use of curcumin (3000 mg/day) for regression of intestinal adenomas (Cruz-Correa et al. 2018).

25 patients with adenocarcinoma of the pancreas received 8 g curcumin daily for 8 weeks, and patients who had stable disease or get better after 8 weeks continued therapy and schedule. Curcumin was determined to downregulate expression of nuclear factor-κB, cyclooxygenase-2, phosphorylate signal transducer, and activator of transcription 3 in peripheral blood mononuclear cells. Clinical biological activity was determined in two patients. One of them had marked tumor regression (73%) and significantly increased serum cytokine levels (interleukin-6, IL-8, IL-10, and IL-1 receptor antagonists) (Dhillon et al. 2008).

In a randomized phase IIa trial, 28 patients with metastatic colorectal cancer received folinic acid/5-fluorouracil/oxaliplatin (FOLFOX) or FOLFOX +2 g oral curcumin/d. The estimated hazard ratios for progression-free survival and overall survival were calculated as 0.57 (95% confidence interval, 0.24, 1.36; $p = 0.2$) and 0.34 (95% confidence interval, 0.14, 0.82; $p = 0.02$), respectively. In the terms of quality of life ($p = 0.248$) or neurotoxicity ($p = 0.223$), significant difference were not detected. Although it is a small study, results suggest that FOLFOX and curcumin combination may provide a safe and tolerable treatment (Howells et al. 2019).

In 60 breast cancer patients receiving paclitaxel chemotherapy, turmeric supplementation for 21 days (capsule containing 500 mg turmeric powder, 2 capsules twice a day) between paclitaxel cycle cause significant improvement in global health status symptom scores (fatigue, nausea, vomiting, pain, appetite loss, insomnia). In addition, increase in hemoglobin ($p = 0.001$), total white blood cell ($p = 0.001$), and red blood cell ($p = 0.35$) count and decrease in platelet count ($p = 0.35$) were recorded after turmeric supplementation (Kalluru et al. 2020).

### 14.6.4 Antidiabetic Activity

In a double-blind randomized controlled clinical trial on 42 non-alcoholic fatty liver disease patients, turmeric consumption (daily six capsules containing 500 mg turmeric powder, for 12 weeks) determined to cause decrease in serum levels of glucose, insulin, homeostasis model assessment index, and leptin (by 1.22, 17.69, 19.48, and 21.33%, respectively) compared to placebo group. But significant changes in weight, body mass index, and liver enzymes were not observed. It is concluded that turmeric may be useful in preventing non-alcoholic fatty liver disease complications by improving glucose indexes and serum leptin levels (Navekar et al. 2017).

Hodaei et al. (2019) evaluated the effect of curcumin supplementation on anthropometric indices, glycemic control, and oxidative stress in 53 overweight patients with type 2 diabetes by a randomized, double-blind, placebo-controlled trial. 1500 mg curcumin supplementation for 10 weeks caused a significant changes in mean weight ($-0.64 \pm 0.22$ vs. $0.19 \pm 0.37$ $p < 0.05$), body mass index ($0.3 \pm 0.03$ vs. $0.1 \pm 0$ $p < 0.05$), waist circumference ($-1.2 \pm 0.4$ vs. $-0.43 \pm 0.11$ $p < 0.05$), and fasting blood sugar ($-7 \pm 2$ vs. $3 \pm 0.2$ $p < 0.05$), while any difference for hemoglobin A1c, insulin, malondialdehyde, total antioxidant capacity, homeostatic model assessment for insulin resistance, and pancreatic B cell function was observed against placebo. Hence, daily consumption of curcumin was thought to be useful for reducing fasting blood glucose and weight in patients with type 2 diabetes (Hodaei et al. 2019).

In another clinical trial, turmeric (500 mg) and piperine (5 mg) combination supplementation for 120 days showed reduction of glycemia (−3.2%) ($p < 0.05$) after fasting, compared to placebo (+9%) in individuals with type 2 diabetes. Significant reduction of hemoglobin A1c (−0.8%) was also observed in contrast with the placebo group ($p < 0.05$). Furthermore, turmeric and piperine supplementation caused reduction of homeostasis model assessment of insulin resistance (−9.4%) and serum triglyceride levels (−20.8%) (Sousa et al. 2020).

In a different study, 67 polycystic ovary syndrome patients were treated with curcumin (500 mg × 3, daily). After the treatment for 12 weeks, fasting plasma glucose levels determined to decrease significantly compared to control (difference of change, −4.11 mg/dl; 95% confidence interval, −8.35, −0.35 mg/dl; $p = 0.033$). Dehydroepiandrosterone levels were also decreased significantly (difference of change, −26.53 μg/dl; 95% confidence interval, −47.99, −4.34 μg/dl; $p = 0.035$). Based on these results, curcumin may be supposed as beneficial and safe supplement for polycystic ovary syndrome-associated hyperandrogenemia and hyperglycemia (Heshmati et al. 2021).

### 14.6.5 Cardiovascular Diseases

Qin et al. (2017) performed a meta-analysis with 7 research conducted on total 649 patients, to assess the effect of turmeric and curcumin in blood lipids in patients with cardiovascular disease risk. Results showed that turmeric and curcumin significantly reduced serum low-density lipoprotein cholesterol (standardized mean difference = −0.340, 95% confidence interval, −0.530 to −0.150, $p < 0.0001$) and triglycerides (standardized mean difference = −0.214, 95% confidence interval, −0.369 to −0.059, $p = 0.007$) levels. In addition, turmeric extract determined to have a greater effect on reducing serum total cholesterol levels (standardized mean difference = −0.584, 95% confidence interval, −0.980 to −0.188, $p = 0.004$) (Qin et al. 2017).

According to a meta-analysis, including 11 studies conducted with 734 participants, curcumin or turmeric supplementation did not display significant effect on systolic blood pressure (−0.69 mmHg; 95% confidence interval: −2.01, 0.64; $I^2 = 18\%$) and diastolic blood pressure (0.28 mmHg; 95% confidence interval: −1.12, 1.68; $I^2 = 53\%$). But subgroup analysis showed up significant reduction in systolic blood pressure levels (−1.24 mmHg; 95% confidence interval, −2.26, −0.22; $I^2 = 0\%$) in case of usages for a long time (≥12 week) (Hadi et al. 2019).

According to meta-analysis of 20 randomized controlled trials with 1427 participants, curminoid supplementation caused significant decrease in plasma triglyceride levels (weighted mean difference, −21.36 mg/dl; 95% confidence interval, −32.18, −10.53, $p < 0.001$) and increase in plasma high-density lipoprotein cholesterol levels (weighted mean difference, 1.42 mg/dl; 95% confidence interval, 0.03, 2.81, $p = 0.046$). On the other hand, significant changes in levels of low-density lipoprotein cholesterol (weighted mean difference, −5.82 mg/dl; 95% confidence interval, −15.80, 4.16, $p = 0.253$) and total cholesterol (weighted mean difference, −9.57 mg/dl; 95% confidence interval, −20.89, 1.75, $p = 0.098$) were not observed (Simental-Mendia et al. 2019).

### 14.6.6 Ulcerative Colitis

In a randomized placebo-controlled trial, 89 ulcerative colitis patients were treated with curcumin (orally, in a dose of 2 g/day) or placebo in addition to sulfasalazine or mesalamine, for 6 months. After the treatment, ulcerative colitis relapsed 4% of patients in the curcumin group, while the relapse ratio was 18% in the placebo group (relative risk 0.24, 95% confidence interval 0.05 to 1.09; $p = 0.06$). Significant reduction in clinical activity index compared to the placebo group was observed (1.0 ± 2.0 versus 2.2 ± 2.3; mean difference −1.20, 95% confidence interval −2.14 to −0.26), as well as endoscopic index (0.8 ± 0.6 versus 1.6 ± 1.6; mean difference −0.80, 95% confidence interval −1.33 to −0.27). These data reveals that curcumin may be evaluated as effective therapy for maintenance of ulcerative colitis remission with mesalamine or sulfasalazine therapy (Kumar et al. 2012).

In another randomized double-blind clinical trial, performed on 70 patients with mild to moderate ulcerative colitis, higher changes in Simple Clinical Colitis Activity Index score compared to placebo group (−2.1 ± 2.6 vs. −5.9 ± 2.08; $p = 0.001$) observed by curcumin intake (1500 mg/day) for 8 weeks. Likewise, the scores of Inflammatory Bowel Disease Questionnaire-9 and quality of life were significantly higher in curcumin group compared to the placebo ($p = 0.006$). Curcumin supplementation caused significant reduction at high sensitivity C-reactive protein (−6.3 ± 13.6 vs. 3.7 ± 11.6 μg/ml; $p = 0.01$) and erythrocyte sedimentation rate (-1.6 ± 2.7 vs. −0.09 ± 2.4 mm/h; $p = 0.02$), but caused no significant changes in the tumor necrosis factor-α levels (Sadeghi et al. 2020).

### 14.6.7 Dermatological Disorders

Turmeric and curcumin have also been shown to cause improvement on psoriasis, another inflammatory disease. In a randomized, prospective intra-individual, right-left comparative, placebo-controlled, double-blind clinical trial, a novel topical microemulgel formulation of hydro alcoholic turmeric extract was evaluated on 34 patients with mild to moderate plaque psoriasis. After 9 weeks of treatment with turmeric, gradual reduction at the mean redness score (from 1.3 to 0.2, $p < 0.05$), thickness of the lesions (from 1.1 to 0.3, $p < 0.05$), scaling of the lesions (from 1.5 to 0.1, $p < 0.05$), and area of lesions were recorded. Mentioned formulation is concluded that it could be evaluated as an alternative therapeutic option for plaque psoriasis (Sarafian et al. 2015). In another research, 63 patients with mild to moderate psoriasis vulgaris received Meriva tablet (a lecithin-based delivery system of curcumin) at a dose of 2 g per day and topical methylprednisolone aceponate 0.1% ointment or placebo with same topical steroid for 12 weeks. Higher significant reduction on psoriasis area severity ındex and interleukin-22 serum levels were observed in patients treated with both topical steroids and oral curcumin (Antiga et al. 2015).

## 14.7 Toxicological Studies

### 14.7.1 Single-Dose Toxicity

Single feeding of 30% turmeric diet or single oral exposure of curcumin (1–5 g/kg) caused no toxic effects in rats. Median lethal dose ($LD_{50}$) for cur-

cumin in mice was found to be higher than 2.0 g/kg (EMA 2018).

### 14.7.2 Repeat Dose Toxicity

A diet containing 1% and 5% turmeric caused hepatotoxicity in mice after 14 days, while no adverse effect was observed in rats that fed with 1% turmeric. But feeding with a diet containing 5% turmeric for 90 days was determined to cause hepatotoxicity and reduction in body weight gain in rats. Gastric ulceration was occurred after oral consumption of curcumin (100 mg/kg) for 6 days at rats (EMA 2018).

### 14.7.3 Genotoxicity

Turmeric (0.5%) or curcumin (0.015%) containing diet showed no chromosomal damage and mutagenic effects in mice. Curcumin containing (0.015%) diet for 12 weeks did not cause genotoxic effects according to the incidence of micronucleated polychromatic erythrocytes and chromosomal aberrations in bone marrow cells in mice. But in some studies, a low level of chromosomal aberrations is observed with curcumin or curcumin preparations in mice and rats (EMA 2018).

### 14.7.4 Reproductive and Development Toxicity

Turmeric (0.5%) or curcumin (0.015%) containing diet did not show effect on pregnancy rate, number of dead embryos, and total implants in mice. In Wistar rats, No observed adverse effect level (NOAEL) for reproductive toxicity of curcumin was determined for F0 and F1 generations as 847 and 959 mg/kg per day for male rats and 1043 and 1076 mg/kg for females, respectively (EMA 2018).

According to clinical research, in subjects who consumed up to 8 g of curcumin a day for 3 months, no toxic reactions were observed. On the other hand, mild side effects such as nausea, dermatitis, and pain in the abdomen were observed by using a turmeric containing (300 mg daily) combination product, and in another clinical study, intake of 2500 mg of curcumin per day caused gastric irritation (EMA 2018).

The acceptable daily intake (ADI) value for curcumin was determined as 0–3 mg/kg by European Food Safety Authority (EFSA) (EFSA 2014; FDA 2018). Besides, there is a curcumin containing dietary supplement which received generally recognized as safe (GRAS) notification from the U.S. Food and Drug Administration up to 1000 mg per day for a 60 kg person (EMA 2018).

## 14.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies

Capsules, solution, coated tablets, and compound preparations prepared from whole or powdered rhizome are available on the market. Crude plant material is used 3–9 g daily; the powdered rhizome is used 2–3 times in a day (daily 1.5–3.0 g) after meals. Infusion could be prepared from 0.5 to 1 g comminuted rhizome in 150 ml of boiling water, and 2–3 cups of tea are consumed between meals. 0.5–1 ml of tincture [1:10, extraction solvent ethanol 70% (V/V)] or 5 ml of tincture [1:5, extraction solvent ethanol 70% (V/V)] in 60 ml water is used 2–3 times in a day (Blumenthal 2000; EMA 2018; PDR 2000; WHO 1999). 90–162 mg dry extract (extraction solvent ethanol 96%) or 100–200 mg dry extract (extraction solvent ethanol 50%) could be used 2 times daily (EMA 2018).

Its usages for dyspeptic complaints are approved by Commission E (Blumenthal 2000). It is also used for acid, peptic ulcers, diarrhea, intermittent fever, edema, bronchitis, colds, worms, leprosy, kidney inflammation,

cystitis, headaches, flatulence, upper abdominal pain, chest infections, colic, pain and inflammation due to rheumatoid arthritis, amenorrhea, dysmenorrhea, epilepsy, blood rushes, bruising, leech bites, eye infections, inflammation of the oral mucosa, inflammatory skin conditions, and infected wounds (PDR 2000; WHO 1999).

Curcumin, its principal content, was found to demonstrate poor systemic bioavailability, because of low absorption by the gastrointestinal tract and rapid metabolism. Very low concentrations in plasma (less than 5 μg/ml) were determined after oral administration of 2 g curcumin in rats. In another investigation, about 75% of orally administrated curcumin (1 g/kg bw) was determined to be excreted in the feces in rats. In addition, it was found in trace amounts in the urine, while its plasma and bile concentrations were remissible (EMA 2018).

After intravenous application, more than 50% of curcumin was excreted in the bile within 5 h. Hence, curcumin was thought to undergo biotransformation during absorption in the intestinal tract and participates to enterohepatic recirculation. Major metabolites determined as the glucuronides of tetrahydrocurcumin and hexahydrocurcumin; dihydroferulic acid and ferulic acid were minor metabolites (EMA 2018).

## 14.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

As noted earlier, *C. longa* is commonly used as folk medicine for arthritis, skin disorders, dyspeptic complaints like constipation, flatulence, colic, and cholagogue and choleretic. Traditional usage of *C. longa* and curcumin, as key active constituents, for digestive complaints and arthritis is partly supported by the in vitro and clinical investigations. But there is still a need for more detailed extensive research.

## 14.10 Challenges and Future Recommendations as Potential Drug Candidate

Multi-biofunctionality properties of turmeric and curcumin have received great attention by the researchers such as anticancer, antiinflammatory, choleretic, antioxidant, antibacterial activities, etc., and researchers are still evaluating them for different therapeutic uses. But curcumin was found to demonstrate poor systemic bioavailability, because of low absorption by the gastrointestinal tract and rapid metabolism. Furthermore, its hydrophobic nature, which causes less accessibility in the cytoplasm, and chemical instability contribute to this situation. To overcome this issue, which restricts its activity, research have focused on synthesis of curcumin derivatives and various pharmaceutical formulations for oral administration including solid dispersions, nano-/microparticles, polymeric micelles, nanosuspensions, lipid-based nanocarriers, cyclodextrins, conjugates, and polymorphs (EMA 2018; Krishnamurthy et al. 2020; Ma et al. 2019). Although great progress has been achieved, there are still many gaps that need to be filled. Thus, there is an urgent need of investigations to enhance bioavailability of curcumin and to understand its working mechanism.

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# *Cydonia oblonga* Mill.

15

Hilal Özbek

**Abstract**

In this chapter the description; synonyms; local names; habitat; traditional usage; bioactive composition; in vitro, in vivo and clinical pharmacological studies; and toxicological studies of *Cydonia oblonga* were presented.

**Keywords**

Rosaceae · *Cydonia oblonga* · Quince · Biological activity

## 15.1 Introduction

### 15.1.1 Description of *Cydonia oblonga* Mill.

*Cydonia oblonga* is a large multi-stemmed shrub or small tree up to 8 m, twigs sparsely tomentose when young, becoming glabrous. It has pubescent to tomentose buds, petioles, leaves and fruits. Leaves entire, up to 10 × 7 cm, ovate to oblong or occasionally suborbicular, bilaterally white-tomentose at first, becoming glabrous above and densely villous beneath; petiole 1–2 cm. The solitary white flowers are 4–6 cm diameter and have 5 petals, 20 or more stamens, 5 styles, an inferior ovary with many ovules; sepals glandular, toothed, reflexed. Fruits pyriform or subglobose, (3-)5–12 cm, yellowish, fragrant (Browicz 1972; Postman 2009).

### 15.1.2 Taxonomical Aspect with Photograph

*Cydonia oblonga* belongs to Rosaceae family, Spiraeoideae subfamily (Fig. 15.1) (Sabir et al. 2015).

### 15.1.3 Synonyms

*Crataegus serotina* Salisb.
*Cydonia communis* Loisel.
*Cydonia cydonia* (L.) Pers.
*Cydonia europaea* Savi
*Cydonia lusitanica* Mill.
*Cydonia maliformis* Mill.
*Cydonia oblonga* subsp. *integerrima* Lobachev
*Cydonia oblonga* var. *integerrimosepala* Lobachev
*Cydonia oblonga* var. *obpyricarpa* Lobachev
*Cydonia oblonga* var. *obpyriformis* Lobachev
*Cydonia oblonga* var. *orbiculatocomplanata* Lobachev
*Cydonia oblonga* var. *ovalicarpa* Lobachev

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https://doi.org/10.1007/978-3-031-07753-1_15

**Fig. 15.1** General view of *Cydonia oblonga* Mill. (http://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:724549-1)

*Cydonia oblonga* var. *ovalis* Lobachev
*Cydonia oblonga* var. *plano-cyclocarpa* Lobachev
*Cydonia oblonga* var. *pomiformis* Lobachev
*Cydonia oblonga* var. *urceolata* Lobachev
*Cydonia silvestris* Risso
*Cydonia sumboshia* Buch.-Ham. *ex* D. Don
*Pyrus cydonia* L.
*Pyrus lusitanica* (Mill.) Steud.
*Pyrus maliformis* (Mill.) Steud.
*Pyrus oblonga* (Mill.) Steud.
*Pyrus sumboshia* Spreng.
*Sorbus cydonia* Crantz
(http://www.plantsoftheworldonline.org/taxon/urn:lsid:ipni.org:names:724549-1#source-KB)

### 15.1.4 Local Names

Sefarjal (Arabic); wen po (Chinese); almindelig kvæde, kvæde, pærekvæde (Danish); kwee, kweeboom, kweepeer (Dutch); quince (English); cognassier, coing (French); echte quitte, quitte, quittenbaum (German); kydoni, strythion (Greek); birsalma, birskörte (Hungarian); cotogno, melo cotogno, melocotogno, pero cotogno (Italian); marumero (Japanese); kvede (Norwegian); pigwa, pigwa pospolita (Polish); marmelo (Portuguese); ajva (Russian); dunja (Serbian); membrillero (Spanish); kvitten (Swedish); ayva (Turkish) (https://www.cabi.org/isc/datasheet/17341#toPictures; PDR 2000; Al-Snafi 2016).

### 15.1.5 Occurrence/Habitat

It grows naturally in damp rich soils in hedgerows and thickets (https://pfaf.org/user/Plant.aspx?LatinName=Cydonia+oblonga).

### 15.1.6 Importance

*Cydonia oblonga* is an important medicinal plant, belonging to Rosaceae family, as it is a rich source of bioactive compounds. It is also used in food industry due to its aromatic and functional properties (Hanan et al. 2020).

### 15.1.7 Objective of This Chapter

Botanical properties, traditional uses, pharmacological activities and toxicological studies of *Cydonia oblonga* have presented in this chapter.

## 15.2 Distribution and Status of Species

*Cydonia oblonga* grows in forests and shrubs. It is native to Western Asia originated from Transcaucasus region including Armenia, Azerbaijan, North Iran, North Iraq, Southwestern Russia and Turkmenistan and spread to Greece, Middle East, Mediterranean and Central Asia and widely cultivated in Turkey followed by China, Iran, Argentina and Morocco for its edible fruits (Browicz 1972; Postman 2009; Sabir et al. 2015).

## 15.3 Comparison of Traditional/Ethnomedicinal/Local Uses: In Turkey and Throughout the World (Asia and Europe)

The seeds, leaves and fruits are used in folk medicine. The seeds are used for constipation, rhinitis, diarrhoea, cold sores, sore throat, cough, wound healing, dysentery, thrush, conjunctivitis, gonorrhoea and pulmonary distress and as skin lotion; the leaves are used for abdominal cramp, nervousness, diarrhoea, dysuria, insomnia, hyperglycaemia, cough, cold and fever; and the fruits are used for diabetes, ulcer, haemolysis, respiratory disorders and urinary complications (Morton 1990; Vokou et al. 1993; Pieroni et al. 2005; Ashraf et al. 2016; Gras et al. 2017; Hanan et al. 2020) generally all over the world. It is used for cough and to improve the kidney, stomach and liver in Southern Xinjiang, China (Abdusalam et al. 2020). The decoction of leaves is used for hypertension (Camejo-Rodrigues et al. 2003; Aumeeruddy and Mahomoodally 2020); the infusion of leaves is used as antiatherosclerotic, antihypercholesterolaemic, hypoglycaemiant, diuretic, laxative, hypouricaemic, and antieczematous, and flower infusion is used as cardiotonic in Portugual (Novais et al. 2004). The fruits are used for cough, diarrhoea and abdominal pains as tea and compote in South Eastern Serbia (Jaric et al. 2015, Matejic et al. 2020). The infusions prepared from leaves and seeds are used for kidney sand and diarrhoea in South Western Serbia (Savikin et al. 2013). The decoction of leaves is used as antihyperglycaemic in South-East Sardinia (Palmese et al. 2001). The infusion of leaves and seeds is used for diarrhoea and stomach ulcers (Saric-Kundalic et al. 2011) and kidney sand in Bosnia and Herzegovina (Savic et al. 2019). The decoction of fruits is used as emollient for the skin in Central Eastern Italy (Pieroni et al. 2004). The raw and cooked fruits are used for diabetes and hair growth in South-Eastern Morocco (Tahraoui et al. 2007; Bouhlal et al. 2014). The fruits are used for colitis in Spain (Rivera et al. 2019). The decoction of leaves is used against diarrhoea in Uzbekistan (Sezik et al. 2004). The leaves are used as tea for cough and respiratory system disease in South Kosovo (Mustafa et al. 2020). The fruits are used for depression in Spain (Alarcon et al. 2015). It is used for cardiovascular, skin and sensory disorders in Algeria (Gonzales-Tejero et al. 2008). The jam and the decoction prepared from the fruits are used against diarrhoea (Cavero et al. 2011; Calvo et al. 2011; Menendez-Baceta et al. 2014), the tisane or direct ingestion of fruits and quince jelly is used as laxative (Agelet and Valles 2003), and the fruit syrup is used as digestive and for bellyache in Iberian Peninsula (Bonet et al. 1999; Parada et al. 2009). The inhalation of latex is used for gastrointestinal disorders and the decoction of fruits and seeds used as sedative in Iran (Mohagheghzadeh et al. 2006; Saki et al. 2014). The fruit pulp and juice are used against diabetes, sore throat, diarrhoea, stomach pain and hypertension and as laxative and to delay ejaculation in Pakistan (Khan and Ahmad 2015; Hussain et al. 2019; Khan et al. 2020). The seed decoction is used for respiratory problems in Southern Spain (Benitez et al. 2010). The boiled fruits are used against fever, migraine and nausea and to speed up parturition in Northwest Argentina (Hilgert 2001). The decoction of seeds is used as antitussive and astringent and leaves for wounds in Bulgaria (Jaric et al. 2018). Seed decoction is used for the skin as anti-inflammatory; leaves decoction is used as astringent, diuretic and mild sedative (Leporatti and Ivancheva 2003); the fruit syrup is used for diarrhoea, bronchitis and intes-

tinal pains in Italy (Bruni et al. 1997; Pieroni 2000). The fresh fruit or fruit extract is used as neuroprotective, gastrotonic, cardiotonic and antithirst and for wound healing and gastric pain in Persian medicine (Naeimi et al. 2020; Fazil and Nikhat 2020). The fruits and seeds were rank among the Genizag prescriptions for eye complaints, swelling and cough (Lev and Amar 2006). The fruits, seeds and leaves were used against diarrhoea and common cold in Thessaloniki (Hanlidou et al. 2004). Fruits were consumed as compote; fruit decoction was used as appetizing and leaves decoction for dyeing wool (Pieroni 2017).

In Turkey, the leaf decoction is used as diuretic, appetizer, digestive, antipyretic, sedative and antitussive and for kidney stones, headache, hypertension, abdominal pain, diarrhoea, diabetes, stomach and colon disorders and respiratory tract problems; the leaf infusion is used for cold, flu, cough, bronchitis, diabetes, kidney stones, abdominal ache, diarrhoea, postpartum pain and haemorrhoid; the seed decoction is used for stomach disorders, diarrhoea, wounds and emollient on the skin; the fruit decoction is used for cough and tonsillitis and the decoction of flowering stems used against bronchitis; the fresh fruits and vinegar prepared from fruits are used as immunostimulant, the cooked fruits for cystitis (externally on vagina); the infusion of flowers cooked with honey are used as galactagogue; the decoction of barks is used against cold and stomachache (Baytop 1999; Yeşilada et al. 1999; Tuzlacı and Tolon 2000; Sezik et al. 2001; Tuzlacı and Eryaşar Aymaz 2001; Uzun et al. 2004; Kültür 2007; Altundag and Ozturk 2011; Polat and Satıl 2012; Bulut and Tuzlaci 2013; Polat et al. 2013; Sargın et al. 2013, 2015; Tetik et al. 2013; Sargin 2015; Güler et al. 2015a, b Paksoy et al. 2016; Tuzlacı 2016; Bulut et al. 2017; Güneş et al. 2017; Polat 2019; Sargin and Büyükcengiz 2019; Sargin 2021).

The usage of *Cydonia oblonga* in our country and others is so similar.

## 15.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques (Classification and Structures of Few Representatives)

Polysaccharides: (4-*O*-Methyl-D-glucurono)-D-xylan, terpenoids: 3-hydroxy-*β*-ionol-*β*-D-gentiobioside, (4R,1′E,3′E)-4-(5′-hydroxy-3′-methyl-1′,3′-pentadienyl)-3,5,5-trimethyl-2-cyclohexen-1-one-*β*-D-glucoside, trans-abscisic alcohol-*β*-D-glucoside, pectins (Lindberg et al. 1990; Winterhalter et al. 1991a, b; Lutz and Winterhalter 1992a; Forni et al. 1994; Vignon et al. 1998).

Phenolic compounds: Neochlorogenic acid (3-*O*-caffeoylquinic acid), cryptochlorogenic acid (4-*O*-caffeoylquinic acid), chlorogenic acid (5-*O*-caffeoylquinic acid), quinic acid, quinic acid derivative, 3-*O*-caffeoylshikimic acid, methyl-5-*O*-caffeoylquinate, 3,4-*O*-dicaffeoylquinic acid, 3,5-*O*-dicaffeoylquinic acid, 4,5-*O*-dicaffeoylquinic acid, 4-*O*-*p*-coumaroylquinic acid, 5-*O*-*p*-coumaroylquinic acid, caffeic acid, trans and cis isomers of *p*-coumarylic alcohol, acyl derivatives of the *E* and *Z* isomers of the coniferyl alcohol, 3,4-dimethoxycinnamyl ω-hydroxylinoleate, 3-methoxy-4-hydroxy aldehydes and 4-hydroxybenzoic acids esterified through the 4-hydroxyl group to palmitic, linoleic and cis-13-docosenoic acids, synapyl acid 4-*O*-*β*-D-glucopyranoside, 4-hydroxybenzylamine (Silva et al. 2000, 2002, 2006, 2008; Fattouch et al. 2007; Marques and Farah 2009; Alesiani et al. 2010; Carvalho et al. 2010; Oliveira et al. 2012; Karar et al. 2014; Szychowski et al. 2014; Wojdyło et al. 2014; Stojanović et al. 2017; Meinhart et al. 2019).

Polyphenols: Stellarin-2 (6,8-di-C-glucosyl chrysoeriol), lucenin-2 (6,8-di-C-glucosyl luteolin), vicenin-2 (6,8-di-C-glucosyl apigenin), schaftoside (6-C-glucosyl-8-C-arabinosyl api-

genin), isoschaftoside (6-C-arabinosyl-8-C--glucosyl apigenin), 6-C-glucosyl-8-C-pentosyl chrysoeriol, 6-C-pentosyl-8-C-glucosyl chrysoeriol, rutin (quercetin-3-*O*-rutinoside), hyperin (quercetin-3-*O*-galactoside), kaempferol-3-*O*-rutinoside, kaempferol-3-*O*-glucoside, quercetin and ist glycosides acylated with *p*-coumaric acid, kaempferol glycosides acylated with *p*-coumaric acid, (+)-catechin, (−)-catechin, (−)-epicatechin, (epi)catechin-4,8′-(epi)catechin, (epi)catechin-4,8′-(epi)catechin-4′,8′′-(epi)catechin-4′′,8′′′-(epi)catechin,(epi)catechin-4,8′-(epi)catechin-4′,8′′-(epi)catechin, (epi)catechin-(4,8′)-(epi)catechin-(4′,8′′/2′,7′′)-(epi)catechin, quercetin, kaempherol, procyanidin B1, B2 and C1, quercetin-3-*O*-galactoside, quercetin-3-*O*-rutinoside, quercetin-3-*O*-glucoside, quercetin 3-*O*-xyloside, quercetin 3-*O*-rhamnoside, quercetin-3-*O*-glucosyl-7-*O*-rhamnoside, quercetin-3-*O*-(6-*O*-rhmanosyl-glucosyl)-7-*O*-rhamnoside, kaempherol-3-*O*-galactoside, kaempherol-3-*O*-rutinoside, kaempherol-3-*O*-glucoside, kaempferol-3-*O*-rhamnoside-7-*O*-glucoside, kaempherol-7-*O*-glucoside, mangiferin, (Brown 1980; Porter et al. 1985; Silva et al. 2000, 2002, 2005, 2008; Ferreres et al. 2003; Fattouch et al. 2007; Alesiani et al. 2010; Carvalho et al. 2010, Oliveira et al. 2012; Karar et al. 2014; Kruger et al. 2014; Wojdyło et al. 2014; Teixeira et al. 2016; Stojanović et al. 2017).

Organic acids: Citric, ascorbic, malic, quinic, shikimic fumaric and oxalic acids (Silva et al. 2005; Oliveira et al. 2008; Hernández-García and Carbonell-Barrachina 2020).

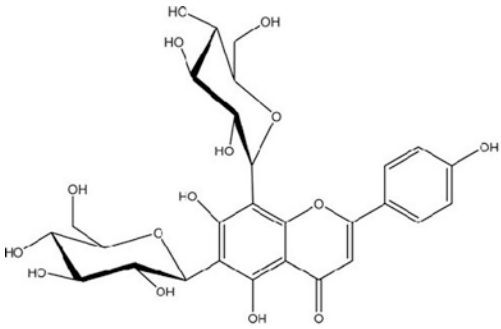
Terpenoids: 3*β*-Linoleoylurs-12-en-28-oic acid, 3*β*-(18-Hydroxylinoleoyl)-28-hydroxyurs-12-ene, oleananic acid, hederagenic acid and its 2*α*-hydroxy derivative, uvaol, ursanaldehyde, ursolic acid, 2*α*-hydroxy ursolic acid, pomolic acid, 3*β*-13*β*-dihydroxyurs-11-en-28-oic acid, oleic acid, cydoniosideA,trans-9-amino-8-hydroxy-2,7-dimethylnona-2,4-dienoic acid glucopyranosyl ester, 2,7-dimethyl-8-hydroxy-4(E,6(E)-octadien-1-yl-*β*-D-glucopyranoside,(2E,4E,7Z)-2,7-dimethyldecatriene-1,10-diol, (2E,4E)-2,7-dimethyloctadiene-1,8-diol, (4E,6E)-2,7-dimethyl-8-hydroxyoctadienoic acid, *β*-D-glucopyranoside of (4E,6E)-2,7-dimethyl-8-hydroxyoctadienoic acid, marmelo oxide, marmelo lactone, quince oxepine, (2E,4E)-2,7-dimethyloctadienedioic acid, 4-(1-hydroxy-4-keto-2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-ol-2-*β*-D-glucopyranoside (roseosid), (3E)-2,7-dimethyloctene-1,8-diol,(2E,4E)-2,7-dimethyl-8-hydroxyoctadienoic acid (Tschesche et al. 1976; Naf et al. 1991; Näf and Velluz 1991; Lutz et al. 1991; Winterhalter et al. 1991a, b; Sousa et al. 2007; Alesiani et al. 2010).

Steroids:3*β*-Oleoyl-24-hydroxy-24-ethylcholesta-5,28(29)-diene, *β*-sitosterol, fucosterol, *β*-sitosterol-3-O-*β*-D-glucopyranoside, fucosterol-3-O-*β*-D-glucopyranoside (Alesiani et al. 2010).

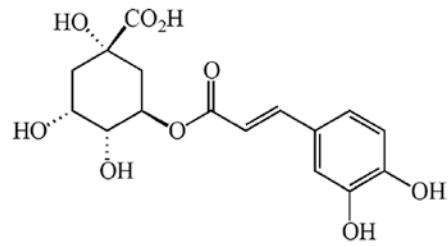
Glucosyl derivatives: Tiglic acid 1-*O*-*β*-D-glucopyranoside (Alesiani et al. 2010).

Carotenoid derivatives: 6,9-Dihydroxymegastigmasta-5,7-dien-3-one-9-*O*-*β*-D-gentiobioside, 6,9-dihydroxy-megastigmast-4,7-dien-3-one-9-O-*β*-D-gentiobioside, (4E,6E)-8-hydroxy-2,7-dimethylocta-4,6-dienoic acid 1-O-*β*-D-glucopyranoside, trans-abscisic alcohol-*β*-D-glucopyranoside, *β*-carotene, lycopene, *β*-cryptoxanthin, lutein, zeaxanthi n (Lutz and Winterhalter 1992b; Alesiani et al. 2010; Lopes et al. 2018).

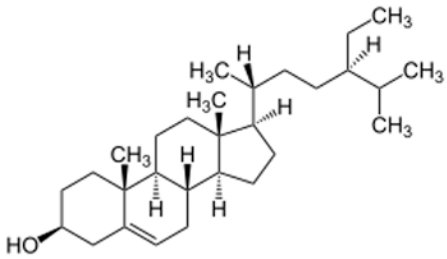
Cyanogenic glycosides: Amygdalin, prunasin (Sabir et al. 2015; PDR 2000).



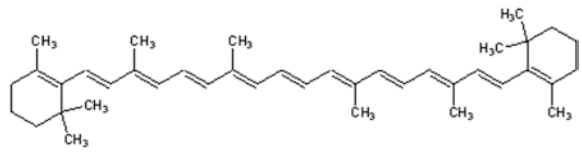
Vicenin-2



Chlorogenic acid



β-Sitosterol



β-Carotene

## 15.5 Scientific Evidences: Pharmacological Activities (All Major Therapeutic Activity with In Vitro and In Vivo Studies, Mechanism of Action)

### 15.5.1 In Vitro Studies

#### Antiproliferative Activity

Methanolic extracts prepared from leaves, fruit seeds, pulp and peels of *Cydonia oblonga* were evaluated for the inhibitory effect on the growth of colon (Caco-2) and human renal (A-498 and 769-P) cancer cell lines with different concentrations (31.25, 62.5, 125, 250 and 500 μg/ml). The leaf extract indicated dose-dependent effect ($IC_{50} = 239.7 \pm 43.2$ μg/ml) on Caco-2 cells while no effect on A-498 and 769-P. The seed extract inhibited 91 and 84% growth of A-498 and 769-P cells at 500 μg/ml, respectively. The pulp extract showed 34 and 18% antiproliferative effect at 500 μg/ml on A-498 and Caco-2 cells, respectively, but no significant effect by the peel extract (Carvalho et al. 2010). The lipophilic quince wax extract (QWE) showed 12.6, 11.85 and 3.90 μg/ml $ID_{10}$ effect in 72 h on the proliferation of the human HepG2 (human hepatocellular carcinoma), A549 (human lung carcinoma) and HeLa (human cervical adenocarcinoma) cell lines, respectively. The aqueous fermented extract (QAFE) exerted 0.32, 0.05 and 4.40 μg/ml $ID_{10}$ effect in the same cell lines, respectively, at the same time (Pacifico et al. 2012). Quince leaves showed antiproliferative activity towards human colon cancer cells with an $IC_{50}$ value of 239.7 μg/ml, but no effect on renal adenocarcinoma cells (Oliveira et al. 2012). The antitumoural activity quince peel and pulp polyphenolic extracts were studied on human colon adenocarcinoma LS174 cell line (CL-188), non-tumourigenic cells human embryonic kidney HEK293 (CRL1573) and mouse embryonic fibroblasts NIH3T3 (CRL-1658). Cell proliferation was measured by MTT and cytotoxicity by LDH assays. The proliferation on LS174 cells was inhibited highly by peel

extract (1–20 µg/ml) in a dose-dependent manner (Riahi-Chebbi et al. 2016). The ethanolic extract of quince leaves were evaluated on C6 and HROG36 glioblastoma cells and primary cerebellar neuronal glial cells at different concentrations (0.88, 1.25, 1.63, 2.00, 2.38, 2.75, 3.13 and 3.75 mg/ml). The extract reduced the vitality of glioblastoma cells. The activity was attributed to chlorogenic acid content of the extract (Zvikas et al. 2021).

## Proliferative Activity

The quince mucilage was evaluated (50, 100, 200 and 400 µg/ml) on human skin fibroblast cell line (HNFF-P18). The concentration of 50 µg/ml increased the fibroblast proliferation after 72 h, 100 and 200 µg/ml increased that after 48 h. 400 µg/ml concentration was not effective (Ghafourian et al. 2015).

## Antioxidant Activity

*Cydonia oblonga* leaves exhibited significant antioxidant activity in ABTS and FRAP test as 116.49 and 65.25 mmol TE/100 g dm, respectively, while the fruits showed 7.85 and 5.43 mmol TE/100 g dm (Teleszko and Wojdyło 2015). Aqueous acetone extracts of *Cydonia oblonga* fruit pulp and peel showed 70–80% inhibitory activity on DPPH radicals. The pulp extract exhibited 3.33 g of TEAC/100 g fw and peel extract 4.27 g of TEAC/100 g fw (Fattouch et al. 2007). The $EC_{50}$ value of quince fruit extract was 7.5 mg/100 ml in DPPH radical scavenging activity (Hamauzu et al. 2005). The immature fruits of quince indicated high antioxidant activity (336.9 ± 6.8 µmol/g) with high total phenolic content (29.9 ± 1 mg/g) when extracted using an environmentally friendly pressurized hot water extraction at 100 °C. Also it showed cytoprotective activity against $H_2O_2$-induced oxidative stress in Crandell-Rees feline kidney cells (Heng et al. 2017). The TEAC activity of quince fruits harvested in July, August, October and November showed 0.773 ± 0.079, 0.708 ± 0.028, 1.170 ± 0.085 and 0.280 ± 0.037 mmol equivalent (eq.) Trolox/100 g, respectively. The FRAP activity was measured as 1.623 ± 0.091, 1.258 ± 0.044, 2.410 ± 0.068 and 0.920 ± 0.029 mmol eq. FeSO4/100 g and ORAC capacity as 0.455 ± 0.010, 0.344 ± 0.003, 0.581 ± 0.005 and 0.386 ± 0.010 mmol eq. Trolox/100 g, respectively (Morales-Soto et al. 2014). The quince aqueous fermented extract was more effective with $ID_{50}$ values as 68.8 µg/ml on DPPH and 73.7 µg/ml on superoxide anion radical, and wax extract was more effective on thiobarbituric-reactive species with 48.9 µg/ml $ID_{50}$ value (Pacifico et al. 2012). Methanolic extract of quince leaves showed an $EC_{50}$ value of 21.6 µg/ml against DPPH free radicals and high reducing power effect (Costa et al. 2009; Oliveira et al. 2012). Methanolic extracts of pulp, peel and seeds were evaluated for their antiradical activity and showed 0.6, 0.8 and 12.2 mg/ml $EC_{50}$ values. Pulp and peel extracts showed similar effects due to their caffeoylquinic acid content (2.5 and 3.2 g/kg, respectively) higher than seed extract (0.06 g/kg) (Magalhães et al. 2009). The antioxidant activity of methanolic extracts of quince fruit (pulp, peel and seed) and jam was evaluated by DDPH assay. The peel, pulp, seed and jam extracts showed antioxidant activity with $IC_{50}$ values of 0.6, 1.7, 2.0 and 8.9 mg/ml, respectively. The peel extract exhibited the highest activity (Silva et al. 2004).

## Antimicrobial Activity

The methanol extract prepared from *Cydonia oblonga* seeds (20 mg/ml) showed antibacterial activity on *Bordetella bronchiseptica* and *Bacillus cereus* at 2 mg/well in agar well-diffusion method (Bonjar 2004). The ethanolic extract inhibited *Staphylococcus aureus* in deep-well broth microdilution method at a MIC value of 15 mg/mL (Bussmann et al. 2010). The aqueous acetone extracts of fruit pulp and peel from *Cydonia oblonga* were evaluated for antimicrobial activity via disk and well diffusion techniques. The peel extract was more effective than the pulp extract. *Staphylococcus aureus* and *Pseudomonas aeruginosa* were well inhibited, *Escherichia coli* and *Candida albicans* were inhibited weaker, and *Salmonella* sp. and *Aspergillus niger* were not inhibited (Fattouch et al. 2007). The antibacterial activities of *Cydonia oblonga* fruit extract and the isolated

compounds were studied against *E. coli* using agar diffusion assay. The extract and quinic acid derivative among the isolated compounds possessed strong antibacterial activity (Karar et al. 2014). Quince fruit extract at a concentration of 0.5 mg/ml significantly ($p < 0.001$) inhibited the influenza virus to $2^7$ in HA titre compared to $2^{10.7}$ in HA titre of control (Hamauzu et al. 2005).

### Anti-inflammatory Activity

Polyphenol extract of *Cydonia oblonga* peels at 20 μg/ml exhibited 55% inhibition on pro-inflammatory effectors TNF-α and IL-8. It also increased the potent immunoregulatory cytokine IL-10 levels at the same concentration (Essafi-Benkhadir et al. 2012).

### Antihaemolytic Activity

The antihaemolytic activity of quince leaves methanolic extract against 2,2′-azobis (2-amidinopropane) dihydrochloride (APPH) was studied, and the extract defended human erythrocytes from haemolysis with an $IC_{50}$ value of 30.7 μg/ml (Costa et al. 2009; Oliveira et al. 2012). The pulp and peel methanolic extracts (250–2000 μg/ml) were studied on human erythrocytes against APPH-induced haemolysis. After 3 h of incubation time, $IC_{50}$ value of pulp extract was 652 μg/ml, and peel extract was 695 μg/ml (Magalhães et al. 2009).

## 15.5.2 In Vivo Studies

### Antidepressant Activity

The antidepressant effect of *Cydonia oblonga* fruits was studied by forced swim test (FST) and tail suspension test (TST). Ethanol and water extracts of fruits (100 and 200 mg/kg) were applied to rats (150–250 g) with methyl isobutyl ketone depression for 15 days. A decrease in the immobility time in TST and a variation in the rigidity time in FST were detected. The SOD, glutathione peroxidase, total cholesterol and catalase levels were increased, and TBARS level was decreased at the blood samples collected from tails (Ganaie et al. 2020).

### Antioxidant Activity

The effect of quince leaf extract was studied for the intoxication (increase in the levels of glucose, AST, ALT, creatinine, urea, uric acid, cholesterol, G6PDH, hepatic LPO, DNA fragmentation, apoptotic erythrocytes, liver enzymes (SOD, CAT and TAC) and decrease in alkaline phosphatase, total protein, albumin, globulin, total lipids, LDH) of 4-nonylphenol (4-NP) on the African catfish *Clarias gariepinus.* The extract enhanced the alterations in antioxidant biomarkers, biochemical parameters, hepatic DNA damage and apoptotic level induced by 4-NP (Sayed and Hamed 2017).

### Wound Healing Activity

The healing effect of quince seed mucilage cream was studied against dermal toxicity in rabbits induced by T-2 toxin. The mucilage creams were prepared in eucerin at 5, 10 and 15% (w/w). These creams were administered on lesions twice a day. The groups of no treatment, eucerin and quince creams 5, 10 and 15% were healed on 14, 14, 12, 10 and 9 days. The quince seed mucilage cream (15%) was the most effective one on dermal toxicity (Hemmati et al. 2012).

The creams prepared from quince seed mucilage at 5, 10 and 20% concentrations in eucerin were evaluated for wound healing activity in male rabbits. They are treated topically twice a day. 20% cream exhibited the best results on wound healing (Tamri et al. 2014).

### Effect on UV Damage

The preventive effect of methanolic extract of *C. oblonga* leaves was studied on African catfish *Clarias gariepinus*. The extract protected the red blood cells from UVA damage, prevented haematotoxic stress occurred by UVA and strengthened the immune system of catfish by increasing the number of white blood cells and lymphocytes ($p < 0.05$) (Osman et al. 2010). The protective effect of quince leaf extract was evaluated in another study. Fishes were randomized into four groups: control, UVA-treated group (3 days, 3 h/day), UVA-treated group (3 days, 3 h/day) with 10 ml extract and UVA-treated group (3 days, 3 h/day) with 20 ml extract. In UVA plus 10 ml

quince leaf extract treated group, the hepatic tissues regained their normal structure with melanomacrophage accumulation and infiltration of inflammatory leukocyte cells. The quince leaf extract repaired the histopathological alterations reasoned by UVA (Sayed et al. 2013).

### Antihyperlipidaemic Activity

The effect of total flavonoids (TF) obtained from *C. oblonga* leaves and fruits on the blood lipid levels in high-lipid emulsion induced hyperlipidaemic rats was evaluated. The rats were divided in six groups (control, hyperlidaemic model, 160 mg/kg/day TF, 80 mg/kg/day TF, 40 mg/kg/day TF, simvastatin 5 mg/kg). TF reduced serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) ($p < 0.01$), alanine amino transferase (ALT), aspartate amino transferase (AST) ($p < 0.01$ or $p < 0.05$), malondialdehyde (MDA) ($p < 0.01$or $p < 0.01$) and increased high-density lipoprotein cholesterol (HDL-C) ($p < 0.05$ or $p < 0.01$) compared with the hyperlipidaemic group (Umar et al. 2015). Ethanolic leaf extract was applied to randomly divided Sprague Dawley rat groups (normal controls, model controls, simvastatin and low-, medium-, high-dose extracts) for 56 days. The medium and high doses of extract reduced TC, TG, LDL-C and MDA levels and liver steatosis, inhibited ALT and AST activity and increased HDL-C level and glutathione peroxidase (GSH-PX), superoxide dismutase (SOD), LPL and HL activity, similar to reference drug simvastatin (Abliz et al. 2014).

### Antihypertensive Activity

The antihypertensive effect of ethanolic leaf extract was studied in two-kidney one-clip (2K1C) Goldblatt model rats, divided into six groups (sham, model, captopril 25 mg/kg, leaf extract 80, 160 and 320 mg/kg). After treatment for 8 weeks, the highest dose of leaf extract significantly reduced blood pressure, angiotensin-II (AII), apelin-12 (A), plasma renin activity (PRA) and endothelin (ET), and increased nitric oxide (NO) had the same effects as captopril (Zhou et al. 2014a, b, c). At the same conditions, blood rheology was tested, too. Hyperlipidaemic rats had higher blood pressure (systolic blood pressure: 193 ± 7 mmHg) than sham group (systolic blood pressure: 138 ± 8 mmHg) after 8 weeks ($p < 0.05$). High concentrated extract reduced whole blood viscosity and improved erythrocyte deformability, while captopril had little effect on blood rheology (Zhou et al. 2014b).

### Antihyperglycaemic Activity

The antidiabetic activity of ethanolic leaves extracts were studied on streptozotocin-induced diabetic male Wistar albino rats (150–200 g) for 5 days at 250 and 500 mg/kg. 500 mg/kg administration of *C. oblonga* extract decreased blood glucose level by 33.8% (Aslan et al. 2010). The aqueous fruit extract was applied to streptozotocin-induced diabetic rats in different concentrations (80, 160 and 240 mg/kg) for 28 day. At the end of the study, the fasting blood glucose were measured as 343 ± 18, 306 ± 28 and 236 ± 23 mg/dl in increasing concentration treated groups. Namely, the highest concentration was more effective (Mohebbi et al. 2019).

### Effect on Male Sexual Dysfunction

The hydroalcoholic extract of *C. oblonga* was administered to male rats for 28 days at doses of 500 and 800 mg/kg. The parameters as mounting frequency, mating performance and attraction to females were increased compared to non-treated rats (Chen et al. 2019).

### Antithrombotic Activity

An aqueous leaf extract in different concentrations (20, 40, 80 mg/kg/day) and aspirin (5 mg/kg/day) were studied on rats using the tail cutting and glass slide methods for 14 days. Carotid artery $FeCl_3$-induced thrombus and inferior vena cava thrombosis obstruction time, 6-keto-prostaglandine F1α and thromboxane B2 plasma levels were measured. Extracts prolonged bleeding time by 2.17, 2.78 and 3.63 times and the clotting time by 1.44, 2.47 and 2.48 times, dose-dependently, while aspirin 2.58 and 1.91 times, respectively. Extracts reduced pulmonary embolus mortality 27, 40 and 53% and aspirin 47%; increased thrombolysis 45, 55, 63% and

56%; shortened ELT to 71, 61, 43% and 43% (Zhou et al. 2014c).

### Nootropic Activity

Nootropic activity of *C. oblonga* leaf decoction was evaluated on 40 rats divided into 4 groups treated with distilled water (control group) and 0.92, 1.85 and 3.70 g/dl of decoction for 28 days. After the application, the AChE activity was decreased although the anxiety, reconnaissance, learning and spatial memory were not changed. The AChE was inhibited in a dose-dependent manner, as responsible for nootropic activity (Karimi et al. 2017).

### Effect on Ulcerative Colitis

The effect of fruit hydroalcoholic extract and juice on rats with ulcerative colitis induced by trinitrobenzene sulfonic acid (TNBS). The extracts are applied to rats in different concentrations and administration methods. Juice was given at 200, 400 and 800 mg/kg orally and 400 mg/kg intraperitoneally, extract at 200, 500 and 800 mg/kg orally and 200 and 500 mg/kg intraperitoneally. The ulcerative colitis lesions were reduced by the highest concentrations (Minaiyan et al. 2012).

### Antiulcer Activity

The effect of fruit phenolics was evaluated on rats with ethanol-induced gastric ulcers. The test solution including 20 mg phenolics was treated to each rat at 1.5 ml intragastrically. Quince phenolics prevented the development of gastric ulcer with a 0.69 ulcer index (Hamauzu et al. 2006). In a similar study, polyphenolic extract (60% acetone) of fruits was administered to each male Wistar rat at 3 ml. The extract reduced ulcer at doses of 5–10 mg (Hamauzu et al. 2008).

### Antiatheresclerotic Activity

Methanolic extract of leaves were evaluated on 24 male New Zealand white rabbits. After oral ingestion of cholesterol for 8 weeks, treatment with 50 mg/kg extract and 0.5 mg/kg atorvastatin decreased lipid level of plasma and increased HDL-C level. Also the liver enzymes were reduced in extract groups (Khademi et al. 2013).

## 15.6 Clinical Studies (Ongoing, Proposed and Completed Studies)

### 15.6.1 Effect on Gastroesophageal Reflux Disease

A randomized, double-blind clinical trial was performed on 96 children with gastroesophageal reflux disease. The children were divided into two groups (ranitidine and ranitidine with quince syrup). 2 (17.8 ± 2.6 vs 23.4 ± 4.0; $p < 0.05$), 4 (11.5 ± 2.3 vs 18.8 ± 3.6; $p < 0.05$) and 6 (12.2 ± 2.3 vs 21.1 ± 4.1; $p < 0.05$) weeks after the administration, the results showed that ranitidine plus quince syrup is more effective to heal gastroesophageal reflux disease (Naeimi et al. 2019). Another double-blind randomized study with 80 children who have gastroesophageal reflux disease was conducted in two groups: quince syrup (0.6 cc/kg/day) and omeprazole (1 cc/kg/day). The quince syrup reduced the symptoms in all groups and had no significant differences when compared to the control group according to the symptom scores at weeks 4 and 7 (Zohalinezhad et al. 2015).

### 15.6.2 Effect on Menstrual Bleeding

A triple-blind, randomized clinical trial was performed on 146 women with heavy menstrual bleeding. They are divided into two groups treated every 6 h with 250 mg quince pill and 500 mg mefenamic acid 1–15 days of three consecutive menstruation periods. Menorrhagia scale of the participants showed that quince pill and mefenamic acid decreased the menstrual bleeding and increased haemoglobin levels, equally (Rahi et al. 2016).

### 15.6.3 Effect on Nausea and Vomiting

The controlled, randomised, multicentric clinical trial was studied on 110 pregnant women (18–40 age) to compare the quince fruit syrup effect

against the medication for nausea (vitamin B6, metoclopramide, etc.) for 14 days. The syrup is standardized as 2 mg total phenols as gallic acid equivalents at 1 g of concentrated syrup. The nausea and vomiting scores were decreased in both quince and medications groups (Jafari-Dehkordi et al. 2017).

## 15.7 Toxicological Studies (Dose and Safety Profile, Acute, Chronic and Mutagenicity Studies to Demonstrate Broad-Spectrum Safety, GRAS Status)

### 15.7.1 Dose and Safety Profile

#### Internal Usage

Extract/decoction: 1 teaspoon of whole seeds is used per cup of water. It may be more viscous from the grounded seeds (PDR 2000). 3% decoction of leaves can be prepared (Baytop 1999).

Compote/juice: It is used in the form of juice obtained by squeezing fresh quince or compote sweetening with honey (Baytop 1999).

Infusion/decoction: The decoction and infusion of leaves can be prepared for medicinal uses (Tuzlacı 2016).

#### External Usage

Leaves softened by water vapour for 1 h are used externally for the treatment of wounds and cracks on the hand (Tuzlacı 2016).

Decoction of seeds is used as emollient for the skin and as gargle for throat diseases (Baytop 1999).

#### Method of Administration

Decoction of seeds and decoction and infusion of leaves are used both internally and externally (Baytop 1999; PDR 2000; Tuzlacı 2016).

#### Contraindications

Health risks or side effects are not recorded with stated administration methods and therapeutic dosages of whole seeds (PDR 2000). Even so it can be sensitivity to *Cydonia* seeds and many of the species in Rosaceae family due to nitriles convertible to hydrogen cyanide (Sabir et al. 2015).

#### Interactions with Other Medications

Quince can decrease the effectiveness of the medication due to its mucilage content. It should be taken at least 1 h after oral medications (https://www.webmd.com/vitamins/ai/ingredientmono-384/quince).

#### Pregnancy and Lactation

*C. oblonga* seeds may have damaging effects in breast-feeding women due to nitriles in their composition which may give hydrogen cyanide after digestion (Sabir et al. 2015).

The quince fruit syrup decreased nausea and vomiting in pregnancy (Jafari-Dehkordi et al. 2017).

#### Works Required Attention

None reported.

#### Overdose

The seeds are to be toxic if consumed in large quantities because of its poisonous hydrogen cyanide content (Sabir et al. 2015).

#### Duration of Use

Quince fruit syrup usage is recommended for up to 4 weeks (https://www.webmd.com/vitamins/ai/ingredientmono-384/quince).

### 15.7.2 Acute, Chronic and Mutagenicity Studies to Demonstrate Broad-Spectrum Safety

#### Acute Toxicity

A small piece of a raw peeled quince had caused an immediate glottic and lingual angioedema at a 57-year-old woman via an IgE-mediated reaction (Allergy to quince 2015).

Acute toxicity study showed that aqueous and ethanolic extracts of *Cydonia oblonga* Mill. fruits (2000 mg/kg, orally) were nontoxic and the $LD_{50}$ values were higher than 2000 mg/kg (Ganaie

et al. 2020). In another study, $LC_{50}$ value of aqueous leaf extract was >10,000, while ethanolic leaf extract was 42 μg/ml (Bussmann et al. 2011).

### Chronic Toxicity

None reported.

### Mutagenicity and Teratogenicity

The genoprotective effects of hydroalcoholic extract of quince fruits were studied on DNA damage induced by genotoxic concentration (100 μM) of methymethane sulfonate by comet assay on HepG2 cells. Genoprotective effect of extract (1, 10, 100 and 500 μg/ml) increased in a dose-dependent manner. Also no genotoxicity was reported in studied concentrations (Mobarekeh et al. 2015).

### 15.7.3 GRAS Status

Quince seed has been accepted in NAT, GRAS-182.40 (https://www.fda.gov/food/food--additives-petitions/food-additive-status-list#ftnQ).

## 15.8 Available Commercial Formulations/Products, Uses, Administration Methods and Pharmacokinetic Studies (with Special Focus on Bioavailability and Metabolism of Active Constituents)

None reported.

## 15.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

The fruits, seeds and leaves of *C. oblonga* were used in traditional medicine. Among these usages anti-inflammatory, antihaemolytic, wound healing, antihyperlipidaemic, antihypertensive, antihyperglycaemic, antiulcer, antiatherosclerotic activities and effects on colitis, stomach disorders and nausea were studied scientifically.

## 15.10 Challenges and Future Recommendations as Potential Drug Candidate

Many studies have scientifically revealed the important effects of *C. oblonga* and offer an insight onto future studies on the way to product.

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# *Cynara scolymus* L.

16

Selen Ilgün

**Abstract**

Artichoke (*Cynara scolymus* L., Asteraceae) is a prevalent cultivated plant frequently consumed in the Mediterranean Regions, the USA, and Africa. *C. scolymus* is used in folkloric medicine to treat hepatitis and hyperlipidemia and its diuretic and choleretic effects. Artichoke includes vitamins, minerals, phenolic components, prebiotics, and terpenoids. It has several biological activities, especially antihyperlipidemic, antispasmodic, antiaging, antioxidant, antimicrobial, hepatoprotective, choleretic, hypoglycemic, and anticancer features. In recent years, *C. scolymus* has been designed and used in various pharmaceutical forms. Clinical analyses have stated that extracts from artichokes may have recuperating characteristics to treat a variety of diseases.

**Keywords**

Cynara scolymus · Globe artichoke · Asteraceae · Hepatoprotective

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## 16.1 Introductions

Globe artichoke (*C. scolymus* L.) is a Mediterranean European plant and belongs to the Asteraceae family. This genus is represented by about 15 species worldwide. Artichoke, a herbaceous perennial plant, is highly resistant to pathogens and small insects with medium salt tolerance (Ceccarelli et al. 2010). *Cynara* spp. reveal the common botanical aspects of the Asteraceae family with capitulum inflorescence, and typical seeds are named achene (Gominho et al. 2011). Artichoke is an allogamous plant, and pollens are carried by the insect. The stem of the plant is usually short, and leaves can reach 50–200 cm. The flower inflorescence is known as a capitulum or head, consisting of inner and outer bracts and a vast receptacle. Flowers are generally in blue and tubular form (Crino et al. 2008; de Falco et al. 2015).

*C. scolymus* is a food that is getting more and more attention today due to its health benefits. However, most parts of the plant (i.e., bracts and leaves) are thrown away by the artichoke processing industry. These parts of capitulum make up 40–50% of its weight and are vital for food additives and nutraceuticals, so they are potential industrial resources (de Falco et al. 2015).

Artichoke is the name used to describe the entire plant containing the capitulum or edible flower heads. Its scientific name is derived from the Latin words *cinis* and *cineris*. The name



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"Kynara" probably comes from the name of Aegean Island. It is also known as "skolymos" in Greek, "thistle" because of the spines surrounding the flowering part of the edible part of the plant (Frutos et al. 2019). Different countries such as Italy, Spain, and Portugal use names such as "carciofo," "alcachofa," and "alcachofra" for the globe artichoke. It is thought to come from the Arabic word "al harshuff." It is estimated that Arabs caused the spread of the plant in the Mediterranean region. There is also information that the name of the plant comes from the Latin word "articoculum" (artus = thorny, cocolum = soil) in Northern Europe, England, France, and Germany (de Falco et al. 2015).

Zayed and Farag (2020) stated that the *Cynara* L. genus consists of eight species and four subspecies. This genus, which is indigenous to the Mediterranean Basin, is widely grown all over the world, because the species belonging to the genus quickly adapt to different soil and climate conditions. *Cynara cardunculus* L. is commonly known as cardoon and is considered to have different varieties (var. *scolymus*, var. *sylvestris*, var. *altilis*) (Zayed and Farag 2020). However, according to recent data, *C. scolymus* is the only accepted scientific name for globe artichoke and has no synonyms (The Plant List 2021).

This section aims to evaluate the botanical features, distribution areas, and ethnobotanical uses of artichoke, a widely consumed plant and grown worldwide. Besides, data on the herb's pharmacological effects, toxicity studies, and bioactive compounds and clinical investigations have been collected.

## 16.2 Distribution and Status of Species

Different studies on the distribution, origin, and ancestors of the species are available in the literature. According to molecular and detailed systematic analysis studies, there are differences of opinion when accepting *C. scolymus* and *C. cardunculus* as different species. Molecular data has shown that the wild ancestors of all species of the *Cynara* genus were moved from the Mediterranean coast to the Sahara region during the fourth glaciation of the Pleistocene due to their need to reach high thermal conditions (de Falco et al. 2015).

*C. scolymus L.* is probably a native of North Africa or Southwest Europe. However, the problems related to the taxonomic status have not been solved yet. Some authors claim that *C. scolymus*, *C. cardunculus*, and *C. syriaca* are different species, while others consider them subspecies of the same species (Ancora 1986). Some authors mention three interrelated wild species in the genus *Cynara*. *C. cardunculus* L., which is widely grouped in the western and middle parts of the Mediterranean Basin; *C. sibthropiana* Boiss. et. Heldr., which ensues mainly in the Aegean Islands (including Crete and Cyprus); and *C. syriaca* Boiss. spread in the Levant and southern Turkey (Zohary and Basnizky 1975). But according to the latest updated data, the *C. auranitica* species was mistakenly registered as *C. syriaca*, so *C. syriaca* is not grown in Turkey (Güner and Aslan 2012).

There are claims that *C. scolymus* and *C. cardunculus* are the culture forms of the newly described *C. cardunculus* subs. *Flavescens* Wiklund subspecies in some taxonomic revision data. *C. scolymus* and *C. cardunculus* species were included in monographs in the European Pharmacopeia as two different culture forms with morphologically indistinguishable properties of a single species (Chinou and Chinou 2011). In the Plant List (2021), *Cynara scolymus L.* is an accepted name in the genus *Cynar*a, and no synonyms are recorded for this name. *Cynara cardunculus* L. subsp. *flavescens* is an accepted subspecies of *C. cardunculus*. *C. cardunculus* L. subsp. *scolymus is a* synonym of this taxon.

Artichoke culture is widely held around the world. It is also produced in Asian countries such as China, North Africa, South America, and the USA (especially California) and especially in the Mediterranean area. The world's largest manufacturer of *C. scolymus*, a vital agricultural resource, is Italy, and Spain and France follow it with production (Frutos et al. 2019).

## 16.3 Traditional/Ethnomedicinal/Local Uses: In Turkey and Throughout the World (Asia and Europe)

The history of the use of artichokes as food and medicine goes back to the Ancient Egyptians, Greeks, and Romans. It is stated in the literature that the Greek Theophrastus mentioned that artichoke was first grown in Sicily. The Egyptian King Ptolemy Euergetes ordered that the soldiers consume artichokes as a source of strength and courage. In the mosaics belonging to the Roman Empire, artichokes were also described. The Roman authors mentioned that the artichoke crushed roots could be rubbed into the body and purified from disturbing odors (de Falco et al. 2015).

It is estimated that artichoke, one of the oldest cultivated plants, was first grown in Ethiopia and then spread to Southern Europe via Egypt. Evidence of the existence of artichokes was first found on ancient Egyptian tablets and sacrificial altars. On the other hand, the ancient Greeks and Romans have proven that artichoke is a food to be consumed by the elite. In sixteenth-century Europe, the artichoke was only consumed by the nobility and the wealthy and was referred to as a rare precious plant (Petrowicz et al. 1997).

In traditional European medicine, it is known that the leaves of the artichoke are used for diuretics and to stimulate bile flow. For example, in France, *C. scolymus* has traditionally been used to heal the functions of the urinary and digestive systems. In Hungary, it has been used to regulate fat metabolism and increase the sense of satiety, digestive problems, nausea, gas, and gallbladder ailments (Salem et al. 2015).

In Turkey, artichoke has been used for liver diseases and diabetes and cholesterol-lowering effects by people traditionally. Various parts of the plant were also used for kidney stones. It has also been noted that fresh herbal receptaculum is effective against osteoporosis and strengthens bones (Tuzlacı 2016). The herb is used in infusion (2–3%) as an appetizer and urinary and biliary diuretic. The roots and seeds of the plant, which do not contain toxic compounds, are also used for the same purposes. It has also been known as an aphrodisiac since ancient times (Baytop 1999).

There are records regarding *C. scolymus* diuretic, stomach tonic, cholagogue and fever, liver disorders, gallstones, blood cholesterol, urticaria, asthma, and eczema in Iranian medicine. *C. scolymus* has been used as it provides weight loss in Brazil traditionally (Mahboubi 2018).

## 16.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques (Classification and Structures of Few Representatives)

Globe artichoke is an essential plant with a rich polyphenic substance content. In particular, the main compounds isolated from polar extracts are caffeoylquinic acids, flavonoids. Besides, the herb has been reported to contain significant amounts of inulin, fiber, and minerals. Fatty acids, triterpenes, and sesquiterpenes are compounds often obtained from apolar fractions. It has been proven in studies that many factors are affecting the presence and quantity of these components. The climate, genetic factors, stress conditions, harvest time, agronomic procedures, and effective drying methods significantly affect the results (de Falco et al. 2015).

Globe artichoke has an essential quantity of minerals (potassium, sodium, phosphorus) and especially vitamin C (10 mg/100 g FW) in the flower head. Artichoke seeds contained crude protein 21.6%, natural fiber 17.1%, crude oil 24.05%, and ash 3.8% (Ceccarelli et al. 2010; Foti et al. 1999; Lattanzio et al. 2009).

Inulin, a water-soluble long-chain carbohydrate, has been identified as an essential active ingredient. Since it cannot be absorbed and digested in the small intestine, it can reach the large intestine, and it is imperative to use it as a prebiotic. The inulin content of artichoke can change according to storage conditions. It is between 30.6% and 36.7% of the dry weight in

roots and 50–70 g/kg in fresh plants. Inulin can be obtained from outer bracts, juicy and mature artichoke roots, and flower heads, and it can be used as a dietary supplement (Christaki et al. 2012).

Caffeic acid derivatives, one of the significant components of artichokes, are abundant in the plant. Chlorogenic acid (39%) is the leading substance, followed by 5-*O*-caffeoylquinic acid (21%) and 3,4-*O*- dicaffeoylquinic acid (11%) (Lattanzio et al. 2009). Cynarin, which is isolated in small quantities from methanol extracts of artichoke, is also a derivative of caffeic acid. This compound has also been identified in the dried leaves, stem, and fleshy parts of the bracts (Ceccarelli et al. 2010). Lattanzio et al. reported that isolated phenolics such as apigenin and luteolin and anthocyanidins such as peonidin and delphinidin only from the capitulum artichokes. They also noted that apigenin and luteolin could be found in the plant leaves in glucoside and rutinoside. Simultaneously, anthocyanin pigments in the form of sophoroside and glucoside were detected in the capitulum (Lattanzio et al. 2009). *C. scolymus* leaves were evaluated in terms of essential oils with gas chromatography-mass spectrometry analysis, and 11 significant components were detected. A clevenger-type apparatus was used to extract the essential oil. These compounds were furfural, benzaldehyde, 1-Octen-3-one, benzene acetaldehyde, nonanal, β-cyclocitral, β-damascenone, geranyl acetone, β-Ionone dicyclohexyl methanone, and dihydroactinidiolide (Ardalani et al. 2020).

It was determined that triterpenes and sesquiterpene lactones are important lipophilic components of *C. scolymus.* Sesquiterpenes are primarily stored in leaves, and moderate amounts are found in the stem and capitulum. The quantity of triterpenes in the leaves was determined at lower rates (Ramos et al. 2013). The authors also regarded "cynaropicrin" as the dominant sesquiterpene component in leaves of *C. scolymus* (Eljounaidi et al. 2015).

Cynarases A, B, and C are proteinases in glycoprotein structure isolated from artichoke flowers (Sidrach et al. 2005).

Table 16.1 shows the main ingredients (phenolic compounds and terpenoids) obtained from artichokes.

## 16.5 Scientific Evidences: Pharmacological Activities (All Major Therapeutic Activity with In Vitro and In Vivo Studies, Mechanism of Action)

### 16.5.1 Antioxidant Activity

Oxidative stress induced by reactive oxygen species is associated with many ailments. Artichoke has positive effects in preventing the production of reactive oxygen species, which have an essential role in the appearance of these diseases, thanks to the secondary metabolites it contains.

In a study, the antioxidant effects of freeze-dried ethanol extracts of *C. scolymus* have been investigated. It was determined that freeze-dried extract showed the highest antioxidant capacity (65.15%) at 10 mg/ml (Vamanu et al. 2011). *C. cardunculus* L. and *C. scolymus* L. have been compared in terms of antioxidant effectiveness. Different parts (head, stem bracts) of two artichokes were extracted by different methods and evaluated. Results have been shown that head of *C. cardunculus* (extracted using ultrasound-assisted extraction method) displayed the highest $DPPH^{\bullet}$ ($IC_{50;}$ 0.91 mg/ml) and $ABTS^{\bullet+}$ scavenging activity (2.08 $mg/g_{Trolox\ Equivalents}$) as compared to *C. scolymus* (Kollia et al. 2017). A study has been performed to evaluate the differences in radical scavenging activities of different cultivated forms of artichokes. It has been stated that the "Blanca de Tudela" form contains high amounts of carotenoids and chlorophyll (3761.91 mg/100 g), so the plants have high ABTS activity and oxygen radical absorbance capacity (ORAC). Artichoke floral stems (AFS) have been interpreted in terms of antioxidant activity in vitro with DPPH and ABTS and the FRAP (ferric reducing ability of plasma) assays. $IC_{50}$ values of methanol extract were calculated at 185.6 and 588.1 μg/mL in DPPH and ABTS

**Table 16.1** Chemical compounds from *Cynara scolymus* L.

| | Compound name | References |
|---|---|---|
| **Phenolic compounds Hydroxycinnamic acids** | | |
| | 1-*O*-Caffeoylquinic acid | (Wang et al. 2003), (Romani et al. 2006) |
| | Cynarin | (Wang et al. 2003) |
| | 1,5-Dicaffeoylquinic acid | (Romani et al. 2006) |
| | Neochlorogenic acid (5-*O*-caffeoylquinic Acid) | (Pandino et al. 2013) |
| **Phenolic compounds Flavonoids** | | |
| | Luteolin | (Abu-Reidah et al. 2013) |
| | Cynaroside | (Farag et al. 2013) |
| | Luteolin 7-*O*-glucoronide | (Pandino et al. 2013),(Pandino et al. 2011), (Romani et al. 2006), (Abu-Reidah et al. 2013) |
| | Scolymoside | (Wang et al. 2003), (Romani et al. 2006) |
| | Luteolin 7-*O*-malonylglucoside | (Pandino et al. 2011) |
| | Apigenin<br>Apigenin 7-*O*-glucoside<br>Apigenin 7-*O*-glucoronide<br>Apigenin 7-*O*-rutinoside | (Abu-Reidah et al. 2013)<br>(Fratianni et al. 2007)<br>(Pandino et al. 2013) |
| | Naringenin<br>Naringenin 7-*O*-glucoside<br>Naringenin 7-*O*-rutinoside | (Sánchez-Rabaneda et al. 2003)<br>(Wang et al. 2003) |
| **Phenolic compounds Anthocyanins** | | |
| | Cyanidin 3,5-diglucoside<br>Cyanidin 3-sophoroside<br>Cyanidin 3-glucoside<br>Cyanidin 3,5-malonyldiglucoside<br>Cyanidin 3-(300-malonyl) glucoside<br>Cyanidin malonylsophoroside<br>Cyanidin pentoside<br>Cyanidin 3-(600-malonyl) glucoside | (Schütz et al. 2006) |
| | Peonidin 3-glucoside<br>Peonidin 3-(600-malonyl) glycoside | (Schütz et al. 2006) |
| | Delphinidin glycoside | (Schütz et al. 2006) |
| **Terpenoids Sesquiterpenes** | | |
| | Aguerin A,B | (Shimoda et al. 2003) |
| | Cynaropicrin | (Tanaka et al. 2013) |
| | Cynarascoloside A,B,C | (Farag et al. 2013) |
| | β-Cubebene | (Hădărugă et al. 2009) |
| **Terpenoids Guaianolides (sesquiterpenes lactones)** | | |

(continued)

**Table 16.1** (continued)

| | Compound name | References |
|---|---|---|
| | 11-H-13 Methylsulfonylgrosheimin 8-Deoxy-11-hydroxy-13--chlorogrosheimin 8-Deoxy-11,13-dihydroxygrosheimin 8-Epigrosheimin Sibthorpine | (Barbetti et al. 1993) |
| **Terpenoids Triterpenes** | | |
| | Cynarasaponins | (Križková et al. 2004) |

assays. In the FRAP assay, methanol extract was displayed the highest reducing power (491.7 mM TE/$g_{extract}$), while the lowest activity was examined in the ethyl acetate extract (137.1 mM TE/$g_{extract}$). Besides, AFS extracts were given to diabetic rats, and results were showed that extracts affected the activation of catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD), manganese-SOD (Mn-SOD), iron-SOD (Fe-SOD), and copper/zinc-SOD (Cu/Zn-SOD) in the liver and kidneys. It was determined that lipid peroxidation and $H_2O_2$ production decreased thanks to artichoke application (Mejri et al. 2020).

Another study was conducted again on diabetic rats by Magielse et al. Different fractions of artichoke leaves extract were evaluated for both in vivo and in vitro antioxidant capacity. ABTS radical scavenger activity of ethanol extract was found to be quite high (499.43 g ± 39.72 Trolox/$g_{dry\ extract}$). Also, it was observed that the administration of ethanol extract to diabetic rats in vivo conditions resulted in increased CAT, SOD, and glutathione (GSH) activities in the liver, kidney, and pancreas of rats. The artichoke was administered orally in streptozotocin-induced diabetic rats; a decrease in malondialdehyde and 8-hydroxydeoxyguanosine levels was detected, while a significant increase in erythrocyte glutathione levels was noted (Magielse et al. 2014).

The antioxidant effects of *C. scolymus* extracts using different solvents have been investigated using DDPH, ABTS, FRAP, and beta-carotene bleaching test methods. As a result, the ethanol extract of leaves was showed the most potent antioxidants activities (DDPH (94.23%), ABTS (538.75 mmol), FRAP assay (542.62 μmol), and β-carotene bleaching (70.74%). The in vivo study was displayed that malondialdehyde (MDA) and advanced oxidation protein products (APP) levels were significantly decreased in the groups given ethanol extract in 400 mg/kg. Also, oxidative stress parameters were measured in paw edema homogenates. It was noted that there was an improvement in SOD (20.75%), GSH (75.66%), and CAT (56.55%) levels (Ben Salem et al. 2017).

The antiaging effects of artichoke extracts have been investigated. DPPH scavenging activity was measured, and reactive oxygen species (ROS) scavenging effects of the extracts were tested in the human keratinocyte cell line (HaCaT cell line) on the aging process. A purified fraction extract of artichoke (CSC) was shown the most vigorous DPPH scavenging activity with $IC_{50}$ 56 ± 6 (μg/mL) values and with the highest percentage of reduction of ROS (94.2 ± 1%) (Marques et al. 2017). Besides, in other studies, it has been proven that artichoke acts by increasing the levels of antioxidant enzymes (SOD (superoxide dismutase), GSH-Px (glutathione peroxidase), and CAT (catalase) activities in D-galactose-induced aging caused by oxidative stress (Song et al. 2012; Sukoyan et al. 2018).

In a study to investigate the prophylactic effects of coenzyme Q10 and *C. scolymus*, a significant increase in both MDA and nitric oxide (NO) levels was observed in the case of doxorubicin-induced toxicity in rats. However, co-administration of coenzyme Q10 and *C.*

*scolymus* has been shown to increase GSH levels significantly (Mustafa et al. 2015).

In studies conducted on various cell lines, it has been found that artichoke leaves have positive effects on the prevention and inhibition of ROS production. Investigations have been showing that artichoke extract suppressed glutathione--s-transferase (GST) activity and gene expression of GPx and glutathione reductase (GR) in cell toxicity induced by ethanol in human liver cells HepG2 (Löhr et al. 2009). In the human monocytic leukemia, cell line (THP-1) exposed to lipopolysaccharide LPS was treated with artichoke extract, and ROS production was decreased (Miláčková et al. 2017). However, in another study where artichoke extract was applied at low doses, it was found that ROS production increased in the MDA-MB-231 human breast cancer cell line (Mileo et al. 2015).

In hepatotoxicity studies, the effects of artichoke extracts on oxidative stress parameters were evaluated. It was observed that artichoke generally had positive results in maintaining the antioxidant-oxidant balance. Kaymaz and Kandemir (2017) stated that in the case of hepatotoxicity induced by amanitine, treatment with extract of leaf *C. scolymus* generated a reduction in MDA levels and a significant rise in SOD GPx and CAT activity (Kaymaz and Kandemir 2017). It was also observed that artichoke leaves decremented MDA and diene conjugate (DC) levels and ameliorated antioxidant enzyme activity (i.e., SOD, GPx, and CAT activity) in hepatotoxicity induced by carbon tetrachloride ($CCl_4$) (Al-Ahdab 2014; Colak et al. 2016; Kaymaz and Kandemir 2017). Similar results were obtained in rats with paracetamol-induced hepatotoxicity and mice with acute alcohol-induced liver damage (El Morsy and Kamel 2015; Tang et al. 2017). Miccadei et al. (2008) reported that artichoke head extract has antioxidant properties. Extracts have been repressed the increase of MDA and loss of GSH and cellular leakage of diminished glutathione levels formed by oxidation (Miccadei et al. 2008). Differently, the administration of the hydroalcoholic extract of artichoke leaves has caused a decrease in liver MDA levels in cadmium toxicity; no significant change in kidney MDA was observed. Also, there was no change in SOD, GPx, CAT, and GSH values in the liver and kidney (El-Boshy et al. 2017).

The high-cholesterol (HC) diet caused a significant increase in malondialdehyde (MDA) and diene conjugate (DC) levels in hypercholesterolemic rats. Only the animals were treated with artichoke leaf extract (ALE); significant reductions in hepatic and cardiac MDA and DC levels and increases in hepatic vitamin E and GSH-Px activities have been monitored (Küçükgergin et al. 2010). In a study in which aqueous methanolic extracts of the green globe and violet artichoke leaves and heads were tested in rats, increased levels of GPx in the liver were also shown (Magied et al. 2016). The antioxidant activity of aqueous-organic extracts of artichoke has been determined by in vitro and in vivo methods. FRAP and inhibition of LDL oxidation method were used for in vitro investigations. In the administration of the extracts to mice, it was observed that glutathione peroxidase activity increased and the amount of 2-aminoadipic semialdehyde and oxidation marker in plasma decreased (Jimenez-Escrig et al. 2003).

### 16.5.2 Anti-inflammatory Activity

Artichoke and artichoke components on lipopolysaccharide (LPS) stimulated RAW264.7 macrophage cell production, and inducible NO synthase (iNOS) induction was investigated. As a result, it was observed that six sesquiterpene lactones obtained from artichoke leaves inhibited nitric oxide (NO) production and inducible nitric oxide synthase (iNOS) induction in RAW264.7 cells stimulated by LPS (Matsumoto et al. 2021). An in vitro heat-induced albumin denaturation experiment was conducted to test the possible anti-inflammatory activity of flowering stems of artichokes. Authors stated that especially ethyl acetate extract showed the strongest (>98%) preventive effect, while methanol extract was found to be low (69.5%) effective (Mejri et al. 2020).

Nuclear factor kappa B (NF-κB) is one of the characteristic transcription factors actively connected with inflammation. It was reported that an

extract from *C. scolymus* L. exhibited the most excellent effect on suppression of NF-κB transactivation. It has also been recorded that cynaropicrin from artichoke inhibits NF-KB-mediated transactivation of primary fibroblast growth factor (bFGF) and matrix metalloprotease-1 (MMP-1) (Dawood and Hareedy 2019; Tanaka et al. 2013). In another study, extracts of *C. scolymus* L. and its active component cynaropicrin have been investigated on human gingival fibroblasts (HGFs) stimulated by LPS, and the potential anti-osteoclastogenic effect was determined on RAW264.7 cells induced by receptor activator of NF-κB ligand (RANKL). Authors observed that cynaropicrin inhibited interleukin 8 (IL-8) and IL-6 mRNA and protein synthesis in LPS-stimulated HGFs. In addition, *P. gingivalis* LPS-induced degradation of IκBα and phosphorylation of NF-κB p65 were also repressed by cynaropicrin (Hayata et al. 2019).

Anti-inflammatory activity of *C. scolymus* leaves extracts has been determined on carrageenan-ınduced paw edema model in rats. The inflammation biomarkers were measured, and paw edema tissues have been analyzed histopathologically. The results have been shown that inflammation caused an increase in edema size for all groups. A notable reduction in paw edema size was seen with artichoke leaf extract (ALE) treatment. Serum proteins of inflammatory markers were measured. The ratio of fibrinogen and C-reactive protein (CRP levels) in the groups of rats treated with extract was significantly decreased. It was detected a meaningful decrease in the number of cellular infiltrates and a reduced spongy-like appearance considerably in the epidermis in the group given ethanol extract (Ben Salem et al. 2017). In another study, the anti-inflammatory effect *of C. scolymus* extracts in Wistar rats was evaluated. The methanol extract was found to cause a significant reduction in paw edema compared to other extracts (ethyl acetate and petroleum ether). Besides, it has been stated that the methanol extract causes differences in serum interleukin6 (IL-6) levels (Majeed et al. 2015).

### 16.5.3 Antimicrobial Activity

The antimicrobial activities of extracts prepared using different plant parts have been evaluated within many studies' scope.

The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values were calculated based on the experiments conducted to evaluate the antimicrobial effects of the extracts prepared from the flowering stems of artichokes. The methanol extract was found effective against all tested microorganisms, especially gram-positive bacteria. *S. aureus* and *E. faecium* were recorded as the most susceptible strains with a large inhibition zone (30–31 mm) and the lowest MIC (1 mg/mL) and MBC (1.5–2 mg/mL) values. The *E. coli*, *S. typhimurium*, and yeast *C. albicans* were found resistant to all extracts (Mejri et al. 2020). Effects of *C. scolymus* leaf extracts against gram-positive and gram-negative bacteria and three different fungal strains were determined. Ethyl acetate and ethanol extracts were discovered to be effective against gram-positive and gram-negative bacteria. In contrast, water and hexane extracts were noted not to affect almost all of the microorganisms tested (SALEM et al. 2021). Antimicrobial effects of artichoke extracts containing different amounts of solvent were investigated on various bacterial strains *(Escherichia coli*, *Bacillus cereus*, *Listeria innocua*, *Candida albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*). As a result, it was observed that the efficacy of ethanol (25%) and methanol extract (75%) extracts was quite limited on these strains. However, it was noted that ethanol (97%) extract showed maximum effect (1,7 cm inhibition zone) against *E. coli* and *Listeria innocua* (Vamanu et al. 2011). In another study performed with artichoke, it was stated that artichoke methanol extracts were highly influential on gram-negative, gram-positive, and fungi tested. Inhibition zones in the range of 21.70–27.55 mm were measured. *E. coli* (27.55 mm), *B. subtilis* (25.35 mm), and *S. aureus* (24.50 mm) were determined as strains with maximum impact (Gaafar and Salama 2013).

Zinc oxide nanoparticles have been investigated for their antimicrobial activity by Rajapriya et al. (2019). Various significant bacterial and fungal strains have been tested, such as *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, as well as *Candida albicans* and C. *tropicalis*. According to results, micro broth dilution assays were utilized, and $MIC_{50}$ (0.7 lg/ml and 25 lg/mI, respectively) was calculated for *S. aureus* and *E. coli* most effective strains. $MIC_{50}$ value also was found 0.35 lg/ml for *C. tropicalis* (Rajapriya et al. 2019).

### 16.5.4 Antiparasitic Activity

A study evaluating the antiparasitic activity of cynaroside, one of the main components of artichoke, determined that the compound has antileishmanial activity depending on the time and dose. The $IC_{50}$ value of this artichoke compound was calculated as 49.49 ± 3.515 μM (Tabrez et al. 2021).

### 16.5.5 Anti-Acetylcholinesterase (Anti-AChE) Activity

It has been confirmed that the pathogenesis of Alzheimer's disease is associated with acetylcholinesterase (AChE) deficiency in the brain. Studies have shown that AChE inhibitors can be used in the treatment of this disease. In the experiments on the anti-AChE activity of the artichoke flower stems, it was determined that the butanol extract of the plant provided high AChE inhibition (33.3%) at 100 μg/mL(Mejri et al. 2020). In a study conducted in 2019, acetylcholinesterase and butyrylcholinesterase inhibition activities of five artichoke varieties were evaluated. As a result, it was noted that the $IC_{50}$ inhibition of AChE varied from 0.09 to 0.12 mg $_{\text{dried bracts}}$/mL, and there was no significant difference between samples. Also, no significant difference was found in the $IC_{50}$ values (0.01 to 0.05 $mg_{\text{dried bract}}$/mL) of butyrylcholinesterase (BuChE) inhibition activity (Turkiewicz et al. 2019).

### 16.5.6 Effects on Lipid and Carbohydrate Metabolism

The effects of artichoke, which is frequently consumed as an essential nutrient globally, on carbohydrate and lipid metabolism have been investigated using many different methods. These studies are particularly associated with antidiabetic, antiobesity, and antihyperlipidemic activities.

New cultivars and hybrids of artichoke have been studied to detect various biological activities. For evaluating the antidiabetic effects, α-amylase and α-glucosidase enzyme inhibition activity were carried out. Notable differences in α-amylase and α-glucosidase inhibitory activities were found in the analyzed cultivated artichoke varieties and hybrids. $IC_{50}$ values ranged from 1.38 to 3.49 for α-amylase, while it was observed in the range of 1.21 to 4.05 for α-glucosidase (Turkiewicz et al. 2019).

Fructooligosaccharides are prebiotics compounds found in artichokes that have hypoglycemic and hypocholesterolemic effects. When artichoke and onion were co-administered, a significant reduction in glucose and lipid profile was seen in the serum of rats compared to control over 8 weeks. Besides, liver lipid levels (very low-density lipoprotein (VLDL-c), triglyceride, high-density lipoprotein (LDL)-cholesterol, LDL/HDL ratio, total cholesterol, serum total lipids), and glycogen content have also been decreased (Moharib et al. 2014). Fiber-free flower head extracts of *C. scolymus* were given to obese and normal rats, and postprandial glucose levels were calculated. The results exhibited that *C. scolymus* have hypoglycemic effects (Fantini et al. 2011). In a study in which the protective properties of the artichoke were tested on alloxan-induced diabetic rats, it was observed that extracts from artichoke leaves provided potent inhibition of α-amylase activity with $IC_{50}$ = 72.22 μg/μL in vitro. Also, it was observed that ethanol extract reduced α-amylase levels and blood glucose levels in the serum of diabetic rats. It was also observed to significantly lower total cholesterol (T-Ch) (18.11%) and triglyceride (TG) (60.47%)

levels. Low-density lipoproteins (LDL-C) (37.77%) were also recorded (Salem et al. 2017). However, in another study, it was noted that extracts obtained from artichoke leaves showed weak α-glucosidase and pancreatic lipase inhibitory activities (Villiger et al. 2015).

Lipid-lowering effects of *C. scolymus* were evaluated with high fat-fed rats. As a result, it was observed that the total cholesterol and LDL-C levels decreased (Mocelin et al. 2016). A study was conducted to determine the effects of artichoke in rats with atherosclerosis. It has been noted that artichoke tincture indirectly reduces the impact of the atherogenic diet administered to mice and contributes to the atherogenic index by increasing HDL-C (Bogavac-Stanojevic et al. 2018). Artichoke leaf was administered intraperitoneally to rats at different doses, and changes in total bile acids, cholesterol, and phospholipid ratios were determined by enzymatic analyses. Throughout the entire experiment, a substantial increase in total bile acid concentration was observed due to the administration of the extract. It was also noted that there was no significant difference in cholesterol and phospholipid content (Rodriguez et al. 2002).

The effects of *Cynara* leaf extract (CLE) on visceral fat and serum lipids were investigated by administering CLE to obese rats fed with a high-fat diet. CLE supplementation has been noted to reduce both body weight and white adipose tissue (WAT) weight and cause a decrease in serum cholesterol, LDL-C, and triacylglycerol. On the other hand, it was observed that an increase in serum HDL-C levels in the group given CLE (Abd El Azeem et al. 2016).

### 16.5.7 Prebiotic Effects

The high inulin content of *C. scolymus* suggested that the herb may exert prebiotic effects. It has been proven that high inulin content stimulates the growth of *Bifidobacterium* in the intestine. In other words, the inulins of *C. scolymus* have been shown to have a bifidogenic structure. In another study, it was stated that the high fructooligosaccharide concentrations in *C. scolymus*, which has prebiotic effects, stimulate the growth of intestinal probiotic microflora. It was determined that inulin obtained from *C. scolymus* increased the number of fecal *Bifidobacterium*, *Lactobacilli-Enterococci*, and *Atopobium* groups (Costabile et al. 2010).

### 16.5.8 Protective Effects

The protective effects of artichoke against organ damage caused by different toxic substances have been studied in many in vivo experimental conditions, and practical results have been obtained.

The protective effects of extracts from the receptacle and stem parts of the artichoke on liver and kidney damage caused by paracetamol were examined. Especially the histopathological findings obtained effectively demonstrated the protective role of the artichoke. The results of the biochemical tests also supported the results. It has been noted that treatment with artichoke lowers serum alanine transaminase (ALT) and aspartate transaminase (AST) levels but does not affect alkaline phosphatase (ALP), creatinine, and blood urea nitrogen (BUN) levels (Sümer et al. 2020).

Mustafa et al. aimed to assess the protective effects of coenzyme Q10 (CoQ10) and *C. scolymus* (CS) in the case of doxorubicin (dox)-induced toxicity. According to the results, the co-administration of CoQ10 and CS had notable healing in hepatic and renal function parameters by affecting the expression of both alpha-smooth muscle actin (α-SMA) and proliferative cell nuclear antigen (PCNA). Q10 and CS have been noted to increase protective enzymes and reduce oxidative stress (Mustafa et al. 2015).

A study evaluating the protective effect of artichoke leaf extract (ALE) against oxidative organ damage due to cadmium (Cd) toxicity showed that Cd administration significantly affected liver and kidney malondialdehyde (MDA) levels. It was also observed that Sera interleukin (IL)-1β, tumor necrosis factor (TNF-α) and IL-10, liver transaminase, urea, creatinine, and peripheral neutrophil count significantly increased. As a

result, the application of artichoke significantly improves hepatorenal functions, antioxidant system, and immune responses (El-Boshy et al. 2017).

Artichoke leaf ethanol extracts were given orally (200–400 mg/kg for 1 month) to alloxane-induced diabetic rats and found to have local guarding effects on pancreatic β cells compared to acarbose. Ethanol extract from *C. scolymus* leaves also been found to have a remarkable protective effect on liver function and metabolism in diabetic rats (Salem et al. 2017). The preventive effects of ethanolic extracts of artichoke against acute alcohol-induced liver damage in mice were studied. According to immunohistochemical reports, it was discovered that artichoke treatment significantly suppressed toll-like receptor (TLR) 4 and nuclear factor-kappa B (NF-B) expression levels in liver tissues. Histopathological observations revealed that artichoke attenuates degeneration, inflammatory infiltration, and necrosis of hepatocytes. The results once again confirmed the protective effects of the artichoke extract on the liver (Tang et al. 2017). Liver histopathology results were examined to evaluate the protective effect of artichoke against changing biochemical parameters in rats fed with a diet containing lead, and mild lymphocyte infiltration was observed in rats treated with artichoke. Also, while looking at the oxidative stress parameters, it was seen that artichoke extract has appropriate chelating properties to reduce lead levels in the blood (Heidarian and Rafieian-Kopaei 2013). Another study concluded that hepatic cellular degeneration and necrosis in mice due to diethylnitrosamine (DEN) administration affected liver cells. However, the changes in biochemical parameters caused by DEN as a result of the co-application of fish oil and artichoke extracts were recorded as normalized significantly. Improvements were observed in the histological structure of the liver in the treated groups compared to the control group. It was accepted that artichoke is a crucial nutrient for protection from hepatocellular carcinoma and has protective effects against angiogenesis (Metwally et al. 2011). It is known that a high-fat diet (HFD) causes kidney dysfunction by inducing oxidative stress that causes it. The protective effects of ethanol extract of artichoke leaves (EEA) on the kidneys of Wistar rats fed with a high-fat diet were studied. After the application, organ weights, lipid profile, kidney markers, and antioxidant enzymes were measured. In conclusion, histological findings showed that artichoke extract has a renoprotective effect, and it was stated that the antioxidant compounds of artichoke exhibited these effects (Ben Salem et al. 2019).

Many biochemical parameters have been tested and compared with histopathological findings in studies conducted to show that artichoke has curative and protective effects against metabolic damage caused by various toxic substances. Studies have supported that the plant has a protective effect by regulating antioxidant enzyme levels against the damages caused by oxidative stress. Many studies have been carried out in the literature to prove the protective effects of the plant, and especially studies on hepatoprotective and renoprotective effects have been concentrate.

### 16.5.9 Anticancer Effects

Artichoke has critical biological activities thanks to its active ingredients. Many studies on the cytotoxic effects of plant extracts and secondary metabolites are available in the literature.

Silver nanoparticles prepared with artichoke extracts were evaluated to examine the effects of the plant on various cancer cell lines. These nanomaterials thought to increase the efficacy of the extract are significantly influential on different human cancer cell lines (colon carcinoma cells (HCT-116), hepatocellular carcinoma cells (HePG-2), breast carcinoma cells (MCF-7), and cervical cancer cells (HeLa)) (Al-Radadi 2018). *C. scolymus* leaves were utilized for testing antiproliferative activity of zinc oxide nanoparticles (ZnO NPs) on human breast cancer cell line (MCF 7) and Vero cells. As a result, $IC_{50}$ values were found 65.31 lg/ll and 957.85 lg/ll, respectively (Rajapriya et al. 2019).

Antiproliferative properties of artichoke extract have been tested on normal gingival

fibroblasts, MCF-7 breast cancer cells, and Caco-2 colorectal carcinoma epithelial cells. While the extracts caused a substantial reduction in the viability of Caco-2 and MCF-7 cancer cell lines at 500 mg/L, healthy fibroblasts remained viable at 1500 mg/L. These results demonstrate the potential effects of artichoke extract on Caco-2 and MCF-7 cells (Noriega-Rodríguez et al. 2020). Also, the antiaging activity of the artichoke was tested on the HaCaT cell line, and the cytotoxic effects of the extracts were determined. Cell viability for the artichoke extract and its purified fraction was measured as 18.3 ± 2% and 21.3 ± 2% at a concentration of 1 mg/mL, respectively (Marques et al. 2017).

In a study aiming to explain the role of artichoke extract in the treatment of hepatocellular carcinoma (HCC), it was observed that thioacetamide-induced hepatocarcinogenesis damages the liver, affects liver enzymes, and causes oxidative stress. Besides, induced oxidative stress causes an increase in metalloproteinase (MMP-3, MMP-9, and MMP-12) activities. As a result, it was found that treatment with artichokes significantly induced apoptosis by inhibition of metalloproteinase (El-Mesallamy et al. 2020). A study was conducted to investigate the effect of artichoke leaf extracts on pleural mesothelioma malignancy. The study revealed that artichoke shows an anti-tumoral activity by influencing the growth, migration, and invasion of human malignant pleural mesothelioma (MPM) cells (MSTO-211H, MPP89, NCI-H28) (Pulito et al. 2015). Extracts obtained from the edible part and leaves of the fresh artichoke were applied to oral squamous carcinoma cell lines, and their effects on the expression of caspase-9, Bcl-2, and Bax genes were examined. Artichoke extract showed a high cytotoxic impact against proliferating cancer cells, depending on time. Expression of the Bax and caspase-9 genes showed a significant increase in cancer cell lines. A considerable reduction in Bcl-2 of cancer cells was discovered, while artichoke extract caused cell growth arrest in the G2/M phase (Hassabou and Farag 2020).

### 16.5.10 Antiaging Effects

In a study that has been performed to estimate the antiaging effects of artichokes, the sun protection potential of artichoke extracts with different formulations was evaluated. The sun protection factor (SPF) of the *C. scolymus* extract and the purified *C. scolymus* fraction have been calculated as 10.99 ± 0.29 and 10.20 ± 0.21 SP. Also, physicochemical and microbiological controls, cytotoxicity, and radical scavenging activity evaluation tests have been completed on HaCaT cells to determine the quality and safety of the formulations. Finally, the safety of formulations has been confirmed by testing with in vivo methods whether they are suitable for topical use (Marques et al. 2017). Another study evaluated the effects of 2% standardized *C. scolymus* extracts on inflammation and improvement of collagen metabolism in a D-galactose-induced skin aging model in mice. Long-term treatment with artichoke extracts has been noted to regulate collagen metabolism and slow the advance of inflammation by reducing the activity of nuclear transcription factor (NF-kB) in the D-galactose-induced skin aging model (Sukoyan et al. 2018).

### 16.5.11 Antispasmodic Activity

Emendörfer et al. have been planned a study to determine the antispasmodic effects of C. scolymus grown in Brazil. The extract fractions prepared from the plant and cynaropicrin isolated from this plant were tested against contracted guinea pig ileum by acetylcholine. As a result, it was determined that the dichloromethane fraction ($IC_{50}$ = 0.93 (0.49–1.77) mg/mL) and cynaropicrin ($IC_{50}$ = 0.065 (0.049–0.086) mg/mL) showed strong activity. The use of artichoke for the treatment of gastrointestinal disorders was confirmed by this study (Emendörfer et al. 2005).

### 16.5.12 Xanthin Oxidase Inhibitory Activity

The xanthine oxidase (XO) inhibitory activity of artichoke leaf extract (ALE) and some of its major compounds and their hypouricemic effects were investigated. As a result, it was noted that the aqueous artichoke extract and the compounds as active ingredients of this plant exhibited weak XO inhibitory effects in vitro, except luteolin in aglycon form. According to the in vivo study results, no hypouricemic activity was observed after oral administration. In conclusion, the accuracy of the use of traditional artichoke (*C. scolymus* L.) leaves in the treatment of hyperuricemia and gout has not been proven by this study (Sarawek et al. 2008).

### 16.5.13 Effects on Cardiac Muscle

A study was conducted to observe the adverse effects of a high-fat diet (HFD) on adult mice's heart muscle and investigate the extent of myocardial damage in aged mice. The role of artichoke in eliminating these effects was also investigated in the study. The researchers noted that in test groups fed with HFD, cardiac myocyte loss, inflammatory cell infiltration, myofiber focal degeneration, myofibrils, sarcomeres, T-tubule system disruption, lipid vacuolations, mitochondrial damage, and nuclear pycnosis were seen in the cross-lane. However, they also emphasized that artichokes have important healing effects on these changes (Dawood and Hareedy 2019).

## 16.6 Clinical Studies

*C. scolymus* L. (globe artichoke) and its products have been recognized as potential phytotherapeutic agents considered suitable for use in various diseases. For this reason, there are various clinical studies on this herb that have been completed. Wojcicki conducted the first clinical study on artichoke in the literature in 1975 to learn the cholesterol-lowering impacts of the plant. Artichoke extract has been applied at 900 mg/day, and the findings were showed that extract had been lowered blood levels of cholesterol, free fatty acids, phospholipids, and total lipids notably (European Medicine Agency 2011).

There are many clinical studies on the effect of artichoke on antioxidant parameters. It has been observed that hydroalcoholic extracts of artichoke leaves applied at 1800 mg/day to patients with metabolic syndrome did not cause a significant change in MDA, SOD, GPx, total antioxidant capacity (TAC) levels, and oxidized LDL levels. There has been no change in glycemic parameters (Rezazadeh et al. 2018a). In a study evaluating the effects of food supplements derived from artichoke leaf extract (1200 mg/day) on antioxidant defense systems, no significant changes have been observed in SOD, GPx, and glutathione reductase (GR) activities, as well as low glutathione levels (GSSG) and thiobarbituric acid concentrations (Skarpañska-Stejnborn et al. 2008).

As a result of many clinical studies investigating the lipid-lowering effects of artichokes, it has been observed that plant extracts applied in different forms reduce total and LDL cholesterol levels (European Medicine Agency 2011). In the recent study, a standard ALE of 1280 mg has been administered every day for 12 weeks to adults with moderate hypercholesterolemia. As a result, it has been found that total plasma cholesterol decreased on average 4.2% in the treatment group. However, it has been also noted that no significant difference was observed between the groups for LDL cholesterol, HDL cholesterol, or triglyceride levels (Bundy et al. 2008).

In a clinical study to define the impact of *C. scolymus* on blood pressure (BP) and body mass index (BMI) in hypertensive patients, the treatment group was given capsules including *C. scolymus* (500 mg twice daily). Systolic blood pressure (SBP), diastolic blood pressure, and BMI were recorded during the study. As a result, a meaningful recovery in BMI was viewed in the *C. scolymus* treatment group (Ardalani et al. 2020).

The effect of very long-chain inulin (VLCI) derived from globe artichoke (*C. scolymus*) on human intestinal microbiota compared to maltodextrin has been clinically investigated. As a result of a 3-week study attended to healthy individuals, it was noted that the numbers of fecal bifidobacteria and lactobacilli increase significantly with VLCI intake. Also, while the levels of the *Atopobium* group increased remarkably, *Bacteroides-Prevotella* counts were seriously reduced, and no meaningful difference was recognized in the fecal short-chain fatty acid (SCFA) concentrations (Costabile et al. 2010).

In 2019, Cicero et al. conducted a 24-week study with dyslipidemic overweight participants. In this study, participants were given supplements containing dried artichoke extract (2 mg chlorogenic acid/pill) along with bergamot extract. As a result, it was found that supplementation of artichoke leaf extract significantly altered fasting plasma sugar (FBS), fasting insulin, or the homeostasis model assessment (HOMA-IR). In a similar study, artichoke extract and berberis extract (500 mg/day, 8 weeks) were administered to hypercholesterolemic patients, and significant changes in FBS were observed. It has also been noted that artichoke leaf supplementation does not alter SBP and DBP (Cicero et al. 2019a; Cicero et al. 2019b). In a study conducted with patients who have non-alcoholic fatty liver disease, artichoke extract (600 mg/day) was given to patients for 8 weeks, and it was found that the use of artichoke and fermented soybean powder supplements did not cause changes in glycemic indexes compared to the placebo group (Panahi et al. 2018). In a study, artichoke and fermented soybean powder supplementation were administered to patients with type 2 diabetes. At the end of the 12 weeks, significant changes were observed in FBS or HOMA-IR compared to control, and supplementation did not change SBP and DBP (Ahn and Kang 2018). 2700 mg artichoke leaf extract were given a day for 8 weeks in volunteers that have non-alcoholic steatohepatitis, and results were evaluated in terms of glycemic index parameters, and FBS didn't change and significantly reduced the mean weight, triglycerides, LDL, and cholesterol levels (Rangboo et al. 2016). In Italy, ın clinical studies involving obese participants, it was noted that FBS, HbA1c, or HOMA-IR values significantly changed when standardized artichoke extract was given to volunteers (Rondanelli et al. 2011; Rondanelli et al. 2014). In another clinical study in which the target population was hypercholesterolemic type 2 diabetic patients, significant changes were noted in FBS, HbA1c, or postprandial glucose levels in volunteers given artichoke extract (400 mg/day) (Fallah Huseini et al. 2012).

One allele of FTO-rs993960 is associated with an increased risk of obesity, type 2 diabetes, and metabolic disorders. Women with metabolic syndrome carrying this allele were treated with 1800 mg of hydroalcoholic *C. scolymus* extract for 12 weeks and, as a result, showed that artichoke extract significantly reduced serum triglyceride levels in carriers of this allele (Rezazadeh et al. 2018b). In another clinical study, the juice of *C. scolymus* leaf was administered as a dietary supplement for 6 weeks in patients on an isocaloric hypolipidemic diet. It was found that moderate hypercholesterolemia positively modulated endothelial function. It has also been noted that the administration reduces vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) and increases brachial flow-mediated vasodilation (Lupattelli et al. 2004). Concentrated artichoke leaf juice (100 mg/day) was given to hypertensive patients for 12 weeks, and the results showed that BW or BMI did not change compared to placebo. Still, it has been noted that supplementation may have a blood pressure-lowering effect in mild hypertension (Roghani-Dehkordi and Kamkhah 2009).

A study was planned to show the valuable impacts of artichoke and *Chlorella vulgaris* in patients with NAFLD. It was noted that serum ALT, AST, systolic and diastolic blood pressure, and BMI diminished in the treated groups after the treatment was completed (Talebi Pour et al. 2015). In a clinical study investigating the effects of artichoke leaf extracts on reducing IBS symptoms, a decrease in irritable bowel syndrome (IBS) incidence and 41% decrease in Nepean

Dyspepsia Index (NDI) total symptom score were observed after 2 months of administration of artichoke extract at doses of 320–640 mg to healthy individuals (Bundy et al. 2004).

A pilot study was conducted to support the bile secretion enhancing effects of the standardized *C. scolymus* extract plant with clinical studies. It was observed that the extract increased the bile secretion significantly after 30 and 60 minutes as a result of the application of a single dose. Therefore, *C. scolymus* has been proven by this study to dramatically increase bile secretion, which affects carbohydrate and fat metabolism in the body (Mahboubi 2018).

Many clinical studies have been described on patients with indigestion and digestive complaints. In these studies, the effects of artichoke extracts were applied to different groups at different doses, and times were recorded. As a result, it has been concluded that artichoke leaf extract reduced upper gastrointestinal symptoms (abdominal pain, bloating, and nausea) and improved the quality of life of dyspepsia patients (Fintelmann 1996; Holtmann et al. 2003; Marakis et al. 2002).

## 16.7 Toxicological Studies

There is very little data on evaluating the toxicity of the artichoke plant, especially in commercial preparations on the market. There are contradictions or a lack of data in the subacute and chronic evaluations of toxicological studies of preparations and components in the literature.

In a study evaluating the possible teratogenic effect of dry extract of *C. scolymus*, Wistar rats treated with artichoke leaves were showed slower body weight gain during pregnancy and had a lower uterine weight. Also, a decrease in fetal weight and length was noted. No fetal skeletal or visceral malformations were detected, but the results showed that artichoke consumption during pregnancy had adverse effects on fetuses (Gotardo et al. 2019).

Comet test and micronucleus test were used in a study in which genotoxic and mutagenic effects of artichoke leaf extract were evaluated. Leaf extracts were applied in increasing doses (500 mg/kg, 1000 mg/kg, and 2000 mg/kg). It was determined that extracts did not raise micronuclei in peripheral blood cells according to genotoxicity results. Also, a significant increase was noted in the bone marrow of the group administered only 2000 mg/kg in comet assay values. According to these results, it was pointed out that artichokes should be consumed carefully (Zan et al. 2013).

Studies in the literature have stated the oral LD40 (2000 mg/kg) and intraperitoneal LD50 (265 mg/kg) of the purified extract rich in caffeoylquinic acid. In mice, the oral LD50 (1900 mg/kg) of cynarin was determined. It has also been noted that no significant adverse effects or toxicity were observed after intraperitoneal administration of 800 mg/kg cynarin in rats or intravenous administration of 1000 mg/kg cynarin in rabbits. However, a shortage of anticoagulants, laxative effects, or hypersensitivity reactions have been reported rarely. Data is appropriate to take 600–1320 mg daily in the dry form of extracts prepared with water (Mahboubi 2018) (European Medicine Agency 2011).

Artichoke has Generally Recognized As Safe (GRAS) status for food use in the USA (FDA.gov. 2020).

## 16.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies (with Special Focus on Bioavailability and Metabolism of Active Constituents)

Standardized extracts of the plant, primarily obtained from its leaves, have been put on the market as a food supplement by many different brands. According to the searches made in herbal medicine databases, it was observed that there are nearly 1650 commercial product records with artichoke content (Naturalmedicines.therapeuticresearch.com 2021).

These extracts, which have different pharmaceutical forms (dry extract, decoction, infusion, tincture, fluid extract), are generally claimed to affect liver and cholesterol metabolism, helping digestion and healthy weight control. For example, in some studies for the treatment of dyspepsia, some specific extracts named ALE LI 220 (Hepar-SL forte, Serturner Arzneimittel), Cynara SL (Lichtwer Pharma), and Prodigest (Indena) were used and administered as 320–640 mg 3 times a day (Holtmann et al. 2003; Joy and Haber 2007; Lazzini et al. 2016). Standard extracts containing artichoke used for hyperlipidemia are Valverde Artischocke (Novartis Consumer Health) and Limicol (Laboratoire Lescuyer) (Joy and Haber 2007). Limicol contains 200 mg of dried artichoke leaves, among other ingredients, and the use of this product 3 times a day for 7–16 weeks has been reported in studies (Barrat et al. 2013). Especially, there are also studies on the use of Hepar-SL forte, Serturner Arzneimittel GmbH (640 mg three times daily) ve Cynara SL, and Lichtwer Pharma (320–640 mg once Daily) in the treatment of irritable bowel syndrome (Braun 2006). Cynarol®, which contains 2% cynarin was used (200 mg three times daily) in the treatment of nonalcoholic fatty liver disease (NAFLD) (Panahi et al. 2018).

*C. scolymus* is generally standardized on cynarin as its main active ingredient. It has been determined that the highest cynarin concentration was found in *C. scolymus* leaf. According to the Pharmacopeia standards, it is stated that the dried leaves of *C. scolymus* must contain at least 0.7% chlorogenic acid (Mahboubi 2018). Pharmacokinetic properties of the compounds belonging to *C. scolymus* have been evaluated. It was stated that they reached the human blood circulation by crossing the stomach and intestinal barriers, and chlorogenic acid could be detected quickly in plasma after oral administration. In the large intestine, it has been observed that colon enzymes hydrolyze chlorogenic acid to aromatic acid metabolites (coumaric acid, benzoic acids). It has also been found that the colon microflora plays a vital role in the release of caffeic acid and converting it into dihydrocaffeic acid and dihydro ferulic acid. It has been noted that intestinal microflora is essential for hydroxycinnamate ester metabolism (Azzini et al. 2007; Mahboubi 2018).

A study was conducted to assess the bioavailability of phenolic compounds after gastrointestinal digestion and the effect of human colon microbiota on compounds in Tudela artichokes (*C. scolymus* cv.). Researchers have stated that cooking artichokes with vacuum and microwave cause transesterification reactions of caffeoylquinic acids. They have also found that during this process, their total phenolic content was preserved or even increased. It was determined that the boiling process reduced the phenolic compound ratio by 25%. Only 1.6% of the total (poly) phenolic compounds remained biologically accessible after gastrointestinal digestion in raw artichokes. The percentage of bioavailability in vacuum-cooked, boiled, and microwaved artichoke samples were found 60.38%, 59.93%, and 39.03%, respectively. The colon microbiota quickly breaks down phenolic compounds during the first 2 hours of incubation after fecal fermentation, and colonic degradation is an important pathway involving the formation of caffeic acid, dihydrocaffeic acid, 3- (3 (−hydroxyphenyl) propionic acid, 3-phenyl propionic acid, and phenylacetic acid (Domínguez-Fernández et al. 2021).

## 16.9 Gap between Ethnomedicinal and Scientific/Clinical Evidences

Studies on plant extracts and secondary metabolites derived from the artichoke have been included in many studies in vitro and in vivo. Traditional uses of the plant were taken as a reference to investigate these activities. Many studies have confirmed the antioxidant, hepatoprotective, choleretic effects of the plant, especially its lipid-lowering and antiatherogenic activity. It has been observed that the plant has been the theme of many clinical investigations since 1975. The results of many experiments conducted in vitro and in vivo have tried to be confirmed by these studies. While the data show

promising results, it is also emphasized that the research should be expanded. The data obtained support the accuracy of the traditional use of the plant. However, only one source has been found showing the herb's traditional use as an aphrodisiac, and no studies have been found to confirm this information.

## 16.10 Challenges and Future Recommendations as Potential Drug Candidate

Traditional medicines have the advantage of being well-tolerated by humans. Still, for the most part, their efficacy is limited because natural extracts contain a limited dose of the required active molecule or contain compounds that act as antagonists against these molecules (Paoli 2021). Therefore, despite the evidence that traditional medicine is an essential resource for treating human diseases, the availability of new, potent, targeted, and safe medicines suggests that more studies need to be done on herbal preparations.

It is not a wrong approach to consider this plant as a potential drug candidate, which is known to have safe pharmaceutical forms that have taken place in the European market with its existing preparations for more than 30 years. But it is emphasized that herbal therapeutic products containing *C. scolymus* should not be utilized throughout pregnancy and breastfeeding. Generally, pharmaceutical forms are acceptable for clinical safety. Lack of data on genotoxicity, carcinogenicity, and reproducibility also indicates that more studies are needed.

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# *Equisetum arvense* L.

17

Saliha Şeyma Şahinler

**Abstract**

*Equisetum arvense* L. is an herbaceous perennial plant originated in the northern hemisphere, which is traditionally used as a medicinal ingredient. It is a medicinal herb having been used traditionally and clinically in many countries for thousands of years. Traditional medical practice records about *Equisetum arvense* L. found in many countries including Brazil, Turkey and Iran, and scientific studies carried out since early twentieth century have supported the idea that the plant can be used as medicine. Recently, a significant number of studies have been carried out, and clinical data has been collected especially on its anti-inflammatory, diuretic, antimicrobial, and antioxidant effects.

**Keywords**

*Equisetum arvense* L. · Horsetail · Phytochemical content · Cytotoxic activity · Antimicrobial activity

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## 17.1 Introduction

*Equisetum* L. is an ancient pteridophyte of which fossils go back to the Devonian era. Thanks to studies carried out so far, *Equisetum* species gained worldwide attention 15. Depending on their stomatal location, those *Equisetum* species are categorized in two different groups in the *Equisetum* genus. The first group is called Hippochaete. The stomata of *Equisetum* species belonging to this group are located under the epidermal cells. The second group is named *Equisetum*. *Equisetum arvense* L. (EA) species is in the second Group (Kokten et al. 2020). Their sterile bodies (*Equisetum* stem) are included in the European Pharmacopoeia. The part forming the "Equiseti herba" is used as a medicine in various countries (ESCOP M. 2018).

Belonging to the Equisetaceae family, *E. arvense* is seen almost everywhere around the world including the United States (except southeast), Europe, Africa, South Asia, Iran, Turkey, China (except southeast), the Himalayas, Japan, and Korea (PDR for Herbal Medicines 2000). It grows in a mild climate in northern Iran (Tufarelli et al. 2021). It also grows in Turkey's northern and eastern Anatolia regions generally along the creeks and fields (Baytop 1999). In Brazil, *E. arvense*, commonly known as "cavalinha," is cultivated for medical use (Carneiro et al. 2019).

*Equisetum arvense* L. (synonymous name: *Equisetum calderi* Bolvin) belongs to the



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Equisetaceae family, *Equisetum* L. genus, and *Equisetum* subgenus. The name equisetum derives from Latin (equi = horse and setum = tail) and is popularly known as horsetail. The term "Arvense" is derived from the tree-like shape of the plant. Around Turkey, *E. arvense* is known as "atkuyruğu, çam otu, çığçığ, ekli ot, katır kuyruğu, kırkboğum otu, kırkkilit otu, tarla at kuyruğu, tilkikuyruğu, zemberek otu." Among English names used in Europe are bottle-brush, field horsetail, common horsetail, Dutch rushes, corn horsetail, horsetail grass, horse willow, pewterwort, paddock-pipes, horsetail rush, shave grass, scouring rush, and toadpipe (Demirezer et al. 2017; Carneiro et al. 2019). As reported in the literature, Arabic names include kinbat, thail el-faras, thanb el-faras; Spanish, cola de caballo; Japanese, sugi-na, tsukushi; Swedish, åkerfräken; German, akerschachtelhalm; and French, prêle des champs (Al-Snafi 2017).

The stems of the plant are leafless, similar to asparagus. When they dry they become hollow, hard, and strong. Its thin branches with small, scaly leaves look like a horse's tail. *E. arvense* is a perennial plant with a distinctive appearance that reaches 20–65 cm in height. It is characterized by primary branched aboveground stems and spirals. There are two types of stems named spore (fertile) and sterile. The fertile stems are simple and have a reddish hue, loose brown sheaths, and an oblong pointed tip disappearing in the summer. The reproductive structure known as strobilus where spore production occurs is located at the terminal end and branches. Sterile stems are green, cracked, and hollow; branches are thin and arranged in pairs. These simple, light green branches exhibit four angles and are jagged and jointed. The deep rhizome goes down as deep as 2 meters. Its shoots, which are dried sterile stems, are used for medicinal purposes. Sterile bodies are composed of cortex, parenchyma, stomata, and silica granules (Sandhu et al. 2010; Carneiro et al. 2019).

## 17.2 Distribution and Status of Species

*E. arvense* is spread over three continents: Europe, Asia, and North America. The spread of the plant is as follows: Europe (Greece, Bulgaria, Poland, Denmark, Germany, Belarus, Latvia, Estonia, Russian Federation-European part, Moldova, Austria, Belgium, Ukraine, Svalbard, Lithuania, Netherlands, Albania, Slovakia, Sweden, Norway, Finland, Switzerland, Serbia, Iceland, Ireland, United Kingdom, Bosnia, Montenegro, Italy, Romania, Slovenia, Spain, Portugal and France); Asia (Turkey, Kazakhstan, Russian Federation, China, Korea, Japan, Armenia, Georgia, Azerbaijan, Tajikistan, Kyrgyzstan, Uzbekistan, Turkmenistan, Mongolia, Iraq, Iran, India, Nepal and Bhutan); and Northern America (United States and Canada) (Al-Snafi 2017).

## 17.3 Comparison of Traditional/ Ethnomedicinal/Local Uses

The vicinity of Chimborazo province which is located in the Andes is considered to be a thousand-year-old city where ethnic groups live together and many different cultures co-occur. In a study conducted in this region, it was found that the leaves of *E. arvense* species were traditionally used as an anti-inflammatory by infusion (Morales et al. 2017).

In an ethnobotanical study carried out in Bozüyük (Bilecik, Turkey), it was determined that the extract taken out of leaves and stems of *E. arvense*, which is locally called Kırkkilit, was traditionally used by infusion for renal lithiasis (Güler et al. 2015).

In Saudi Arabia *E. arvense* is used as a traditional medicine for the treatment of renal disorders, gastroenteritis, and urinary infections and known as a diuretic (Al Mohammed et al. 2017).

In an ethnobotanical study, *E. arvense* ranked fifth among the species found to be of high dermatological importance with a strength of 70.47%. A study by Uğurlu et al. stated that *E. arvense* was used as a traditional medicinal plant in the treatment of bronchitis and gallbladder inflammation (Kokten et al. 2020).

*E. arvense* L. is traditionally used to treat kidney and bladder-related disorders, nail fractures and hair loss, and difficult-to-heal wounds and used as a hemostatic for nose, lung, and stomach bleedings (PDR for Herbal Medicines 2000). It is also reported to be used in the supplementary treatment of chronic leg swelling, sprains, and fractures that are hard to heal, dermatological disorders, rheumatism, arthritis, jaundice, sore throat, and hemorrhoid. In addition, the plant is used as a painkiller, chlorothiazide, blood refiner, diuretic, and anti-inflammatory (WHO Monographs 2010; Demirezer et al. 2017). It is known that teas prepared with the plant are consumed against diabetes and renal disorders in Iran (Soleimani et al. 2007). In some sources, it has been reported that this plant is used in the treatment of diseases such as pelada, eye inflammation, constipation, indigestion, low back pain, and osteoporosis (Demirezer et al. 2017).

## 17.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques

Through different studies, *E. arvense* was determined to contain the main flavonoids [apigenin, isoquercitrin, luteolin, quercetin-3-O-glucoside, and various compounds], phenolic glycosides [onitin, onitin-9-O-glucoside, equisetumoside A, B, and C], triterpenoids [ursolic acid, taraxerol, isobauerenol, oleanolic acid, germanicol, betulinic acid], alkaloids [palustrinine, palustrine, nicotine], phytosterols [β-Sitosterol, epicholestanol, cholesterol, isofucosterol, campesterol], and minerals [calcium, silicic acid, potassium, silicates, sulfur, aluminum, manganese magnesium] (Badole and Kotwal 2014).

In a 2017 review, the presence of alkaloids, carbohydrates, flavonoids, sterols, proteins, phenol, amino acids, saponins, triterpenoids phytosterols, tannin, silicic acid, ascorbic acid, and essential oils were reported among many biologically active components (Al-Snafi 2017).

The strain *E. arvense* is known to be very rich in minerals and contains mainly $SiO_2$ (5% to 10%) and silicon (Si), with a small proportion in the form of water-soluble silicates. Silicic acids, silicates, polyenoic acids, dicarboxylic acids, and styryl-pyrone as well as phenolic acids, methyl esters of protocatechuic, and caffeic acid were detected in its content. In addition, lower proportions of potassium, calcium, and phosphorus ions such as sodium, magnesium, zinc, aluminum, and manganese were detected. Flavonoids such as luteolin, apigenin, isorhamnetin, quercetin, and kaempferol were found in percentages ranging from 0.2% to 0.09%. A complex originally categorized as having a saponin structure (equisetonin) was later identified as a mixture of sugar and flavonoid (Carneiro et al. 2019).

In a study comparing the oil acid composition in leaves of four different *Equisetum* species (*E. telmateia*, *E. ramossissim*, *E. palustre*, and *E. arvense*) collected from Bartın Province, Turkey, linolenic, palmitic, linoleic, presence heksadekatrienoik, and oleic acid were found to be the primary compounds. Stearic, palmitoleic, juniperonic, and trienoic acids were found at lower levels. Other fatty acids (hexadecadienoic, myristic, lauric, pentadecanoic, arachidic, margaric, behenic, and gadoleic acids) were also measured at less than 1%. The results indicated that *E. arvense* contains 26.22% palmitic acid, which is the highest among its equivalents. Oleic acid (3.88%), palmitoleic (2.55%), and trienoic acid (0.68%) were found to be at the lowest. The highest linolenic, hexadecatrienoic, and juniperonic acids were obtained from *E. arvense* with 42.57%, 8.04%, and 1.88%, respectively. The study also showed that the proportion of total unsaturated fatty acid was lowest in *E. arvense*. On the other hand, it was determined to have the highest total saturated fatty acid level (30.79%) (Kokten et al. 2020).

One study determined that the stem part of the plant contains silicates and silicic acid (5–8%), potassium (1.8%), and calcium (1.3%), together with some other minerals such as zinc, aluminum, phosphorus, sulfur, magnesium, manganese, and sodium (Al-Snafi 2017).

The volatile organic compounds of the sterile stems of *E. arvense* were investigated through GC, GC/MS, and 13C-NMR. Trans-phytol (10.06%), thymol (12.09%), cis-geranyl acetone (13.74%), and hexahydrofarnesyl acetone (18.34%) were reported among the major constituents (Radulović et al. 2006; Al-Snafi 2017).

In a recent study, when "horsetail" was added to the diets of chickens, the color of the egg yolk was observed to improve. It has been determined to be caused by the high flavonoid content in the diet. The horsetail plant has been reported to contain large amounts of polyphenols, fixed and essential oils, and various active substances of pharmacological importance (Tufarelli et al. 2021).

## 17.5 Scientific Evidences

Previously, antimicrobial, antiplatelet aggregation, antioxidant, cytotoxic and anticarcinogenic, vasorelaxant, hepatoprotective, remineralization, anti-inflammatory, and anti-leishmanial effects of *E. arvense* were investigated in various in vitro studies; likewise in vivo studies addressed its anxiolytic, anti-diabetic, analgesic, and anti-inflammatory activity against benign prostate hyperplasia, wound-healing, remineralizing, antilithiatic, bladder myorelaxant, and diuretic activities (Carneiro et al. 2019).

In the studies on *E. arvense*, its antioxidant, anticonvulsant, diuretic, hypoglycemic, antimicrobial, anticancer, anti-inflammatory, and anti-anxiety activities were determined (Uslu et al. 2019).

Approximately 25% of the dried form of the horsetail plant is used as a silica supplement (the oxide form of silicon). Researchers have stated that the silica in horsetail cures the formation of calcification and bone accumulation (Tufarelli et al. 2021).

Active ingredients in horsetail allow it to be used to treat ulcers, stop bleeding, and heal wounds and renal diseases. It also shows antioxidant properties. In addition, studies have shown its anticonvulsant, sedative, and antioxidant activities (Yaşar et al. 2020).

### 17.5.1 Antioxidant Effect

The antioxidative activity of the aqueous and ethanolic extracts of the aboveground parts of field horsetail was tested using four different methods. It was determined that the total amount of phenolic components in ethanolic extraction fractions was larger than the water extraction fractions, and also, these fractions had significant antioxidative activity similar to 5 mM ascorbic acid. It was found that the aqueous extract shows a high proportion of superoxide anion radical scavenging activity. Hydroxyl radicals were effectively scavenged with the ethanolic extract. The plant is known to be rich in vitamins E and C and contains high amounts of zinc and copper. It has been reported that superoxide dismutase acts against active oxygen species thanks to these substances in the plant (Nagai et al. 2005; Al-Snafi 2017).

While DPPH scavenging activity of *E. arvense* was 96.2% in leaves and middle stem, it was 94.7% for rhizome rooted stem and root at the same concentration (4.0 mg/ml) (Huh and Han 2015).

In a different study, onitin and luteolin compounds isolated out of the methanol extract of *E. arvense* showed a superoxide scavenging effect at (IC50 = 5.9 ± 0.3 microM and 35.3 ± 0.2 microM, respectively) (Oh et al. 2004; Al-Snafi 2017).

### 17.5.2 Anticancer Effect

The anti-proliferative activity of *E. arvense* extracts prepared with different solvents was investigated through the sulforhodamine B colorimetric assay on human cancer cell lines HeLa, HT-29, and MCF7. Its extract with ethyl acetate

has been determined to exhibit the most significant antiproliferative effect on human tumor cell lines without inducing any cell growth stimulation (Četojević-Simin et al. 2010). Aqueous extract from sterile stems of *E. arvense* showed dose-dependent cytotoxic effects on human leukemic U 937 cells. DNA fragmentation, externalization of phosphatidylserine, and the collapse of mitochondrial transmembrane potential were observed in the cells cultured with plant extract for 48 h. The researchers concluded that the cytotoxicity of *Equisetum* and its aqueous extract against U 937 cells was caused by apoptosis (Alexandru et al. 2007; Al-Snafi 2017).

When the antiproliferative effect of *E. arvense* extract was measured using melanoma B16 cells, it was determined to show a significant antiproliferative effect at a concentration higher than 0.5 mg/ml (Trouillas et al. 2003).

The cytotoxicity of the dried aboveground parts of *E. arvense* in methanolic extract was examined using a variety of cancer cell lines, including breast adenocarcinoma, lung fibroblast, cervical adenocarcinoma, and human embryonic kidney cells. The cytotoxic effect was found to be concentration-dependent, that is, 50 µg/ml has a greater effect than 20 µg/ml. Likewise, 50 µg/ml concentration was determined to have a higher cytotoxic effect than 20 µg/ml on embryonic kidney cell lines (Aldaas 2011; Al-Snafi 2017).

In a study to find out about the anticancer activity of the ethanol extract of aboveground parts of *E. arvense* (EA), A549 lung carcinoma cells were treated the extract of different concentrations (100 µg/mL and 150 µg/mL). As a result, it was found that EA exerts cytotoxicity and reduces the cell viability of A549 cells in a concentration-dependent manner. In addition, EER induced apoptotic cell death monitoring by acridine orange staining. *E. arvense* has been found to have a potential apoptotic and cytotoxic effect on the A549 lung carcinoma cell line, and these effects have been determined to be caused by the presence of anticancer compounds in the extract (Al Mohammed et al. 2017).

### 17.5.3 Antimicrobial Effect

In one study, the methanolic extract of the aboveground parts of *E. arvense* showed antibacterial activity against *Escherichia coli* at high concentrations (1 g/ml) (Aldaas 2011). *E. arve*nse extracts were found to have antimicrobial effects against *Staphylococcus epidermidis* and *E. coli*, but had no significant effect against *Candida albicans*. Another study employed the disk diffusion method to evaluate the antimicrobial activity of the volatile compounds of the plant against *Klebsiella pneumoniae*, *Staphylococcus aureus*, *E. coli*, *Salmonella enteritidis*, and *Pseudomonas aeruginosa*. The antifungal activity of the volatile compounds against *C.albicans* and *Aspergillus niger* was investigated. The 1:10 dilution of the volatile oil extract was determined to have a very strong antimicrobial activity at a broad spectrum against all bacteria and fungi tested (Uslu et al. 2013; Al-Snafi 2017).

In a study testing the antibacterial activity of aqueous and ethanolic extract of *E. arvense* against certain some urinary tract pathogens such as *K. pneumonia*, *E. coli*, and *Enterococcus faecalis*, it was found that both extracts of different concentrations exhibited antibacterial activity against all bacterial strains tested. The ethanolic extract, however, exhibited a higher degree of activity compared to the aqueous extract. The ethanolic extract showed greater effect against *Staphylococcus saprophyticus*, *Proteus mirabilis*, and *E. coli* with inhibition zones of 24 mm, 23 mm, and 24 mm diameter (at 1000 µg concentration), respectively. It had the lowest impact on *P. aeruginosa* with an inhibition zone of 11 mm (at a concentration of 1000 µg). The diameter of the inhibition zone was found to be 18 mm in *K. pneumoniae* and *E. faecalis* and 14 mm in *S. aureus* at the same concentration (Geetha et al. 2011).

The antibacterial activity of the ethanolic stem extract of the plant (50–400 µg/ml) was investigated in vitro on two Gram-positive (*Bacillus subtilis* and *Micrococcus luteus*) and four Gram-

negative (*Shigella dysenteriae*, *Shigella flexneri*, *Vibrio cholerae*, and *E. coli*) bacteria. Of the six bacterial species (except *V. cholera* and *S. dysenteriae*), four were found to be very sensitive to plant extract at all concentrations (Al-Snafi 2017).

A more recent study examined a possible interaction between *E. arvense* and antiretroviral therapy in two HIV-positive patients. It was reported that this interaction may have triggered a virological breakthrough in patients who followed the same treatment containing lamivudine, zidovudine, efavirenz, emtricitabine, and tenofovir for years. Because of the limited data on the pharmacological properties of *E. arvense* in terms of potential drug-herb interactions, the authors concluded that the interaction could occur when these agents were taken simultaneously, and therefore clinicians were advised to avoid this combination until sufficient data is available (Al-Snafi 2015).

In a study on 12 medicinal plants, including *E. arvense*, it was found that the plants showed high activity against the influenza virus. The IC50 value of *E. arvense* was calculated as 6.45 (CI95%: 4.5–9.23). DPPH radical scavenging activity of *E. arvense* has been proven to show high antioxidant activity with an IC50 value of 6.8 μg/mL (Moradi et al. 2017).

In a study aiming to investigate the in vitro antimicrobial activity of some medicinal plants against selected species among food industry pathogens, disk diffusion method and minimum inhibitor concentration (MIC) methods were used to detect antibacterial properties of the plants. According to results, *E. arvense* exhibited the greatest inhibition zones against Gram-negative and Gram-positive bacteria tested. The highest antimicrobial activity was produced with *Urtica dioica*, *Taraxacum officinale*, and *E. arvense*, against *Yersinia enterocolitica* and *Salmonella enterica* subsp. *enterica*. Also, *T. officinale* and *E. arvense* were determined to be the most effective plants against *E. coli* (Kačániová et al. 2020).

*E. arvense* extract was determined to have the lowest inhibitory concentration for Gram-negative bacteria at MIC50 (9.59 μg/mL) and MIC90 (10.20 μg/mL) and for Gram-positive bacteria (*L. monocytogenes* and *S. aureus*) at MIC50 (12.8 μg/mL) and MIC90 (14.29 μg/mL). In a study by Milovanović et al. the antimicrobial effect of *E. arvense* extract was described with a 12.1 ± 0.5 mm inhibition zone (Kačániová et al. 2020).

In a study on the essential oil of *E. arvense*, significant antimicrobial effects were observed against all strains tested. While inhibition zone diameter ranged from 23 to 37 mm, it was shown to cause inhibition both on Gram-negative bacteria (*Klebsiella pneumoniae* (37 mm), *Salmonella enteritidis* (35 mm)), and Gram-positive bacteria (*Staphylococcus aureus* (28 mm)). It was stated that its antimicrobial activity is greater than, or at least as much as, traditional antibiotics. Additionally, it was observed against *Aspergillus niger* fungi and *Candida albicans*. The study suggested that Gram-negative bacteria (*Salmonella enteritidis*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*) are more susceptible to essential oils than Gram-positive *S. aureus*. In addition, among all the bacteria tested, Gram-negative *E. coli* was determined to be the most resistant bacteria (Radulović et al. 2006; Kačániová et al. 2020).

### 17.5.4 Activity on Smooth Muscles

The vasorelaxant effect of dikaffeoyl-meso-tartaric acid isolated from *E. arvense* was studied on rat aortic strips. As a result, it was determined that inhibition of norepinephrine-induced vasocontraction was due to a fall in calcium flux from the extracellular space caused by norepinephrine and that dikaffeoil tartaric acid created vasorelaxant activity regardless of its stereochemistry (Sakurai et al. 2003).

In a different study, the effect of the extract prepared with alcohol and dried powder of *E. arvense* on isolated guinea pig ileum was investigated, and the extract was observed to antagonize the effect of acetylcholine on the isolated guinea pig ileum preparation (Al-Snafi 2017).

### 17.5.5 Central Nervous Effect

In a study investigating the sedative and anticonvulsant effects of *E. arvense*, it was found that aqueous-alcoholic extracts of the plant at concentrations of 200 and 400 mg/kg increased barbiturate-induced sleep time 46% and 74%, respectively. Extracts were also found to increase the initial convulsion delay in pentylenetetrazole seizures, to reduce the severity of convulsions and the number of animals that develop convulsions by 50% and 25%, respectively, and to protect animals from death (Dos Santos et al. 2005).

The sedative, pre-anesthetic, and anti-anxiety effects of *E. arvense* were studied in rats. The plant extract at varying doses (100, 200, 400 mg/kg, i.p.) and diazepam (0.5 mg/kg, i.p.) were injected into the rats. The aqueous-alcoholic extract of *E. arvense* caused a significant increase in ketamine-induced sleep, and at the 200 mg/kg i.p dose injection, its anxiolytic, sedative, and pre-anesthetic effects were detected (Rezaie et al. 2011). The regular administration of the aqueous-alcoholic extract of *E. arvense* stems reversed the cognitive impairment in elderly rats. In the in vitro analysis, it was determined that the extract reduced thiobarbituric acid-reactive substances and nitrite formation, but did not change the catalase activity (Dos Santos et al. 2005; Al-Snafi 2017).

### 17.5.6 Dermatological Effects

The wound-healing effect of *E. arvense* was investigated on rabbits in comparison with sodium chloride and povidone-iodine. Skin wounds were created on the dorsum of rabbits, and postoperative wound surfaces were examined macroscopically. In the rabbits treated with a 5% concentration of *Equisetum*, a significant effect on wound contraction was observed between the postoperative fourth day and postoperative day 14 (Hayat et al. 2011).

The efficacy of topical application of *E. arvense* ointment in healing wounds, reducing inflammation, and relieving post-episiotomy pain among nulliparous mothers were investigated. The double-blind clinical study involved 108 postpartum nulliparous mothers (54 women were in the *E. arvense* group and 54 women were in the placebo group). The number of painkillers used during the 10-day treatment period and their side effects were recorded. As a result, it was reported that *E. arvense* ointment would support healing wounds and relieving pain in the 10-day period after episiotomy (Asgharikhatooni et al. 2015).

Hydroxypropyl-chitosan nail polish is a medicinal solution aimed at relieving the symptoms of nail dystrophy. Hydroxypropyl-chitosan (HPCH) contains *E. arvense* and methyl sulfonylmethane. In one study, the effects of HPCH and another nail polish with the same composition on brittle nails were comparatively investigated. Thirty-four healthy women with onycholysis (onychophagia) on their fingernails were included in this study. Both products were randomly applied to the affected nails of both hands once a day for 4 weeks. As a result, although 35% of the patients were suffering severe onycholysis at the beginning, 80% of volunteers using HPCH nail polish was observed to make a good recovery (Sparavigna et al. 2014; Al-Snafi 2017).

### 17.5.7 Antidiabetic Effect

In a study investigating the antidiabetic effect of *E. arvense*'s methanol extract (50, 100, 250, and 500 mg/kg daily for 5 weeks) on streptozotocin-induced diabetic rats, it was concluded that different doses of the methanol extract significantly reduced blood sugar (Safiyeh et al. 2007; Al-Snafi 2017).

A study was conducted to evaluate the effects of streptozotocin-induced diabetes on sperm and in vitro fertilization (IVF) potential and the protective effect of *E. arvense* methanolic extract on diabetic mice. The study concluded that the methanolic extract of *E. arvense* could inhibit the detrimental effects of diabetes on the quality of sperms and the rate of fertilization (Fajri et al. 2020).

### 17.5.8 Anti-inflammatory and Antinociceptive Effects

The anti-inflammatory and antinociceptive effects of the aqueous-alcoholic root extract obtained from *E. arvense* were studied on mice. Extracts varying 10, 25, 50, and 100 mg/kg, i.p., reduced acetic acid-induced frizz by 49, 57, 93, and 98%, respectively. In the formalin test, 50 and 100 mg/kg i.p. extracts reduced the licking activity by 80 and 95% in the first stage, but in the second stage, only the last dose reduced the licking time (35%). In both stages, naloxone was unable to reverse the analgesic effect of the extract. In the 2-h and 4-h carrageenan-induced paw edema procedures, the 50 mg/kg extract was observed to reduce the inflammation by 25% and 30%, respectively. The 100 mg/kg extract, however, resulted in a decrease by 29% in paw edema just 4 h after carrageenan administration (Do Monte et al. 2004; Al-Snafi 2017).

It is known that the control of pro-inflammatory cytokine production in the early stages of periodontal diseases is essential to maintain periodontal health. In a study investigating the plant extracts that could increase the anti-inflammatory effect of glycyrrhizin added to toothpaste and mouthwash solutions to prevent periodontal disease, the effects of extracts from six different plants on *Aggregatibacter actinomycetemcomitans* (Aa)-LPS-stimulated human oral keratinocytes (RT7) were examined through glycyrrhizin-suppressed TNF-α expression. As a result, it was determined that *E. arvense* extract (butylene glycol, water) had the strongest supra-additive effect for the suppression of TNF-α by glycyrrhizin at both mRNA and protein levels. The combination of glycyrrhizin with *E. arvense* has been shown to exert a synergistically stronger effect than individual effects through different mechanisms (Shiba et al. 2020).

It has been reported that the isococitrin (quercetin-3-O-glucoside) included in the flavonoids in *E. arvense* extracts creates an anti-inflammatory effect by interfering with the multifunctionality of immunocompetent cells (Gründemann et al. 2014).

In a study evaluating the effect of four anti-inflammatory medicinal plants, including *E. arvense*, against chronic obstructive pulmonary disease (COPD), Wistar rats were exposed to cigarette smoke for 8 weeks. Throughout the exposure period, a solution containing 4% of the alcoholic extract of each plant was administered orally to one group. The results show the synergistic and protective effects of herbal medicines used in animals exposed to cigarette smoke, which might be considered as a potential treatment strategy (Possebon et al. 2018).

In a different study, it was observed that the combination of *Chelidonium majus* L. and *E. arvense* extracts had a proliferative effect on some tumors (Di Giorgio et al. 2015; Possebon et al. 2018).

### 17.5.9 Effects on Urinary System

The diuretic effect of the dried extract of *E. arvense* was evaluated clinically on the volunteers by monitoring the water balance over a 24-h period. The extract (900 mg/day) produced a stronger diuretic effect than the negative control group and an effect equivalent to that of hydrochlorothiazide without causing significant changes in the elimination of electrolytes (Carneiro et al. 2014; Al-Snafi 2017).

The mechanism of action of ethanolic extract of *E. arvense* root on the urinary bladders of rats was investigated. One group was treated with a diet involving 0.2% extract, while the control group rats were only fed on the regular diet. As a result, the maximum bladder contraction pressure was found to be much lower in the *E. arvense* group compared to the control group. In addition, plasma adrenaline and noradrenaline levels were found to be lower in the *E. arvense* group than in the control group. The increase in urinary adenosine triphosphate levels was, as well, lower in the *E. arvense* group. Thus, researchers have reported that ethanol extract of *E. arvense* root affects bladder activity by reducing the release of adenosine triphosphate (Zhang et al. 2015; Al-Snafi 2017).

### 17.5.10 Inhibition of Platelet Aggregation

*E. arvense* extract displayed a dose-dependent inhibition of thrombin and ADP-induced platelet aggregation. This kind of activity of the herb may have partially resulted from the polyphenolic compounds in the extract, suggesting that they could be utilized in the treatment or prevention of platelet aggregation complications associated with cardiovascular diseases (Al-Snafi 2017).

### 17.5.11 Hepatoprotective Effect

In a study, it was shown that luteolin and onitin isolated from methanol extract of *E. arvense* had a hepatoprotective activity (20.2 ± 1.4 microM and 85.8 ± 9.3 microM EC50) on tacrine-induced cytotoxicity in Hep G2 cells obtained from the human liver (Oh et al. 2004; Al-Snafi 2017).

### 17.5.12 Anti-leishmanial Effects

In a study on the knowledge that *E. arvense* aqueous extract exhibited anti-leishmanial effects, the number of *Leishmania tropica* was gradually reduced using the aqueous extract at concentrations of 0.5–2.5 µg/ml. An inverse relationship between the concentration of the extract and the average growth of the parasite was reported. The inhibitory concentration of 50% of promastigotes (IC50) was recorded as 1.5 µg/ml. *L. tropica* promastigotes treated with IC50 of the tested *E. arvense* extracts ended up with a decrease in protein, carbohydrate, and total nucleic acid (Saeed et al. 2015; Al-Snafi 2017).

### 17.5.13 Effect on Bones

As individuals age, the amount of silicon in the body decreases; thus, *E. arvense* is recommended to be used especially in the geriatric population (Bühringová 2010).

In a study, the effects of an aqueous-methanol extract of *E. arvense* were evaluated on in vitro human osteoclastogenesis. It was concluded that the extract reduced osteoclast development and function in both osteoclast precursor cell cultures and osteoclastic and osteoblastic cell cultures (Bessa et al. 2012).

### 17.5.14 Effect on RBC Membrane Stability

The effect of the aqueous-alcoholic root extract of *E. arvense* on the RBC membrane stability of male rats was studied by exposing the rats' blood samples to 6, 8, and 10 mg/kg/body weight aqueous-alcoholic extract. After exposure to the extract, membrane-stabilizing activity decreased significantly compared to the control group (Shadanyian et al. 2014; Al-Snafi 2017).

### 17.5.15 Hyaluronidase Inhibitory Activity

In a study investigating the hyaluronidase inhibitory activity of various *E. arvense* extracts, it was reported that the hyaluronidase inhibition of the leaves and central stem at a concentration of 4.0 mg/ml was 24.3%, and the rhizomatous stem and root was 27.3% at the same concentration (Huh and Han 2015; Al-Snafi 2017).

## 17.6 Clinical Studies

In a report published by the EMA Herbal Medicines Committee (CHMP), the oral use of *E. arvense* was supported to facilitate the discharge of the kidneys and treat post-traumatic and stasis edema and bacterial and inflammatory urinary tract diseases and for irrigation-induced treatment of kidney-bladder stones. The German Commission E approved the use of *E. arvense* as a herbal diuretic (in the form of powder or tea) for the treatment of stasis swelling and bacterial

and inflammatory lower urinary tract diseases at an average daily dose of 3 to 6 g, or equivalent amounts of other preparations for 2- or 3-day intakes. In addition, a 50 g/L decoction of *E. arvense* in compresses or baths, or topical use of 50 drops of a liquid extract diluted in water, has been suggested as an adjuvant in the treatment of difficult-to-heal wounds (Carneiro et al. 2019).

In Brazil, the country's health authority ANVISA has recommended the use of *E. arvense* as an infusion or decoction of 3 g/150 mL water 2 to 4 times a day to treat edema (swelling) caused by fluid retention (Carneiro et al. 2019).

A study was conducted to evaluate the efficacy of five different medicinal plants, including *E. arvense*, for the treatment of chronic musculoskeletal pain. The findings show that the mixture of five herbs, with the combination of vitamin B1, provides a significant reduction in the score on the pain scale and significantly improves the functional mobility of the body parts affected by chronic joint, back, and muscle pain. No side effects were reported as a result of the study (Hedaya 2017).

The efficacy of topical application of the ointment prepared with *E. arvense* has been tested for wound healing and relief of inflammation and pain after episiotomies in nulliparous mothers. It was determined that 3% ointment accelerated wound healing and relieved pain within 10 days after episiotomy (Asgharikhatooni et al. 2015).

A cosmetic nail polish containing hydroxypropyl-chitosan (HPCH) was used in the groups involved in a study aiming to evaluate the topical effect of *E. arvense* on brittle nails. The tested preparation was reported to be effective in controlling the symptoms of the syndrome (Carneiro et al. 2019).

In a double-blind, randomized clinical study on the diuretic effect of *E. arvense*, dry extract of the plant (900 mg/day), placebo (900 mg/day), or hydrochlorothiazide (25 mg/day) were administered alternately for 4 consecutive days. The diuretic effect was evaluated according to the 24-h water balance and serum electrolytes. The extract produced a stronger diuretic effect comparing to the negative control treatment and was equivalent to that of hydrochlorothiazide (25 mg) without affecting the excretion of electrolytes (Carneiro et al. 2014).

## 17.7 Toxicological Studies

In a study evaluating acute hepatotoxicity in rats, no anatomical pathology changes were found in liver tissue or liver enzymes (Baracho et al. 2009).

When the 0.03% to 3% aqueous-alcoholic extracts of *E. arvense* were added to the diet of male and female rats, no toxic effect occurred in terms of clinical and hematological findings, urine or serum biochemical parameters, body weight, and internal organs weight (Dos Santos et al. 2005).

When the aqueous-alcoholic extract of *E. arvense* was given to rats at doses of 2 and 5 g/kg (IP), it caused 12% and 37.5% mortality, respectively. Since the LD50 is >5 g/kg, the extract was found to be nontoxic (Dos Santos et al. 2005).

It has been reported that *E. arvense* is contraindicated for children under 12 and women during pregnancy and lactation, due to the lack of specific studies regarding the alkaloid content and as it contains nicotine. Since the diuretic effect of *E. arvense* may cause potassium loss, it has been reported that individuals with kidney or heart failure should avoid the use of this herb. It is considered that patients with heart failure who are treated with digitalis drugs or other drugs that reduce serum potassium are considered to be affected by this condition more seriously (Carneiro et al. 2019).

An evaluation based on pharmacological inferences has stated that *E. arvense* may cause vitamin B1 (thiamine) deficiency due to the presence of the enzyme thiaminase. According to Luengo, patients with active gastroduodenal ulcers should avoid using *E. arvense* as it might irritate the gastric mucosa due to the presence of tannins, silicic salts, and acids in its content (Carneiro et al. 2019).

Rare cases of allergy to this plant have been reported in patients sensitive to the chemical

components of *E. arvense*. Long-term use and abuse may cause exudative edema, dysphagia, headache, tenesmus, and loss of appetite; in high doses, as well, it has been reported that stomach and urinary tract irritation may occur due to the presence of nicotine (Carneiro et al. 2019).

It has been stated that due to their pharmacological interactions, the combined use of *E. arvense* with lithium and digitalis medications is not recommended. Likewise, *E. arvense* should be avoided during an anti-retroviral treatment as it could trigger a virological breakthrough with a possible interaction (Cordova et al. 2017).

Although it is known that the high-dose use of *E. arvense* can cause nicotine tolerance and addiction, it has been determined that it can help quit smoking at low doses (Al-Badri et al. 2016).

The use of *E. arvense* in alcoholic individuals with thiamine deficiency is generally contraindicated; therefore, it has been reported that thiamine deficiency will increase along with the use of the herb, and it will also be contraindicated in patients with edema due to impairment in heart and kidney functions (Al-Snafi 2017).

In a toxicity study on animals, symptoms of *E. arvense* poisoning were noted primarily in young, fast-growing horses, cows, and sheep. The poisoning symptoms caused by the plant emerged gradually. It was observed that when the poisoned animal was left untreated after intoxication, it could lead to loss of muscle control, gait abnormality, and tension. Accordingly, it was reported that the treatment should be aimed at eliminating the source of poisoning, and to achieve this, an immediate intravenous, then a follow-up 2–3 days intramuscular thiamine (vitamin B1) administration was recommended (Al-Snafi 2017).

Acute hepatotoxicity of *E. arvense* (30, 50, and 100 mg/kg over 14 days) was evaluated on rats. Some lobular structure was seen in the anatomopathological examination of the liver tissue, but no significant change was found in the activities of hepatic enzymes compared to the control group (Baracho et al. 2009).

In a single-dose toxicity study to determine the LD50 value in rats, the toxic dose was found to exceed 5000 mg/kg (Yaşar et al. 2020).

## 17.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies

A study was conducted to determine the acute/subacute toxicity characteristics of ISY-CP®, a herbal mixture. The product contains a mixture of nettle leaf (*Urtica dioica*), yarrow (*Achillea millefolium*), thyme (*Thymus vulgaris*), and horsetail (*E. arvense*). In order to identify possible acute and subacute toxicity, clinical observations were made at the end of the treatment, and according to the data obtained, no significant difference was found between the control and treatment groups in the biochemical, hematological, and histopathological assessment. Only the phosphorus scores were statistically different between the subacute toxicity group and the control group. As a result, about ISY-CP® herbal mixture doses, no acute and subacute toxic was reported (Yaşar et al. 2020).

In a randomized double-blind placebo control study, the efficacy of Urox®, consisting of a combination of *Lindera aggregata* root, *E. arvense* stem, and *Crataeva nurvala* root bark extracts in reducing various bladder symptoms compared to the same placebo, was tested. According to the data obtained, the urinary day frequency was found to be significantly lower compared to placebo in response to treatment. A significant improvement in the quality of life has been reported after treatment (Carneiro et al. 2019).

In a study investigating the use of *E. arvense* dietary supplement during osteoporosis for its silicon content, it was found that silicone improved the formation and density of bone and cartilage tissue and stimulated osteosynthesis through enhanced collagen biosynthesis. The use of Osteosil Calcium®, a silicon-based food supplement extracted from *E. arvense* and calcium, has been determined to facilitate an increase in plasma and tissue silicon concentrations. As a result, the product has been considered effective in osteoporosis, as the silicone in its content sup-

ported bone and cartilage formation from the early stages. Therefore, to treat osteoporosis without any side effects, it has been reported that Osteosil Calcium® could be used as 2 tablets/day for 45 days, afterward, in suspension for 15 days in 3–4 cycles per year (Saudelli et al. 2018).

In a clinical study, the effect of Eviprostat®, a commercial preparation containing *Chimaphila umbellata*, *Populus tremula*, *Pulsatilla pratensis*, *E. arvense* extracts, and wheat germ oil was tested for the treatment of benign prostatic hyperplasia (BPH). The effect of each component on reactive oxygen species (ROS) was evaluated. The results suggest that the ROS suppression of Eviprostat® might be regarded as a therapeutic anti-inflammatory in BPH (Oka et al. 2007; Carneiro et al. 2019).

In another clinical study on the clinical efficacy of Eviprostat®, 100 patients with BPH received 2 tablets of Eviprostat® 3 times a day for 12 weeks; it was determined that the product had a positive effect on all parameters. The rate of clinical side effects was recorded as 1% (Song et al. 2005).

## 17.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

In the 10-day period after episiotomy, topical application of *E. arvense* 3% ointment accelerated wound healing and relieved pain (Asgharikhatooni et al. 2015). The authors of the studies reported that the positive impact on wound contraction may have been due to the silica, silicic acid, silicon, and saponin in the extracts. Clinical research results support the conventional topical use of water decoction in wound healing (Carneiro et al. 2019).

It has been determined that the antimicrobial activity of *E. arvense* is greater or similar to traditional antibiotics (Kačániová et al. 2020).

## 17.10 Challenges and Future Recommendations as Potential Drug Candidate

*E. arvense* is an herb traditionally used for a broad range of ailments. Data on traditional use of *E. arvense*, preclinical pharmacological studies, and more recent clinical studies have been reported by the EMA, Commission E, and the Brazilian Ministry of Health. Certain criteria have been determined to assess the toxicity and safety of this herb; however, some possible toxicity factors remain unclear. Therefore, *E. arvense* should not be used by children under the age of 12 and pregnant or breastfeeding women. Patients suffering from diseases requiring fluid restriction (heart or kidney failure) should also avoid aqueous preparations.

According to the report of EMA, toxicology data on *E. arvense* is still insufficient; therefore, it has been concluded that the classification of the plant as a traditional medicinal product in Europe is maintained by the committee. However, significant advances in research indicate that the status of *E. arvense* as a phytotherapeutic agent has become more likely.

In addition to being a well-known agent used in traditional and folk medicine, *E. arvense* has been proven to be a potentially useful phytotherapeutic medicine in various medical fields, thanks to current clinical studies. In particular, it has the potential to be an effective and safe diuretic. However, together with its therapeutic effects, further research is needed on the pharmacokinetic, pharmacodynamic, and toxicological characteristics of this herb.

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# *Foeniculum vulgare* Mill.

# 18

Leyla Paşayeva

**Abstract**

*Foeniculum vulgare* Mill., commonly known as fennel, is one of the widespread plants that originated from Southern Europe and Mediterranean regions. This species is an economically important herb that has been used in traditional medicine and as a spice in culinary. The various parts and essential oil of fennel have been used widely in different ailments related to digestive, endocrine, reproductive, and respiratory systems. Based on their traditional uses, numerous pharmacological activities were reported by researchers such as antimicrobial, antiviral, anti-inflammatory, apoptotic, cardiovascular, antitumor, hepatoprotective, hypoglycemic, and memory-enhancing property. According to phytochemical investigations of *F. vulgare*, the flavonoids, phenolic compounds, fatty acids, and volatile compounds such as trans-anethole, estragole, and fenchone were reported as the major constituents responsible for various activities. This chapter presents an overview of the origin, distribution, taxonomic position, traditional uses, phytochemical, pharmacological, toxicological properties, and herbal formulations/products of *F. vulgare*. It also compiles available scientific evidence for the ethnobotanical claims and identifies gaps required to be filled by future research. *F. vulgare* has emerged as a good source of traditional medicine and provides a remarkable foundation for developing new drugs and the future.

**Keywords**

Fennel · Traditional medicine · Culinary · Spices · Phytochemical composition

## 18.1 Introduction

### 18.1.1 Botanical Description

*F. vulgare* (FV) is a biennial or perennial herbaceous aromatic plant with a height of 1–1.8 m, feathery leaves, and yellow flowers. The fruits are 6–10 cm long and 1.5–4 cm thick, cylindrical, usually curved, glabrous, petiolate, usually brownish-green, or greenish-yellow. There are five strong ribs in the mericarp or the wide secretory canal in each valeculum. The fruits are collected 3–4 times at 10–15 days intervals (Baytop 1999; Davis 1972; Grover et al. 2013). There are two subspecies of FV as *Foeniculum vulgare* Mill. Subsp. *vulgare* and *Foeniculum vulgare* Mill. Subsp. *piperitum* (Ucria) Coutinho. *Foeniculum vulgare* Mill. Subsp. *vulgare* var.

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*vulgare* and *Foeniculum vulgare* Mill. Subsp. *vulgare* var. *dulce* (Miller) Thellung are the 4 varietes of *Foeniculum vulgare* Mill. Subsp. *vulgare.* These varieties are pharmaceutically important. As it is rich in fenchone, the taste of *F. vulgare* subsp. *vulgare* var. *vulgare* is bitter. But the variety of *F. vulgare* subsp. *vulgare* var. *dulce* is rich with anethol, so it is known as "sweet fennel" (Muckensturm et al. 1997; Heinrich et al. 2017; Karlsen et al. 1969).

*F. vulgare* is a widespread species commonly known as a fennel (Fig.18.1). The taxonomic status of species is as follows: Kingdom: Plantae, division: Tracheophyta, subdivision: Spermatophytina, class: Magnoliopsida, order: Apiales, family: Apiaceae (Umbelliferae), genus: *Foeniculum*, species: *vulgare*, and botanical name: *Foeniculum vulgare* Mill. (Davis 1972).

There are a great number of synonyms used for *F. vulgare* as follows: *Anethum dulce* DC., *Anethum foeniculum* L., *Anethum minus* Gouan, *Anethum panmori* Roxb., *Anethum rupestre* Salisb., *Foeniculum azoricum* Mill., *Foeniculum divaricatum* Griseb., *Foeniculum dulce* Mill., *Foeniculum giganteum* Lojac., *Foeniculum officinale* All., *Foeniculum panmorium* (Roxb.) DC., *Foeniculum piperitum* C. Presl, *Foeniculum rigidum* Brot. Ex Steud, *Foeniculum vulgare* var. *capillaceum* Burnat, *Foeniculum vulgare* subsp. *capillaceum* (Burnat) Holmboe, *Foeniculum vulgare* var. *inodorum* Maire, *Foeniculum vulgare* subsp. *piperitum* (C. Presl) Bég., *Foeniculum vulgare* var. *piperitum* (C. Presl) Ball, *Foeniculum vulgare* var. *sativum* C. Presl, *Foeniculum vulgare* subsp. *sativum* (C Presl) Janch ex Holub, *Ligusticum foeniculum* (L) Roth, *Ligusticum foeniculum* (L) Crantz, *Meum foeniculum* (L) Spreng, *Selinum foeniculum* E. H. L. Krause, *Seseli foeniculum* Koso-Pol, and *Tenoria romana* Schkuhr ex Spreng (The plant list n.d.).

The local names of species are as follows: Turkey: rezene, arapsaçı, irziyan, mayana, raziyane, tatlı rezene, Arabic: shmar, shumar, bisbas; Chinese: hui xiang; French: aneth doux, fenoui; Germany: Echter Fenchel, Garten-Fenchel Hindi: Badi saunf, Bari saunf, Moti saunf; Indonesia: adas, adas londo, hades; Iran: Razianeh, Italy: finocchio; Japan: ui-kyo; Netherlands: venkel Philippines: anis, haras; Portuguese: funcho; South Africa: vinkel; Spanish: fonol, hinojo; Sweden: faenkaal, fänkål; and Thailand: phakchi-duanha, thian-klaep, yira (Al-Snafi 2018).

FV is an ancient herb native to southern Europe and the Mediterranean region, especially on dry soils near the sea coast and on the river

**Fig. 18.1** *Foeniculum vulgare* Mill.

banks. The plant is cultivated in temperate and tropical regions of the world (Europe, Asia, North Africa, South America) for its medicinal and culinary uses (Tanira et al. 1996).

FV is an economically important plant with medicinal, cosmetic, culinary, and aliment use. There is some use of FV in traditional medicine. The prepared infusions or herbal teas from plant parts have been used to treat gastrointestinal, respiratory, and urinary diseases in Europe and Asia from ancient times (Raffo et al. 2011). The essential oil and anethole from different fennel parts are used in perfumes, lotions, skin creams to give aroma and in toothpaste, mouthwashes, soaps, detergents as an antiseptic (Peter 2012). Besides the leaves, seeds, and flowers, the essential oils also gave an aroma and taste to meat, fish, and other Western countries' dishes. However, the leaves and flowers are used as a salad by people in some regions. On the other hand, the fennel seeds are used as a flavouring in alcoholic and herbal beverages due to the anise like aroma (Díaz-Maroto et al. 2005; Grieve 1970).

This chapter aims to report the wide usage of FV in traditional medicine, culinary and cosmetic, its phytochemical composition, existing biological activity and lead new research in light of this knowledge. We hope that based on the economic importance of the plant, it will be beneficial for the development of novel products in the pharmaceutical, cosmetic, and food industries.

## 18.2 Distribution and Status of Species

The species of *Foeniculum* were distributed generally in southern Europe, western Asia, and northern Africa. Due to the economic importance of FV, this species is also cultivated in different countries of the World for medicinal, culinary, and cosmetic purposes. Gujarat is one of the regions of India which contributes to 85–90% of the world fennel need. The variety *Foeniculum vulgare* subsp. *vulgare* var. *vulgare is* commonly cultivated in Russia, Rumania, Hungary, Germany, France, Italy, India, Japan, Argentina, and the USA. In other states such as Karnataka, Maharashtra, Uttar Pradesh, Punjab, Bihar, and Jammu and Kashmir, this species is grown on a small scale (Afify et al. 2011; Khan and Musharaf 2014; Kooti et al. 2015).

## 18.3 Comparison of Traditional/Ethnomedicinal/Local Uses in Turkey and Throughout the World (Asia and Europe)

The different parts of FV are used in traditional medicine for thousands of years. The leaves and roots of the plant were considered for diabetes, urinary and digestive disorders, the barks for blood-related diseases, the flowers and seeds were recommended for flatulence, respiratory infections, and improving the milk supply of a breastfeeding mother (Kooti et al. 2015; Abe and Ohtani 2013). The decoction, infusion, and essential oil of plant parts generally were used for digestive, urinary and respiratory disorders and poultice from the plant was used to alleviate breast swelling in nursing mother (Jodral 2004).

In the middle ages, the people have chewed the seeds of plants to eliminate abdominal noise in the East Asian countries. In ancient Rome, the plant has been used as a sedative in the fifth century (Siyahi et al. 2009; Taherian et al. 2007). The plant also had been used by ancient Egyptians as a remedy and food 4000 years ago. Furthermore, the plant has been recommended as a remedy for snakebite in ancient China and for digestive and urinary disorders in Arabia (Tanira et al. 1996). Besides that, the fruits of the plant were considered for sperm defection in China traditional medicine (Khan and Abourashed 2011). Additionally, fennel was used in Persian traditional medicine for starting menstrual action and relieve the pain (Kotani et al. 1997; Dadkhah et al. 2016).

Among the ethnomedicinal uses of FV, the use in gastrointestinal diseases is prominent. So due to its carminative properties, the seeds have been used to prepare some herbal teas in India. For this purpose, fennel tea was prepared with a tea-

spoonful of fennel seeds in boiling water. It was known that the fennel seeds had been eaten raw, by people to treat eye inconvenience in some regions in India (Agarwal et al. 2008). In Turkish traditional medicine, the 2% infusion of fruits were used to prevent gas formation in babies and the leaves as woundhealing. Also, the plant roots are well known as a diuretic in Turkish folk medicine (Baytop 1999).

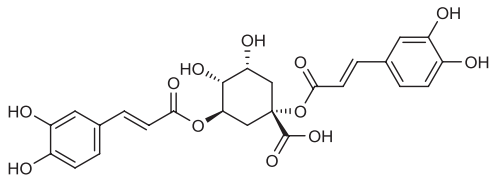
Besides medicinal use, FV is also used as a food in China and known as 'Xiaohuixiang' and leafy stem in the Aegean region of Turkey. Additionally, the flowers of the plant were used in perfumes as a fragrance (Baytop 1999; Grover et al. 2013). In some regions of India and the Middle East, the seeds from the fennel were used widely as a condiment in their cooking. The bulb of the plant was also used by people as stewed, braised, or as raw in Mediterranean cuisine (Grieve 1970).

## 18.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques (Classification and Structures of Few Representatives)

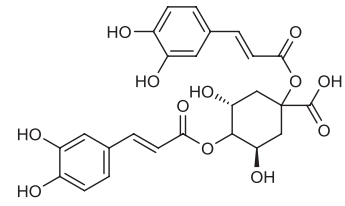
### 18.4.1 Essential Oil

All the organs of the plant are rich in essential oil. The fruits of *F. vulgare* subsp. *vulgare* var. *vulgare* contain 2–6% essential oil (Heinrich et al. 2017; Arslan et al. 1989). This essential oil consists of more than 60% trans-anethole, more than 15% fenchone, and less than 5% estragole (Zoubiri et al. 2014; Diao et al. 2014). These constituents have been reported as the main components of essential oil (Fig 18.2). The essential oil obtained from *F. vulgare* subsp. *vulgare* var. *dulce* fruits do not contain less than 80% anethole. It was shown that the major components of Egypt FV essential oil were estragole (51.04%), limonene (11.45%), l-fenchone (8.19%), and trans-anethole (3.62%) and the major constituents of Chinese fennel essential oil were trans-anethole (54.26%), estragole (20.25%), fenchone (7.36%), and limonene (2.41%) (Ahmed et al. 2019). The essential oil obtained from the fruits of both varieties contains anisaldehyde and some terpene hydrocarbons (α and β-pinene, α-thujene, β-fenchene, camphene, 3-carene, sabinene, α-phellandrene, myrcene, limonene, α and γ-terpinene, cis-ocimene, terpinolene, trans-ocimene, fenchyl acetate, apiole, and p-cymene), besides anethole, fenchone, and estragole (Miguel et al. 2010). *F. vulgare* subsp. *piperitum* extract contains the major compounds, namely 1,2-epoxy-1-vinylcyclododecene (24%) and ethyl linoleate (32%) (Conforti et al. 2006). The methanol extract of fennel seed was analysed and estragole (71.099%), gallic acid (18.895%), and L-limonene (11.967%) were found the most prevalent constituents (Mohamad et al. 2011). The chemical composition of fruit oils from FV collected during three different years was analysed and trans-anethole, estragole, fenchone and limonene were detected as main contituents of the oil (Aprotosoaie et al. 2010).

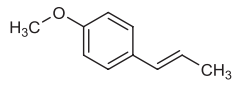
It was reported that the essential oils obtained from seeds of sweet fennel which was harvested from 8 different regions in Turkey contain trans-anethole (75.68%–86.52%), limonene (4.25%–9.15%), estragole (3.25%–5.21%), fenchone (1.05%–2.80%), γ-terpinene (0.86%–1.57%), and α-pinene (0.47%–1.14%). In the samples, anisaldehyde, anisketone, and cis-anethole were detected as the autoxidation product of trans-anethole. It has also been stated that some samples contain carvone, citral, octanal, citronellal, and α-terpineol. Trans-anethole, estragole, and fenchone were found as the main constituents in the seed oil of bitter fennel grown in Turkey (Cosge et al. 2008; Raal et al. 2012). The HPLC results revealed high variation in 23 fennel samples from Iran according to their major flavonoid (quercetin, apigenin, and rutin) and phenolic (chlorogenic, caffeic, and 1,5-dicaffeoylquinic acid) compounds (Salami et al. 2016). It was reported that the main component of sweet fennel grown in Egypt was 49.93% in roots, 43.40% in



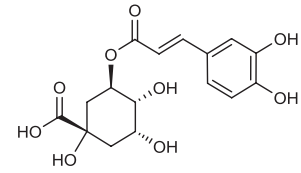

1,3-dicaffeoylquinic acid



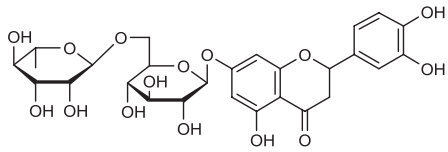

1,4-dicaffeoylquinic acid



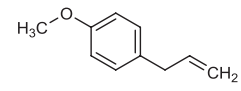

*trans*-Anethole



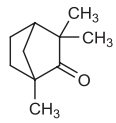

Chlorogenic acid



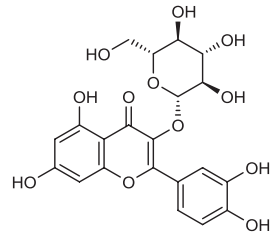

Eriocitrin



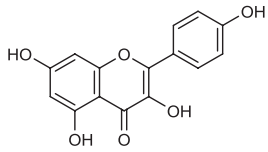

Estragole



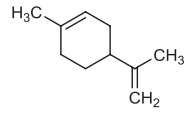

Fenchone



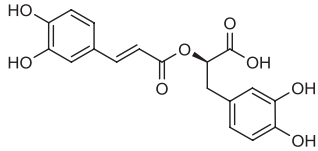

Isoquercitrin



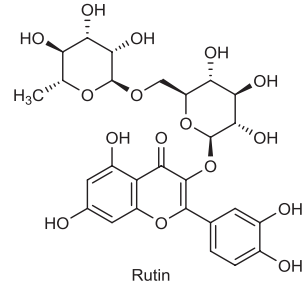

Kaempferol




Limonene




Rosmarinic acid




Rutin

**Fig. 18.2** Representatives of some compounds from *Foeniculum vulgare* Mill.

leaves, and 32.26% in flowers, as well as 5.39%, 24.00%, and 38.67% trans-anethole in roots, leaves, and flowers (Saleh et al. 1996). The main component of seed essential oil of Algerian FV was detected as trans-anethol (72%) (Zoubiri et al. 2014; Belabdelli et al. 2020). The fenchone (16.9–34.7%), estragole (2.5–66.0%), and trans-anethole (7.9–77.7%) were reported as the main compounds of six fennel fruits from Portugal (Mota et al. 2015). Two major compounds, namely 2-hydroxy-1-(hydroxymethyl) ethyl ester (1.84%) and 9-octadecenoic acid (18.56%), were detected as the main constituents of essential oil obtained from seeds of FV from India (Upadhyay 2015). The analyses of FV essential oil from Italy showed that o-cymene, α-phellandrene, α-pinene, and estragole are the major constituents (Garzoli et al. 2018). Trans-anethole (36.8%) and *p*-anisaldehyde (7.7%) were found as the major constituents of essential oil of FV from Tajikistan (Sharopov et al. 2017). Trans-anethole was the main volatile compound in the essential oil of FV samples from two different regions of Spain (Díaz-Maroto et al. 2006).

### 18.4.2 Phenolic Compounds

However, the phenolic compounds found in the chemical composition of different parts of the plant are 3-O-caffeoylquinic acid, chlorogenic acid, 4-O-caffeoylquinic acid, eriocitrin, rutin, 1,3-O-dicaffeoylquinic acid, 1,5-O-dicaffeoylquinic acid, 1,4-O-dicaffeoylquinic acid, rosmarinic acid, kaempferol 3-O-α-L-(2″,3″-di-*p*-cumaroyl)-rhamnoside, afzelin, isoquercitrin, isorhamnetin 3-O-β-D-glucoside, quercetin-3-O-β-D--glucuronide, quercetin-3-arabinoside, kaempferol-3-arabinoside, kaempferol-3-glucuronide, eriodictyol-7-O-rutinoside, quercetin-3-O-galactoside, kaempferol-3-O-glucoside, 4-O-β-D-glucosyl sinapyl alcohol, 4,9-di-O-β glucosyl sinapyl alcohol, and 4-β-glucosyl oxybenzoic acid (Harborne and Saleh 1971; Križman et al. 2007; Nakayama et al. 1996; Parejo et al. 2004a; Soliman et al. 2002).

### 18.4.3 Other Compounds

The coumarins found in leaves are columbianetin, ostenol, psoralene, scoparone, seselin, xanthotoxin, bergapten, isopimpinellin, scopoletin, umbelliferone, imperatorin, and marmesin (Soliman et al. 2002; El-Khrisy et al. 1980).

Seeds contain 9–12% fixed oil and fixed oil contains fatty acids such as palmitic, palmitoleic, hexadecanoic, stearic, oleic, linolenic, petrocelinic acid, and cis-vaccenic acid (Singh et al. 2006; Nassar et al. 2010). Besides proteins, the seeds also contain organic acids such as citric, malic, oxalic, and tartaric acid. Fruits carry the stilbene derivative compounds such as myabenol C, cis-myabenol C, foeniculoside I, foeniculoside II, foeniculoside III, and foeniculoside IV (Ono et al. 1997). The sterols in fruits are *β*-sitosterol and stigmasterol (El-Khrisy et al. 1980). The linoleic acid (56.0%) and oleic acid (5.2%) were detected as the main constituents of FV ethanol and methanol extracts (Gulfraz et al. 2008).

### 18.4.4 Nutritional Composition

It has been reported that FV is also rich in nutritional components as protein (9.5%), fat (10%), minerals (13.4%), fibre (18.5%), carbohydrates (42.3%), calcium, potassium, sodium, iron, phosphorus, thiamine, riboflavin, niacin, and vitamin C (Anubhuti et al. 2011).

### 18.4.5 Extraction Techniques

Some innovative and efficient extraction techniques have been reported to isolate volatile and non-volatile components from *F. vulgare*. One of them is direct thermal desorption (DTD) coupled to gas chromatography-mass spectrometry. The small size volatiles have been obtained by this extraction method (Díaz-Maroto et al. 2006). The steam distillation and supercritical carbon dioxide ($SCCO_2$) extraction techniques were compared and it was found that $SCCO_2$ extraction resulted in a higher yield than steam

distillation (Topal et al. 2008; Simandi et al. 1999). For analyses of the volatile oil of fennel, rapid headspace solvent microextraction followed by gas chromatography-mass spectrometry (HSME-GC-MS) was also described. This method was found more simple, inexpensive, and effective than solid phase microextraction (SPME)-GC-MS and steam distillation (SD)-GC-MS methods (Fang et al. 2006). Subcritical water extraction has been reported for the extraction of volatile components and this method was described as more rapid, efficient, and clean than hydrodistillation and dichloromethane manual extraction (Gamiz-Gracia and Luque de Castro 2000). Besides that, for direct determination of chemical composition in the plant fruits, Microscopic Raman methods also used (Strehle et al. 2005; Baranska et al. 2004). On the other hand, classical extraction methods as maceration, infusion, microwave decoction, and dissolution have been reported for the extraction of non-volatile compounds (Bilia et al. 2000; De Marino et al. 2007; Parejo et al. 2004b).

## 18.5 Scientific Evidences: Pharmacological Activities

### 18.5.1 In Vitro Studies

#### Larvicidal Activity

The larvicidal activity of FV essential oil was investigated against *Culex pipiens* larvae and pupae. As a result, 50% and 90% mortality was observed after 2 and 4 h exposition time and at 40 mg/L and 60 mg/L concentration (Zoubiri et al. 2014). The larvicidal activity of the FV essential oil and its major constituent limonene were evaluated against third instar larvae of Ae. aegypti for 24 h. A 99% mortality was estimated at 37.1 and 52.4 μL $L^{-1}$ of essential oil, respectively (Rocha et al. 2015).

#### Acaricidal Activity

The components of fennel essential oil with acaricidal effect were examined against *Tyrophagus putrescentiae*. The biological active compound (+)-carvone ($LD_{50}$ = 4.62 μg/$cm^2$) was found most toxic (Lee et al. 2006). The compounds of fennel essential oil with acaricidal effect were examined against *Dermatophagoides farinae* and *D. pteronyssinus*. The active compounds, namely (+)-fenchone and *p*-anisaldehyde, were found more effective. The $LD_{50}$ values against *D. farinae* of *p*-anisaldehyde, (+) fenchone were 11.3 mg/$m^2$ and 38.9 mg/$m^{2,}$ respectively. However, the *p*-anisaldehyde and estragole were determined more toxic against *D. pteronyssinus* with 10.1 mg $m^2$ and 389.9 mg/$m^2$ $LD_{50}$ values. (Lee 2004).

#### Antiosteoporotic Activity

To investigate the effects of FV extract on proliferation and osteogenesis progress, the human mesenchymal stem cells were treated with different concentrations of plant extracts (0.5 to 100 μg/ml). MTT assay and alkaline phosphatase activity showed that FV extract, at a range of concentration of 5 to 50 μg/ml, may positively affect cell proliferation and mineralization (Mahmoudi et al. 2013).

#### Anti-hyaluronidase Activity

The compounds miyabenol C and cis-miyabenol C obtained from methanol extract of FV fruits were investigated for the anti-hyaluronidase effect. They were found more strong than other isolated substance (Ono et al. 1997).

#### Antimicrobial and Antifungal Activity

The antibacterial activity of FV essential oil was evaluated against several food-borne pathogens. According to the MIC and MBC results, *S. dysenteriae* was found the most sensitive to essential oil, showing the lowest MIC and MBC values of 0.125 and 0.25 mg/mL, respectively (Diao et al. 2014). It was reported that the ethanol, acetone, *n*-butanol, and ether extracts from fennel were inhibited for the growth of *Escherichia coli* and *Staphylococcus aureus* (Khaldun 2006). The antifungal effect of the extracts and essential oil on *Candida albicans* and the antimicrobial effects of the essential oil obtained from fruits were determined (Afzal and Akhtar 1981; Ramadan et al. 1972). In a study, the antibacterial properties of methanolic extracts of 23 fennel samples

were evaluated. The seed extracts showed moderate to good inhibitory activities (MICs = 62.5–125 μg/ml) against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, and Salmonella typhimurium* (Salami et al. 2016). It has been represented that fennel essential oil shows strong antibacterial activity against *Escherichia coli, Staphylococcus aureus, S. epidermidis, Salmonella typhimurium, S. dysenteria, Listeria monocytogenes*, *Saccharomyces cerevisiae,* and antiplasmid activity against *E. coli* (Ruberto et al. 2000). FV essential oil was investigated for its antibacterial and antifungal activity against seven infectious microbial pathogens. According to the results, essential oil showed the Diameter of Inhibition Zone (DIZ) ranging from 19.4 ± 0.07 to 26.4 ± 0.09 mm at a concentration level of 28 μg/disc in all the strains and the minimum inhibitory concentration (MIC) against bacterial and fungal strains in the range of 7.0–56 μg/ml (Upadhyay 2015). The antimicrobial activity of FV oil, ethanol, and methanol extracts was evaluated. The lowest MIC values of fennel oil for *Candida albicans* (0.4% v/v), *Pseudomonas putida* (0.6% v/v), and *E. coli* (0.8% v/v) were obtained. (Gulfraz et al. 2008). The essential oils obtained from the leaves of two different cultivars of fennel were represented as an appreciable effect, generally higher on Gram-positive bacteria (Senatore et al. 2013). However, aromatic water of FV was found not effective against tested strains (Sağdıç and Özcan 2003). Furthermore, essential oil (6 μL) inhibited the zones of *Aspergillus niger, A. flavus*, *Fusarium graminearum,* and *F. moniliforme* (Singh et al. 2006). The essential oil of FV from Algeria revealed higher antifungal activities, particularly against *C. albicans* and *Aspergillus* species with MIC values of 0.16–0.2 mg/ml (Belabdelli et al. 2020). The antimicrobial activity of essential oils obtained from fruits of fennel from Portugal was evaluated. The minimal inhibitory concentration (MIC) values varied from 62.5 to 2000 μg/mL (Mota et al. 2015). The essential oil has also been found effective on *Aeromonas hydrophila, Alcaligenes faecalis,* and *Clostridium sporogenes* (Marotti et al. 1994). It was described that the essential oil of FV with 0.007 g/ml concentration had prevented *P. aeruginosa* and with 0.002 g/ml concentration has prevented *B. subtilis* from the growth (Foroughi et al. 2017). In a similar study, the results indicated that the essential oil of FV with 0.007 g/ml concentration had prevented *E. coli* and with 0.003 g/ml concentration has prevented *S. aureus* (Foroughi et al. 2016). Also, it was observed that fennel essential oil stopped the growth of the *Phytophthora infestans* in the 0.4–2.0 μg/mL concentration range and completely prevented the growth of the specified microorganism at a concentration of 6.4 μg/mL (Soylu et al. 2006). Due to fennel essential oil completely inhibiting the growth of various strains of *Streptococcus mutans* above 80 ppm concentrations, it was thought that fennel essential oil may be included in oral hygienic products to protect oral health (Park et al. 2004). The antifungal activity of FV essential oil was evaluated from different aspects, such as MIC and minimum fungicidal concentration, mycelia growth, spore germination, and biomass. In a result, the essential oil was found more active on *Trichophyton rubrum, Trichophyton tonsurans, Microsporum gypseum,* and *Trichophyton mentagrophytes* (Zeng et al. 2015). Twenty compounds identified in the active fraction of *F. vulgare* var *dulce* were tested against one sensitive and three MDR strains of *Mycobacterium tuberculosis* using the Alamar Blue microassay. Compounds that showed some degree of antimycobacterial activity against all strains tested were the following: linoleic acid (MIC 100 μg/mL), oleic acid (MIC 100 μg/mL), 1,3-benzenediol (MIC 100–200 μg/mL), undecanal (MIC 50–200 μg/mL), and 2,4-undecadienal (MIC 25–50 μg/mL) (Esquivel-Ferrino et al. 2012).

## Antioxidant Activity

The higher total phenolic contents were observed in fennel seed extracts from Egypt and China (42.24 and 30.94 mgPE/g, respectively). A stronger DPPH radical-scavenging capacity was found in these extracts with 6.34 and 7.17 mg/g $IC_{50}$ values, respectively. (Ahmed et al. 2019). The antioxidant capacity of essential oil has been found to be comparable to reference substances such as α-tocopherol, butylhydroxyanisole

(BHA), and butylhydroxytoluene (BHT) (Ruberto et al. 2000; Osée Muyima et al. 2004; Misharina and Polshkov 2005; Stashenko et al. 2002). It has been reported that the radical-scavenging and chain-breaking antioxidant properties of fennel essential oil, which is rich in anethole and estradiol, are comparable to synthetic antioxidant substances (Guerrini et al. 2006). The fennel essential oil and extracts also exhibited strong DPPH radical-scavenging activity, showing $IC_{50}$ 32.32 and 23.61–26.75 μg/ml, and inhibition of peroxidation 45.05 and 48.80–70.35%, respectively. The same study reported that the fennel seed extracts contained appreciable levels of total phenolic contents (627.21–967.50 GAE, mg/100 g) and total flavonoid contents (374.88–681.96 CE, mg/100 g). (Anwar et al. 2009). The antioxidant effects of plant and fruit oil were investigated. As a result, it was reported that with the DPPH method, the plant oils showed better antioxidant activity than the oils of the fruit. With the TBARS method and at higher concentrations, fennel essential oils showed a pro-oxidant activity. None of the oils showed a hydroxyl radical-scavenging capacity, but they showed an ability to inhibit 5-lipoxygenase (Miguel et al. 2010). The inhibitory effect of some compounds from fennel fruit on linoleic acid oxidation was evaluated. It was reported that miyabenol C, cis-miyabenol C, foenikulozitI, foenikulozit 11, foenikulozit III, and foenikulozit IV showed stronger antioxidant activity than the reference substance BHA (Ono et al. 1997). The antioxidant properties of water and methanol extracts of FV were investigated. The data showed that the $DPPH^{\bullet}$-scavenging effect of extracts was found less than ascorbic acid at 30 μg/ml concentration. However, the methanolic extract showed that the highest OH-scavenging potential of 71.61% at 240 μg/ml concentration and the reducing ability (FRAP activity) of the extracts were in the range of 7–48 μm Fe (II)/g. The various essential oil samples of the fennel did not show any results with the FRAP test. The DPPH test showed a weak capacity of the samples to catch the free radicals from the solution, attributable to their content in anethole (Senatore et al. 2013). It was determined that 100 g of water or ethanol extract inhibited linoleic acid peroxidation by 99.1% and 77.5%, respectively, and the α-tocopherol showed inhibition of 36.1% in the same system (Oktay et al. 2003). In a study, the antioxidant properties of methanolic extracts of 23 fennel samples were evaluated. Among the samples, the Kh1 sample from Iran possessed the highest TFC (14.8 mgQUE $g^{-1}$), TPC (262 mg/g DW), and antioxidant activity ($IC_{50}$ = 76 μg/ml) (Salami et al. 2016). The shoots of FV seem to have the highest radical-scavenging activity and lipid peroxidation inhibition capacity ($EC_{50}$ values <1.4 mg/ml), which is in agreement with the highest content in phenolics (65.85 ± 0.74 mg/g) and ascorbic acid (570.89 ± 0.01 lg/g) found in this part. (Barros et al. 2009). The oxidative stability of fennel seed extracts was compared in olive oils in concentrations of BHA (75 ppm), BHT (75 ppm), and 1:1 BHA to BHT ratio. As a result, it was shown that the seed extract showed the best antioxidant activity at a concentration of 150 ppm (Chang et al. 2013).

## Antiplatelet Activity

A study examining the inhibitory effects of fennel essential oil and its components on the aggregation of rabbit platelets induced by ADP, collagen and arachidonic acid, fennel essential oil, anethole, and estradiol was found to be as effective as aspirin against platelet aggregation with all three inducers. Anethole has been identified as the main inhibitory component in fennel essential oil against platelet aggregation (Yoshioka and Tamada 2005). Anticoagulant compounds of fennel fruit were investigated and the results were compared with aspirin. Fencone effectively inhibited collagen and arachidonic acid-induced platelet aggregation with 3.9 μM and 3.9 μM $IC_{50}$ values, respectively, while estragole inhibited collagen-induced platelet aggregation with 4.7 μM $IC_{50}$ value. Fencone and estragole showed a more effective inhibitory effect on collagen-induced platelet aggregation than aspirin (Lee et al. 2006). It has been reported that fennel essential oil prevents clot formation by showing an antiplatelet effect (Tognolini et al. 2006).

## Antitumour Activity

The potential cytotoxic activity of FV essential oil from Tajikistan was studied against HeLa (human cervical cancer), Caco-2 (human colorectal adenocarcinoma), MCF-7 (human breast adenocarcinoma), CCRF-CEM (human T lymphoblast leukaemia), and CEM/ADR5000 (adriamycin resistant leukaemia) cancer cell lines. The data showed that the $IC_{50}$ values were between 30–210 mg/$L^{-1}$ and thus exhibited low cytotoxicity compared to the reference compounds (Sharopov et al. 2017). Among the compounds from dichloromethane extract of fennel roots, falcarinol has been found to show significant toxicity against acute lymphoblastic leukaemia CEM-C7H2 cells 3.5 μmol/l $IC_{50}$ value (Zidorn et al. 2005). Anethole inhibited cellular responses induced by tumour necrosis factor (TNF) at a concentration below one mM. It has been reported that this may explain the suppressive effect of anethole on inflammation and carcinogenesis (Agarwal et al. 2008; Chainy et al. 2000). The ethanol extract of FV seeds was studied for reducing lung cancer growth and the underlying molecular mechanisms of action. It was reported that the extract decreased the viability and triggered apoptosis in the lung cancer cell lines NCI-H446 and NCI-H661 and induced apoptosis mainly through inhibition of Bcl-2 protein expression, reduction of mitochondrial membrane potential, and release of cytochrome C (Ke et al. 2021). The in vitro cytoprotective activity of 70% methanolic extract of FV and 50% *Helicteres isora* extract against normal human blood lymphocytes by micronucleus assay and antitumour activity against B16F10 melanoma cell line by Trypan blue exclusion assay was investigated. The results indicate that both extracts showed good antitumour activity at the concentration of 200 μg/ml (for *F. vulgare*) and 300 μg/ml (for *Helicteres isora*) (Pradhan et al. 2008).

## Insect Repellent Activity

It has been described that anethole has a strong insecticide effect against *Tribolium castaneum*, while fennel essential oil was not found active (Shukla et al. 1989). The toxic effects of anethole on the pest of *Ceratitis capitata* have been studied. The hydrolysed protein formulation containing 5% anethole was given to *C. capitata* as food. After 24 h, the mortality was found as 85%. It has been reported that after oral administration, irreversible damage has occurred in the intestines of the insect (Bazzoni et al. 1997). It was determined that fennel fruits contain insecticidal compounds against *Stophilus oryzae, Callosobruchus chinensis,* and *Lasioderına serricorne*. It was described that the effective components were (E)-anethol, estragole, and (+)-fencone (Kim and Ahn 2001). The repellent effect of methanolic extract of fennel fruits against female *Aedes aegypti* fly was examined using skin and patch tests. Biologically active compounds of the plant responsible for the effect have been identified as (+)-fencone and (E)-9-octadecenoic acid (Kim et al. 2002). In another study, it has been reported that the repellent effect of fennel essential oil was comparable with Citronellal and Geranium essential oils against female *Aedes aegypti* fly (Kim et al. 2004). The essential oils obtained from the leaves, flowers, and fennel roots have been found to have a fly repellent and larvacidal effect on *Culex pipiens inolestus* fly (Traboulsi et al. 2005).

## Anaesthetic Activity

The local anaesthetic effect of trans-anethole was evaluated in vitro by rat phrenic nerve-hemidiaphragm technique. Trans-anethole reduced the electrically evoked contractions of rat phrenic nerve-hemidiaphragm. The amount of reduction was 10.3% at a concentration of 0.001 μg/ml, 43.9% at 0.01 μg/ml, 79.7% at 0.1 μg/ml, and 100% at a concentration of 1 μg/ml (Ghelardini et al. 2001).

## Secretolytic and Expectorant Activity

After 90 seconds of applying 200 μl fennel infusion to the isolated ciliated epithelium of the frog oesophagus, 12% increase in mucociliary transport rate was detected (Mueller-Limmroth and Froehlich 1980).

## Effect on the Muscular System

It has been reported that fennel essential oil has a spasmolytic effect on smooth muscles in the

range of 50–100 γ/ml concentrations. The 30% ethanol extract of *F. vulgare* subsp. *vulgare* var. *vulgare* reduced contractions in acetylcholine and histamine-induced isolated guinea pig ileum at a concentration of 2.5–10 ml/L (Forster et al. 1980). In another study, 30% ethanol extract of bitter fennel was found to reduce carbachol-induced contractions at concentrations of 2.5 and 10 ml/L (Forster 1983). Evaluating the relaxation effect of fennel essential oil on tracheal and ileal smooth muscles, it was found that the essential oil had a more relaxing effect on ileal muscles than tracheal muscles (Reiter and Brandt 1985). Fennel essential oil inhibited isolated rat phrenic nerve stimulation and diaphragmatic contraction at the concentrations of $2 \times 10^{-5}$ and $2 \times 10^{-4}$ g/mL (Lis-Balchin and Hart 1997). Fennel oil reduced the severity of contractions induced by oxytocin at doses of 25 and 50 μg/mL and PGE2 at doses of 10 and 20 μg/mL of isolated rat uterus (Ostad et al. 2001).

Furthermore, the effects of herbal tea mixture marketed as SJ-200 (Himcospaz) in India were investigated on the smooth muscles of the gastrointestinal tract of guinea pigs, rats, rabbits and mice. SJ-200 has been reported as a herbal mixture containing *Z. offjicinale* rhizomes, *Apium graveolens* fruits, and FV fruits. This herbal tea inhibited contractions caused by acetylcholine, histamine, and barium chloride of guinea pigs, spontaneous contractions of rabbit and rat colon, and oxytocin-induced contractions of rat uterus in a dose depending manner. As a result, it has been shown that SJ-200 has nonspecific antispasmodic activity in experimental models (Venkataranganna et al. 2002). The effects of the water and ethanolic extract of FV and its essential oil on isolated trachea contracted with methacholine and KCl of guinea pigs were investigated. While the water extract did not have a relaxing effect, it was determined that the ethanolic extract and essential oil had bronchodilator effects. It has been reported that the possible mechanism of this effect is that the plant opens the potassium channels and this leads to a bronchodilator effect (Boskabady et al. 2004).

### 18.5.2 In Vivo Studies

#### Effect on the Nervous System

It was reported that FV oil was found to have promising anxiolytic activity in elevated plus-maze model at a dose of 100 and 200 mg/kg and a dose of 200 mg/kg in an open field test (Mesfin et al. 2014). Furthermore, the antidepressant activity of methanol extract of FV was observed with a force swim test in rats at a dose of 250 and 500 mg/kg. It is concluded that the dose of 250 mg/kg and 500 mg/kg of the extract significantly ($p < 0.001$) reduced the immobility times in rats (Jamwal et al. 2013). To evaluate the anti-amnesic and antidepressant effect of FV seeds, the seeds were administrated at a concentration of 2% and 4% with a diet to mice and rats. According to the results, FV showed memory-enhancing and antidepressant actions (Abbas et al. 2020). It was described that FV has anti-stress, memory-enhancing, and antioxidant effects. It was shown that the extract altered the stress-induced urinary biochemical levels of VMA from 395.79 ± 11.23 to 347.12 ± 12.28. Additionally, the memory deficits induced by scopolamine was reversed by FV dose-dependently. (Koppula and Kumar 2013). The potential effect of methanol extract of FV as a nootropic and anticholinesterase agent in mice was assessed. For this purpose, the extract was administered for eight successive days to ameliorate the amnesic effect of scopolamine (0.4 mg/kg) and ageing-induced memory deficits in mice. It was reported that the FV extract increased step-down latency and acetylcholinesterase inhibition in mice significantly (Joshi and Parle 2006).

#### Anti-inflammatory and Analgesic Activity

To investigate the anti-inflammatory effects of fennel in lipopolysaccharide (LPS)-induced acute lung injury model, it was administrated at a dose of 125, 250, 500 μl/kg to mice. As a result, fennel significantly and dose-dependently reduced LDH activity and immune cell numbers in LPS-treated mice. Also, fennel effectively suppressed the LPS-induced increases in the production of the inflammatory cytokines interleukin-6

and tumour necrosis factor-alpha, with 500 µ l/kg fennel showing maximal reduction (Lee et al. 2015). In a study, methanol extract of FV fruits was administered orally at a dose of 200 mg/kg to mice and 69% inhibition obtained the paw oedema induced by carrageenan and 70% inhibition the ear oedema induced by arachidonic acid. The results show that the plant is active on cyclooxygenase and lipoxygenase pathways (Choi and Hwang 2004). It is proposed that the anti-inflammatory activity of FV essential oil on acetic acid-induced colitis in rats may involve the inhibition of the NF-kB pathway. FV essential oil (100, 200, 400 mg/kg) was administered to the animals by oral gavage and continued for five consecutive days. The essential oil and dexamethasone decreased MPO activity and the expression of TNFα-positive cells in the colon tissue compared to the acetic acid group (Rezayat et al. 2018). In another study, 80% methanol extract of FV was administered orally at a dose of 100 mg/kg to rat and 36% inhibition obtained the paw oedema induced by carrageenan and 45% inhibition was observed after administration of the indomethacin at a dose of 5 mg/kg (Mascolo et al. 1987).

## Antidiabetic Activity

The antidiabetic effects of water extract of FV were investigated in streptozotocin-induced diabetic rats. It was reported that the extract decreased the blood glucose level from 339.3 + 0.48 mg/dl to 101.4+ 0.34 mg/dl and the levels of HbA1c from 11.09 ± 0.56 mg/dl to 6.26 ± 0.2 mg/dl (Anitha et al. 2014). Prolonged treatment with the petroleum ether fraction of the FV demonstrated improvement in blood glucose, lipid profile, glycated haemoglobin, and other parameters in streptozotocin-induced diabetic rats (Dongare et al. 2012).

## Antigenotoxic Activity

The protective effects of FV essential oil were investigated against genotoxicity induced by cyclophosphamide (CP) at 1 and 2 mL/kg doses continuously for three days at intervals of 24 h on mice. The results showed that CP produced a significant increase in the average percentage of aberrant metaphases and CAs, excluding gap and micronuclei formation in polychromatic erythrocytes (PCEs), which produced cytotoxicity in mouse bone marrow cells, and induced abnormal sperms in the male germ line (Tripathi et al. 2013). In the mouse bone marrow micronucleus test, trans-anethole was administrated to mice 2 and 20 h before the intraperitoneal injection of genotoxins at doses of 40–400 mg/kg. As a result, it has been reported that anethole has a protective effect against genotoxins as dose-related. An increase in genotoxicity after administration of trans-anethole at a dose of 40–400 mg/kg was not observed (Abraham 2001).

## Antioxidant Activity

In a study, the methanol extract from FV fruits was administered to rats at a dose of 200 mg/kg/day for three weeks. As a result, an increase in plasma superoxide dismutase (SOD), catalase activity, and high-density lipoprotein-cholesterol level was observed (Choi and Hwang 2004).

## Antiosteoporotic Activity

Antiosteoporotic effects of fennel essential oil were investigated in the osteoporosis model in ovariectomized rats. The rats were treated with fennel essential oil (500, 750, 1000 mg/kg) for 30 days and were compared with rats treated with estradiol valerate. It was determined that the essential oil had a preventive effect on the development of osteoporosis in ovariectomized rats (Jaffary et al. 2006).

## Antitumour Activity

The chemopreventive effect of different doses of test diet of FV seeds was examined on DMBA-induced skin and B(a)P-induced forestomach papillomagenesis in mice. A significant enhancement in antioxidant enzymes' activities was observed, especially at 4% and 6% test diets of fennel (Singh and Kale 2008). Polysaccharides isolated from FV have been reported to show 55.1% inhibition in mice implanted with sarcoma 180 cells (Moon et al. 1985). In a study in which the effect of trans-anethole on proliferative liver lesions was investigated in vivo, rats were fed with different concentrations of trans-anethole

for two years and the histopathological changes that occurred were evaluated. Although the livers of the rats fed with 0.25% trans-anethole did not show significant treatment-related microscopic changes, there was a slight increase in parenchymal cell hyperplasia. Hepatic changes were seen in rats fed with 0.5% trans-anethole due to enzyme induction. In rats given trans-anethole at a concentration of 1%, the decrease in hepatocellular neoplasms incidence was shown (Newberne et al. 1989). Cytotoxic activity of ethanol extract of fennel seed was evaluated in a mouse model of Ehrlich ascites carcinoma (EAC) and on different types of human cell lines in vitro. A 100 mg/kg of the extract was injected intraperitoneally into mice bearing EAC. It was reported that the extract exhibited an antitumour effect by modulating lipid peroxidation and augmenting the antioxidant defence system in mice with or without radiation exposure. Also, the fennel extract have remarkable anticancer potential against MCF7 ($IC_{50}$ = 50 ± 0.03 μg/mL) and Hepg-2 ($IC_{50}$ = 48 ± 0.22 μg/mL) cell lines (Mohamad et al. 2011). The anticarcinogenic effect of anethole was investigated on the tumour induced by Ehrlich ascites tumour (EAT) cells in the paw of albino mice. Anethole was administered orally at doses of 500 and 1000 mg/kg for 60 days to mice with tumours in the paw. In a group administrated anethole, there was an increase in survival, tumour weight, and volume, and a decrease in body weight compared to the control group. In a group in which 500 mg/kg anethole was administrated, the survival time increased from 54.6 days to 62.2 days and in a group in which 1000 mg/kg anethole was administrated, the survival time increased to 71.2 days (al-Harbi et al. 1995). Various herbal mixtures containing fennel seed extract inhibited tumour growth by 53% to 87% in immunocompromised mice carrying cwr22r and pc3 prostate cancer xenograft (Ng and Figg 2003). The polysaccharides isolated from FV showed 55.1% inhibition in mice implanted with sarcoma 180 cells (Moon et al. 1985). In a study, rats were fed with different trans-anethole concentrations for two years and the histopathological changes that occurred were evaluated. Although no significant treatment-related microscopic changes were observed in the group's livers fed with 0.25% trans-anethole, a slight increase was observed in parenchymal cell hyperplasia (Newberne et al. 1989).

## Effect on the Liver

After administration of the mixture of both and either of Dill (*Anethum graveolens* L.) and FV oil to $CCL_4$-induced hepatotoxic rats, the significant ($p < 0.05$) decrease levels of serum AST and ALT and significantly increase the level of serum total protein and albumin was observed (Rabeh et al. 2014). As a result of acute $CCL_4$ administration, it was observed that hepatotoxicity was inhibited by fennel essential oil in rats. In rats treated with fennel essential oil, serum AST, ALT, ALP, and bilirubin levels were decreased. In a study, the hepatoprotective effect of fennel essential oil was investigated on chlorpyrifos (CPF)-induced hepatotoxic male rats. The two doses of oil (0.3 and 0.5 ml/kg b.wt.), either with or without CPF (1/10 $LD_{50}$), were administered orally for 28 days. In fennel oil-CPF groups, the aforementioned alterations were alleviated, especially with the higher dose. This may be due to the antioxidant activity of essential oil, ability to scavenge free radical generated by CPF, and inhibition of cytochrome P450 and oxon formation (Mansour et al. 2011). Fennel essential oil decreased AST, ALT, ALP, and bilirubin in $CC^{14}$-induced rats. Histopathological studies have shown that essential oil prevents chronic liver damage (Özbek et al. 2004). In a study, trans-anethole (100 mg/kg) and [$^{14}$C] parathion (1.5 mg/kg) were administered intraperitoneally to rats. It was reported that trans-anethole was not active on the metabolism and excretion of parathion (Marcus and Lichtenstein 1982). Subcutaneous injection of fennel essential oil in partially hepatectomized rats for ten days significantly increased liver regeneration (Gershbein 1977).

## Estrogenic Effect

The fennel extract effects on serum level of estrogen, progesterone, and prolactin were evaluated in female mice. The extract was administrated to mice at a concentration of 100 and 200 mg/kg for five days intraperitoneally. Data analysis revealed

that there is a significant difference in the mean level of serum estrogen, progesterone, and prolactin between four different groups ($p < 0.0001$) (Sadeghpour et al. 2015). With the administration of acetone extract of fennel seeds to mature male rats at a dose of 1.5–2.5 mg/kg for 15 days, the total protein concentration in the testis and vas deferens decreased, but the total protein concentration in the seminal vesicle and prostate increased. Oral administration of the same extract to female ovariectomized rats at a dose of 0.5–2.5 mg/kg for ten days provided vaginal cornification and estrus. Estrogenic effects were seen in a dose-dependent manner (Mallni et al. 1985). It has been reported that after trans-anethole administration at a dose of 80 mg/kg for three days to female rats, the uterine weight increased significantly. The increase in uterine weight was found as 2 g/kg in rats given trans-anethole, 3 g/kg in rats given ostradiol valerate at a dose of 0.1 μg/rat/day subcutaneously, and 0.5 g/kg in the control group (Dhar 1995). A study describes that the aqueous extract of fennel seed showed a beneficial effect (especially at a dose of 150 mg/kg b.w.) on renal function after intragastric administration of extract in PCOS (poly-cystic ovary Syndrome) rats (Sadrefozalayi and Farokhi 2014). Estrogenic effects of fennel extract were investigated in the e-screen model and evaluation of uterotropic effects in mice. Fennel extract was administered to mice at a dose of 10 g/kg and 17β-estradiol at a dose of 0.5 mg/kg to another group of mice for nine days. It has been reported that both extract and 17β-estradiol increased uterine weight in female mice and shortened cell division time (Liu et al. 2004).

## Effect on the Digestive System

It was represented that the stomach movements increased after administration of fennel orally at a dose of 24 mg/kg to rabbits (Niiho et al. 1977). It was observed that gastric secretion was increased when 10% aqueous extract of fennel was perfused into the stomachs of anaesthetized rats (Vasudevan et al. 2000). As described in a study, the rats were fed a diet containing 0.5% FV for six months. As a result, it was observed that the transition time of food was shortened by 12% (Platel and Srinivasan 2001). The anti-ulcerogenic and antioxidant effects of aqueous extracts of FV were investigated on ethanol-induced gastric lesions in rats. The extract significantly reduced the MDA levels, while significantly increased GSH, nitrite, nitrate, ascorbic acid, retinol, and $\beta$-carotene levels at a dose of 300 mg/kg (Birdane et al. 2007).

## Other Effects

The oculohypotensive water extract activity of FV was evaluated in rabbits with normal intraocular pressure (IOP) and with experimentally elevated IOP. It was described that the 17.49, 21.16, and 22.03% reduction of intraocular pressure (IOP) was observed in normotensive rabbits at 0.3%, 0.6% and 1.2% (w/v) concentrations, respectively. The 0.6% concentration was further evaluated in acute and chronic glaucoma models and a 31.20% maximum mean difference was observed between vehicle-treated and extract-treated model (Agarwal et al. 2008). The antifertility effect of hydro-alcoholic extract from fennel seed extract was evaluated in male rats. It was described that the number of spermatogonia after doses of 140 and 280 mg/kg and Sertoli cells after a dose of 140 mg/kg decreased significantly (Mansouri et al. 2016). The wound healing efficacy of the FV compounds, fenchone and limonene, using an excisional cutaneous wound model in rats was investigated. Ten days after treatment, a significant increase was observed in wound contraction and re-epithelialization in both fenchone and limonene treated groups. The beneficial effect of compounds on wound healing maybe related to the anti-inflammatory and antimicrobial activities of fenchone and limonene increased collagen synthesis and decreased the number of inflammatory cells during wound healing (Keskin et al. 2017). In a study, the effect of hydro-alcoholic extract of fennel was evaluated on some hematological indices in male rats. The data indicate that the fennel extract increased mean RBC ($7.54 \pm 0.53 \times 106$) and WBC ($5.89 \pm 0.78 \times 103$) values, especially at a dose of 250 mg/mL and CT ($2.45 \pm 0.20$) at a dose of 500 mg/mL compared to the control group (Mansouri et al. 2015). The water extract of

fennel administered orally at a dose of 190 mg/kg for five days to spontaneously hypertensive rats significantly reduced systolic blood pressure. The extract increased the urine output of spontaneously hypertensive rats and increased the renal excretion of sodium and potassium (El Bardai et al. 2001). Inhalation of anethole did not alter the amount of respiratory tract secretion in rabbits, but decreased the specific gravity of the respiratory tract fluid in a dose-dependent manner (Boyd and Sheppard 1971). The local anaesthetic effect of trans-anethole was examined by conjunctival reflex test in a rabbit. Trans-anethole (10–100 μg/ml) increased the number of stimuli required for the awakening reflex in a dose-dependent manner (Ghelardini et al. 2001).

## 18.6 Clinical Studies

### 18.6.1 Effect on the Nervous System

To evaluate the effect of FV on anxiety and depression symptoms in postmenopausal women, a double-blind, randomized, placebo-controlled trial was carried out. Following the intervention, the Hospital Anxiety and Depression Scale (depression and anxiety subgroups) and Zung's Self Rating Depression Scale did not show any significant decrease (Ghazanfarpour et al. 2018).

### 18.6.2 Insect Repellent Effect

In the field test, preparations containing 5% (aerosol) and 8% (cream) of fennel essential oil were evaluated on five volunteers. As a result, the repellent effect was observed as 84% and 70% for aerosol and cream, respectively (Kim et al. 2004).

### 18.6.3 Estrogenic Effect

For treatment of infertility in infertile women, the synergistic effect of FV and oestradiol was investigated. Oestradiol was administrated to both groups as 2 mg tablet three times a day and to the treatment group FV tea also administrated. As a result, no significant difference was found in the treatment (ET = 13.1 ± 3.2 mm) and control group (ET = 14.2 ± 3.5 mm) (Yavangi et al. 2018). The 2% *F. vulgare* var. *dulce* essential oil (25 drops orally, every 4 h) was tested compared to mefenamic acid (orally, 250 ml every 6 h) on 60 female patients suffering from primary dysmenorrhea. It was reported that sweet fennel essential oil could be a safe and effective herbal remedy for primary dysmenorrhea (Namavar Jahromi et al. 2003). In a study, the assessment of fennel essential oil capsules on symptoms of the polycystic ovarian syndrome (PCOS) was investigated. The study was a double-blinded, randomized controlled study and carried out on thirty female students with PCOS.

The results of the Man-Whitney and chi-square tests showed that the Fennel was not effective in alleviating the ovarian cyst symptoms in polycystic women (Ghavi et al. 2019). The mefenamic acid and fennel essential oil were investigated on primary dysmenorrhea pain. In a study, 110 school-age girls with an age of 13 were included. Pain complaints completely disappeared or decreased in 80% of the patients in the group using essential oils and in 73% of the patients in the group using mefenamic acid. There was no significant difference between the two groups in relieving pain complaints due to primary dysmenorrhea (Modaress Nejad and Asadipour 2006). This trial was designed to assess the efficacy of fennel in the management of menopausal symptoms in postmenopausal women. For this purpose, the participants received eight weeks of treatment with soft capsules containing 100 mg fennel or a placebo. After the intervention, the treatment group showed a significant decrease in the mean MRS score (Rahimikian et al. 2017). To investigate the effect of fennel seed extract on vaginal atrophy, a double-blind, randomized, placebo-controlled trial was carried out on 60 postmenopausal women. It was reported that fennel had no significant positive effects on vaginal atrophy in postmenopausal women (Ghazanfarpour et al. 2017). Ethanol extract of fennel fruit has been studied in a double-blind study in the treatment of idiopathic

hirsutism. Thirty-eight hirsutism patients included in the study were treated with creams containing 1% and 2% fennel extract and the results were compared with placebo. As a result of the treatment, the diameter of the hairy area decreased by 7.8% in patients using 1% cream and 18.3% in patients using 2% cream. In both, concentrations were more effective than placebo (Javidnia et al. 2003).

The effect of FV ethanol extract was investigated on folliculogenesis in female mice. The data indicated that the total follicle numbers were 26.5 ± 5.24 at a 100 mg/kg concentration of extract and 27.2 ± 4.1 at a 200 mg/kg concentration of extract. It was reported that FV extract induced folliculogenesis in female mice ovary and increased the number of growing ovarian follicles (Khazaei et al. 2011). In a double-blind, randomized placebo-controlled trial, the effect of FV vaginal cream (%5) was evaluated on vaginal atrophy in postmenopausal women. It was concluded that the number of superficial cells increased significantly in the fennel group after eight weeks compared to the control group (76.1 ± 15.3 vs 11.8 ± 8, $p < 0.001$), the number of intermediate and parabasal cells decreased significantly in the fennel group, and the vaginal pH decreased significantly at the 8-week follow-up in the fennel group (100% vs. 7.4%, $p < 0.001$) (Yaralizadeh et al. 2016). To evaluate the effects of oral fennel drop for treating primary dysmenorrhea, sixty college students suffering from primary dysmenorrhea were randomly assigned to two groups. Comparison of pain intensity in the two groups showed that there was no significant difference in pain relief between the two groups (PV on the first day, second day, third day, fourth day, and fifth day 0.948, 0.330, 0.508, 0.583, and 0.890, respectively) (Bokaie et al. 2013).

### 18.6.4 Effect on the Digestive System

In a randomized clinical trial, a phytotherapeutic mixture containing *Pimpinella anisum*, *F. vulgare*, *Sambucus nigra,* and *Cassia augustifolia* was investigated for chronic constipation. The patients received the phytotherapeutic mixture for five days and colonic transit time, perception of bowel function, adverse effects, and quality of life were observed. The findings of this randomized controlled trial allow us to conclude that the phytotherapeutic mixture assessed has laxative efficacy and is a safe alternative option for the treatment of constipation (Picon et al. 2010). Fennel seed oil emulsion was given to 125 infants aged 2–12 weeks with infantile colic and the results were compared with placebo. As a result of the study, it was found that 65% of the babies who used fennel oil ceased this disorder. In the control group, an 23.7% improvement was observed. Compared with the placebo group, the reduction in colic frequency in the treated group was considered to be very excellent. Also, no side effects were observed (Alexandrovich et al. 2003). The effect of standardized extract prepared from *F. vulgare*, *Matricaria recutita,* and *Melissa officinalis* on infantile colic complaints in breastfed babies was investigated in a double-blind, randomized study. Ninety-three babies in the study were randomly divided into two groups after a 3-day monitoring period. The standardized phytotherapeutic extract was administered to one group and placebo to the other group twice a day for a week. Crying time decreased by 85.4% in the extract administrated group and 48.9% in the placebo group (Savino et al. 2005). In another study, it was reported that a herbal tea mixture containing *F. vulgare*, *M. recutita*, *Glycyrrhiza glabra, Verbena officinalis,* and *M. officinalis* was active on infancy colic complaints (Crotteau and Wright 2006).

## 18.7 Toxicological Studies

### 18.7.1 Acute Toxicity

The ethanolic extract of fennel was administered orally to mice at doses of 0.5, 1 and 3 g/kg, and its acute toxicity was studied after 24 h. Compared with the control group, there was no change in mortality, the weight of the body, vital organs, morphological, haematological, or spermatogenic parameters (Shah et al. 1991). The $LD_{50}$ value of fennel oil in rats has been reported as

3.12 g/kg and 3.8 g/kg in different studies. In another study, the oral $LD_{50}$ value of bitter fennel oil in rats was determined as 4.52 mL/kg. In a recent study, the oral $LD_{50}$ value of fennel oil in rats was 1326 mg/kg. The $LD_{50}$ value of trans-anethole in rats was reported as >3000 mg/kg and this value was noted as highly reliable (Ostad et al. 2001). In another study, the intraperitoneal $LD_{50}$ value of trans-anethole was 0.9–2.67 g/kg in rats and 0.65–1.41 g/kg in mice (Dhar 1995). The ovary removed rats were treated with 500, 750, and 1000 mg/kg doses of fennel essential oil for 30 days in the established osteoporosis model. The results showed that the essential oil had an inhibitory effect on osteoporosis development in rats (Escop 2003).

### 18.7.2 Subchronic Toxicity

The ethanolic extract of fennel was administered orally to mice at a dose of 100 mg/kg for three months. A significant difference in mortality, haematological, and spermatogenic parameters compared with the control group was not shown (Shah et al. 1991). The rats were treated with 500, 750, and 1000 mg/kg doses of fennel essential oil for 30 days in the established osteoporosis model. The results showed that the essential oil had an inhibitory effect on osteoporosis development in rats whose ovary was removed. In this study, the essential oil was more effective at a dose of 1000 mg/kg than estradiol but more toxic (Jaffary et al. 2006).

### 18.7.3 Reproductive Toxicity

In a study, trans-anethole was orally administered to adult rats on days 1–10 of pregnancy. As a result, an anti-implantation effect was reported in a dose-depending manner. Trans-anethole administration to rats at doses of 50, 70, and 80 mg/kg prevented implantation by 33%, 66%, and 100%, respectively (Dhar 1995).

### 18.7.4 Mutagenicity, Carcinogenicity, and Teratogenicity

Aqueous and methanol extracts of fennel gave negative results in the Ames test using TA 98 and TA 100 strains of *Salmonella typhimuri*. These extracts also showed negative results in the rec-assay test against *Bacillus subtilis* (Morimoto et al. 1982). Fennel oil (2.5 mg) and trans-anethole (2 mg) showed a weak mutagenic effect in the Ames test using TA 98 and TA 100 strains of *Salmonella typhimurium*. Mutagenic effect increased with S13 activation (Marcus and Lichtenstein 1982). The mutagenicity of trans-anethole has been studied in three different microbial test systems. It was reported that the trans-anethole was found mutagenic in the Ames test using TA 100 strain of *Salmonella typhi* at a dose of 30–120 μg/pill. Positive results in the rec-assay (DNA repair test) test in which *Bacillus subtilis* was used were observed. A negative result was obtained in the *Escherichia coli* WP2 uvrA reversion test (Sekizawa and Shibamoto 1982). Another study on this subject has shown that trans-anethole has a weak mutagenic effect, confirming its metabolic activation (Escop 2003). Sweet fennel oil gave a positive result in the DNA repair test using *Bacillus subtilis* (Sekizawa and Shibamoto 1982). In another study, fennel oil was found negative in an in vitro chromosomal aberration test using Chinese hamster fibroblast cell culture (Ishidate et al. 1984). Estragole, a compound found in fennel oil, has shown a mutagenic effect in some Ames tests and a carcinogenic effect in animal models. It has been reported that 1-0H metabolites are potent hepatocarcinogens (Escop 2003; De Vincenzi et al. 2000). The available data are not sufficient to determine the carcinogenic risk of fennel infusion. However, it is estimated that this risk was very low (Escop 2003). The teratogenic effects of fennel essential oil on the cells obtained from the rat embryo on the 13th day were investigated. It has been reported that the essential oil has toxic effects on fetal cells, but there is no evidence of teratogenic (Ostad et al. 2001).

### 18.7.5 GARS Status

Currently, trans-anethole has GRAS (Generally Regarded As Safe) status accorded by the FDA in the United States and is utilized as a flavouring agent in beverages, candy, baked goods, and chewing gum, in concentrations up to 1500 ppm in finished goods. Fennel oil has been approved for food use by the FDA and was granted GRAS status by the F.E.M.A. (1965). The Council of Europe (1970) included fennel oil in the list of fruits and vegetables for which no restrictions were proposed (Opdyke 1973). Common and sweet fennel also has GRAS status (GRAS 182.10 and GRAS 182.20, respectively) (Charles 2012).

## 18.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies

*Active milder magen und darmtee*: used in gastrointestinal symptoms such as bloating, flatulence, and mild spastic gastrointestinal problems as drinking 1 cup of freshly prepared tea 3–4 times a day between meals.

*Benetransit natural laxative*: used as a laxative and taken orally 1–2 tablet daily with a glass of water in the evening before sleep.

*Bio-Garten – Tee gegen Blähungen*: used in flatulence as drinking 1 cup of freshly prepared tea 3–4 times a day half an hour before meals.

*Brady's – stomach drops*: used for mild indigestion (such as bloating, gas) and taken as 5 mL for mild digestive disorders after a meal, for loss of appetite before meals, with water.

*Bronchialtee*: used for cough as drinking 1 cup of freshly prepared tea.

*Carminativum Babynos colic drops*: used as carminative and administrated orally undiluted or diluted with tea or water to babies and infants (take three times daily 3–6 drops), children older than one year (take three times daily 6–10 drops), and school children (3 times daily 10–15 drops).

*Carminativum Hetterich Balance oral drops*: traditionally used to support the digestive function and administrated orally in liquid with meals (while eating) to adults and children over 12 years (25–30 drops three times a day), children from 4 to 12 years (10–15 drops three times a day). Infants from 1 to under four years of age (take 5–10 drops three times a day), infants up to 1 year of age (3–5 drops three times a day).

*Cefabronchın oral drops*: traditionally used to facilitate the liquefaction of mucus in the airways and relieve throat irritation caused by cold and administrated orally neat or diluted with some liquid (water) to adults (every 2 h 20 drops up to 6 times per day) and children over four years of age (every 2 h 10 drops up to 6 times a day).

*Crislaxo*: used as a laxative. Administrated to adults and children over 12 years (2 tablets once a day), children 6 to under 12 years (1 tablet once a day), and children 2 to under six years (1–2 tablets once a day).

*Dicalmir*: used in gastrointestinal disorders as drinking after maceration of 1–2 sachets in about 100 ml of water after meals or in the evening before sleep.

*Eucarbon*: used as a laxative and taken orally 1–2 tablet three times daily with water at or after meals.

*Euka*: used for the temporary relief of pain and itching associated with minor skin problems and administrated externally to adults and children two years of age and older (applied to affected area not more than 3 to 4 times daily).

*Floradix Gallexier*: used in digestive system disorders and administrated orally to adults and children over 12 years of age (20 ml daily, before or after a meal).

*Hepatoflorine*: used to prevent gingivitis and reduce plaque and administrated to adults and children two years of age and older after meals, at least twice a day or as directed by a dentist as brushing teeth thoroughly.

*Herbesan*: used to enhance lactation during breastfeeding as drinking after maceration of 1 sachet in about 100 ml of water three times daily.

*Kneipp Flatuol*: used to treat bacterial and fungal infections inside the mouth (thrush) and skin and administrated to adults and children two

years of age and older after meals, at least twice a day or as directed by a dentist as brushing teeth thoroughly.

*PulmaCo*: used in respiratory disorders and taken as orally one tablet three times daily or as directed.

*Revitonil*: used to prevent gingivitis and reduce plaque and administrated to adults and children two years of age and older after meals, at least twice a day or as directed by a dentist as brushing teeth thoroughly.

*Poconéol*: used as a homeopathic treatment in general drainage to stimulate elimination functions and taken as 15 drops a day diluting in a small amount of water.

## 18.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

Their traditional uses and scientific evaluation indicate that FV is the most widely used herbal plant. One of this chapter's purposes is to compile available scientific evidence for the ethnobotanical claims and identify gaps required to be filled by future research. Studies have shown that various fennel extracts possess a range of pharmacological actions, such as antiaging, antiallergic, anticolitic, antihirsutism, anti-inflammatory, antimicrobial, and antiviral activity supporting its traditional use. However, there are still numerous ethnobotanical studies on this plant that need to be supported by scientific research. This chapter may provide a scientific basis that explains FV's ethnophytopharmacological role to facilitate and guide future research.

There are sedative uses of the plant in ancient Rome, sperm defection in China traditional medicine, and the woundhealing use in Turkish traditional medicine. To the best of literature and knowledge, it was seen that these effects of the plant were not investigated. Besides that, it was seen that some activity studies of the plant such as anti-inflammatory, antioxidant, antitumour, hypotensive, hepatoprotective, local anaesthetic, and secretolytic activities were not completed with clinical trials.

## 18.10 Challenges and Future Recommendations as Potential Drug Candidate

FV was used as a herbal remedy, spice, and food from ancient times. This plant is rich with numerous phytochemical compounds such as *trans*-anethole, estragole, fenchone, coumarins, and polyphenolics, most of which exhibited significant biological activities like antimicrobial, antiviral, anti-inflammatory, antimutagenic, antinociceptive, antipyretic, antispasmodic, hypoglycemic, and memory-enhancing property. On the other hand, it was reported that fennel also contains mineral and trace elements like aluminium, barium, calcium, cadmium, cobalt, fat-soluble vitamins such as vitamins A, E, and K, water-soluble vitamins like ascorbic acid, and thiamine which have beneficial effects on human health. In this chapter, all the available data on traditional use and the scientific literature regarding FV's medicinal uses were compiled. This may lead to new research related to various aspects of this medicinal plant.

Most of the pharmacological activities described in the literature about FV were conducted using uncharacterized crude extracts. So, standardization of used extracts, bioactivity-guided identification of bioactive compounds in extracts, and validation of the mechanism of action-responsible compounds from the various beneficial effects should be carried out. On the other hand, the medicinal values at a molecular level with the help of different biotechnological techniques should be investigated. These new approaches may enhance the economic value of this plant. Besides, it is clear that many in vitro and in vivo studies of FV are not supported by clinical evidence. These scientific studies should be completed with clinical trials. Furthermore, the factors such as geographical and seasonal variation play an important role in the authentication of the chemical constituents responsible for the activity, which also can be an area of interest.

Hence, it is worth noting that although FV is an ingredient in several patents and herbal formulations, studies are required to assess the pharmacokinetic studies and the possible side effects or toxicities due to the interaction of the medicinal plants with other herbs.

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# *Fraxinus ornus* L.

19

Nuraniye Eruygur

**Abstract**

There are 43 varieties of manna ash (*Fraxinus* L.; Oleaceae) present in temperate and subtropical regions of the northern hemisphere. *F. ornus* L. is found in the wild in the Aegean and Mediterranean regions, as well as south-central Europe, northwards to the south Czech Republic, and north-eastern Romania. Chemical constituents of *F. ornus* plant include various seconder metabolites: secoiridoids, hydroxycoumarins, phenylethanoids, flavonoids, and lignans. Therefore, this plant has different biological activities depending on the various secondary metabolites it contains, which have been well documented by various biological activity studies including antioxidant, antimicrobial, skin-regenerating, anti-inflammatory, antiviral, anticococidial, and hypoglycemic activity. The aim of this study is to update and review the scientific research on botanical properties, phytochemical composition, and pharmacological activities *of F. ornus* species. This review suggests that this plant is important because of its various biological activities and that it may be used for discovering new drugs, but further supporting studies and adequate clinical and toxicological studies are mandatory in terms of bridging the gap in the future pharmaceutical research field on it.

**Keywords**

*Fraxinus ornus* · Phytoconstituents · Pharmacological activity

## 19.1 Introduction

The genus *Fraxinus* L., known as Manna, is mainly found in the northern hemisphere's temperate and subtropical regions, namely in North America and East Asia, and then in Europe and western Asia. This genus represents 43 species. *Fraxinus* is one of the 24 genera in the Oleaceae family and the only member of the Fraxininae subfamily, which is the Oleinae subgroup's sister group in the Oleeae tribe (Wallander 2008).

*Fraxinus ornus* L. (Oleaceae) is a small to medium deciduous tree that can grow up to 25 meters tall (Caudullo and de Rigo 2016). Bark beech trunk is smooth as an old trunk and without cracks. Young shoots are gray or greenish-gray color and are glabrous. Young twigs are brown or brownish-gray, glabrous. Leaflets 2–4 (−5) paired, petiolate (petiole 2–18 mm), ovate to lanceolate, generally 6–10 (−13) × (2−) 2.5–6 cm in size, and abruptly and shortly acuminate or long-acuminate (Fig. 19.1). Both sides of the leaflets

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are glabrous or the lower face is middle brownish-hairy along the vein and main veins, regularly notched-saw-toothed on the edge (each side 25–45 teeth). Combined cluster is in the armpit on large, tip-shaped, and often leafy shoots. The flowers are fragrant. Petal leaf lobes are striped (thin and long), 4 pieces, usually 6 (−10) mm, and longer or about the same size than the white stamen. Samara lane-inverted lanceolate is 20–25 × 3–4 mm in size, with cylindrical and permanent sepals (Eminagaoglu et al. 2014). *F. ornus* is an insect-pollinated tree. The fruits are single-seeded, elongated, and winged samaras that develop in clusters. The species has male and hermaphrodite trees in a breeding population and only hermaphrodites produce fruits (Yilmaz and Tonguç 2013).

*F. ornus* (L.) (Syn: *Fraxinus mannifera* Steud, *F. rotundifolia* Mill., Manna, *Ornus europaea* Pers) (Oleaceae) is known as Manna ash, ash tree, flake manna, flowering ash in English, and called locally as "çiçekli dişbudak", "kudret helvası" in Turkish. This tree is used for afforestation of non-forest areas, roof landscape design, forest restoration, and manna production (Tonguc 2019). The cortex and the juice obtained from stem barks of eight- to ten-year-old trees' incision give the drug "kudret helvası" or "manna" (Fig. 19.2) and are used for medicinal purposes (Kıvçak 2017). Manna is a pale yellow or white sugary material made from dried exudates obtained from *F. ornus* bark and used as a traditional snack, emergency food, or medication for the treatment of minor ailments due to its laxative activity in different parts of the world. Manna has been produced for years to obtain mannitol, which has nutritious and sweetening properties (Debord et al. 1987).

### 19.1.1 Distribution

*F. ornus* L. is found in the wild in the Aegean and Mediterranean regions, as well as south-central Europe, the Czech Republic, and north-eastern Romania (Kostova 2001). In Turkey, it is found naturally in the Marmara, Aegean, and Mediterranean regions (Fig. 19.3) (Eminagaoglu et al. 2014).

### 19.1.2 Traditional/Ethnomedicinal/ Local Uses

In Bulgarian folk medicine, the bark of *F. ornus* L. is used to treat inflammation, arthritis, and dysentery (Asenov and Nikolov 1988). It was reported that the stem bark and young shots of *F. ornus* were used for eye diseases in Turkish folk medicine (Bulut and Tuzlaci 2013). In the northern region of Pakistan, plants from the genus *Fraxinus* have long been used to treat malaria and pneumonia (Sarfraz et al. 2017).


**Fig. 19.1** *Fraxinus ornus* L. (Source: http://votaniki.gr/xlorida/eidi/ksilodi-eidi-tis-elladas/fraxinus-ornus/)


**Fig. 19.2** *Fraxinus* Manna. (Source: https://realignsinc.com/natural-dietary-supplement/)


**Fig. 19.3** Distribution map of *Fraxinus ornus* (manna ash). (Source: https://commons.wikimedia.org/wiki/File:Fraxinus_ornus_range.svg)

Daily dosage of *F. ornus* bark is 20–30 g for adults and 2–16 g for children. However, manna, like other laxatives, should not be used for a prolonged period of time. Internal administration of comminuted herb and other galenic preparations is possible.

## 19.2 Bioactive/Nutraceutical and Nutritional Composition

### 19.2.1 Nutraceutical and Nutritional Composition

The presence of simple hydroxycoumarins with OH and/or OMe groups in the benzene ring, as well as oleoside type secoiridoids, is the most distinguishing characteristic of *Fraxinus* species. Phytochemical investigations revealed that *F. ornus* contains secoiridoid glucosides (Iossifova et al. 1993, 1995), hydroxycoumarins, secoiridoids, phenylethanoids, flavonoids, and lignans (Iossifova et al. 1999, 2002; Kostova and Iossifova 2002a, b, 2007; Nykolov et al. 1993). The major coumarinic components of the *F. ornus* bark are esculin, esculetin, fraxin, and fraxetin (Table 19.1) (Al-Snail 2018).

The existence of various hydroxycoumarins and oleoside type secoiridoids in *Fraxinus* species has chemotaxonomic significance. When compared to other morphologically related *Fraxinus* species, *F. ornus* has several qualitative and quantitative variations in chemical composition (Iossifova et al. 1997).

### 19.2.2 Extraction

The shade-dried plant material is powdered and can be extracted with hot ethanol. The extracts filtered through the filter paper can be concentrated at low pressure and are used to examine biological behavior and isolate pure components.

To isolate hydroxycoumarins, the crude ethanol extract of manna bark can be separated into fractions using liquid vacuum chromatography with petroleum ether, chloroform, ethyl acetate, and methanol. The petroleum ether fraction does not contain any coumarins. A dichloromethane-methanol solvent mixture is gradient-eluted on a silica gel column to isolate coumarins from the chloroform fraction. The fractions obtained from silica gel column chromatography were studied by a TLC. Coumarins can be identified by UV, IR, NMR, and MS, as well as direct comparison with real samples (Kostova and Iossifova 2002a, b).

## 19.3 Pharmacological Activities

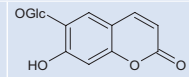
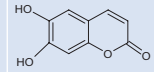
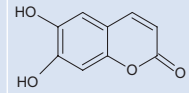
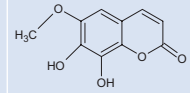
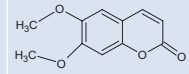
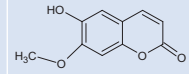
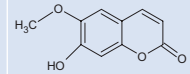
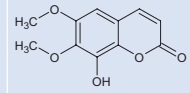
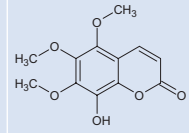
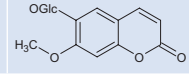
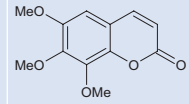
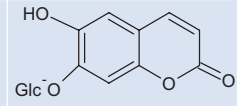
### 19.3.1 Antioxidant Activity

The ethanolic extract of *F. ornus* bark and their coumarin compounds such as esculetin, esculin, fraxetin, and fraxin were investigated for antioxidant activity by autoxidation of triacylglycerol of sunflower oil and lard. The extract and fraxetin showed strong antioxidant activity, while fraxin and esculin demonstrated very weak antioxidant activity (Marinova et al. 1994). In a study, the antioxidant activity of crude ethanolic extract, chloroform, ethyl acetate, n-butanol, and water fractions, as well as the major hydroxycoumarins esculin, esculetin, fraxin, and fraxetin, was investigated using the DPPH and TEAC methods. Among fractions, chloroform fraction had the maximum antioxidant potential with the $IC_{50}$ of 16.7 and 4.24 μg/mL for DPPH and TEAC method, respectively. Among the tested compounds, esculetin showed highest DPPH and ABTS radical scavenging activity, followed by fraxetin, and their glycosides fraxin and esculin (Wu et al. 2007).

### 19.3.2 Antimicrobial Activity

The ethanolic extract of *F. ornus* bark has been reported to show bacteriostatic activity against *Staphylococcus aureus* (I. N. Kostova et al. 1993). The antimicrobial activity of some isolated coumarins, secoiridoids, and phenylethanoids obtained from *F. ornus* bark invested on *Cladosporium cucumerinum*, *Pseudomonas stutzeri, S. aureus*, *E. coli,* and *Candida albicans* by agar dilution test. According to the results, fraxetin and fraxetin diacetate showed antibacterial activity with MIC value of 125 μg/mL and 500 μg/mL against *S. aureus* (Iossifova et al. 1994).

**Table 19.1** Phytochemical compounds in *Fraxinus ornus* L.

| Chemical compound | Plant part | Compound's name | Structure | References |
|---|---|---|---|---|
| Coumarins | Bark, Flowers, leaves | Esculin |  | Kostova (1992, 2001), Liu et al. (2005) |
| | | Esculetin |  | |
| | | Fraxin |  | |
| | | Fraxetin |  | |
| | Bark | Scoparone |  | |
| | | Isocopletin |  | |
| | | Scopoletin |  | |
| | | Fraxidin |  | |
| | | Fraxinol |  | |
| | | 7-Methylesculin |  | |
| | | 6,7,8-trimethoxycoumarin |  | |
| | Flower, leaf | Cichoriin |  | |

(continued)

**Table 19.1** (continued)

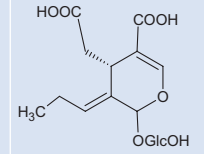
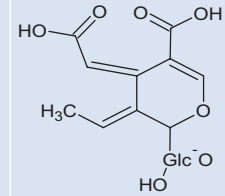
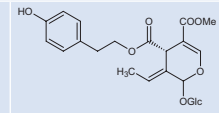
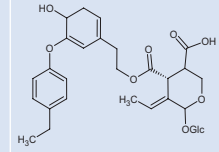
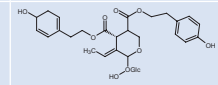
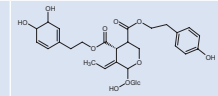
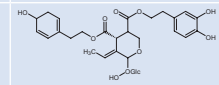
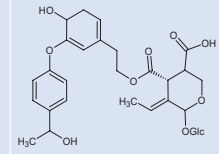
| Chemical compound | Plant part | Compound's name | Structure | References |
|---|---|---|---|---|
| Secoiridoids | Bark | Oleuropein |  | Iossifova et al. (1993, 1998, 2002), Kostova (2001) |
| | | Oleoside |  | |
| | | Ligstroside |  | |
| | | Ornoside (insularoside, uhdoside) |  | |
| | | Framoside |  | |
| | | Hydroxyframoside A |  | |
| | | Hydroxyframoside B |  | |
| | | Hydroxyornoside |  | |

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**Table 19.1** (continued)

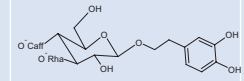
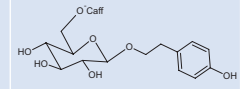
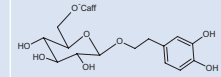
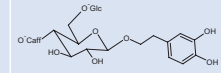
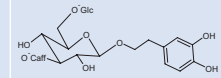
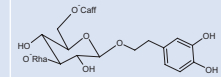
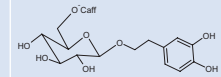
| Chemical compound | Plant part | Compound's name | Structure | References |
|---|---|---|---|---|
| Phenylethanoid glycosides | Bark | Verbascoside |  | Iossifova et al. (1999) |
| | | 2-(4-hydroxyphenyl)-ethyl-(6-O-caffeoyl) -β-D-glucopyranoside |  | |
| | | Calceolarioside B |  | |
| | | Lugrandoside |  | |
| | | Isolugrandoside |  | |
| | | Isoacteoside |  | |
| | Leaves | Calceolarioside |  | |

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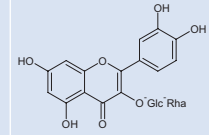
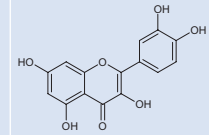
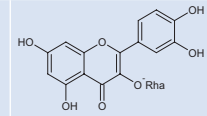
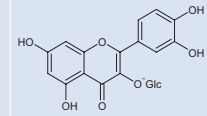
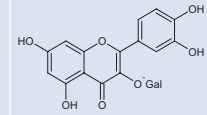
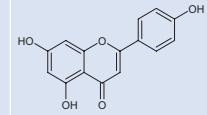
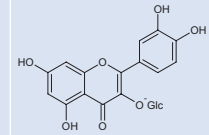
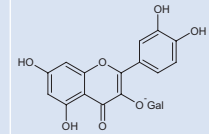
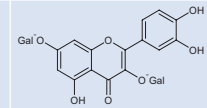
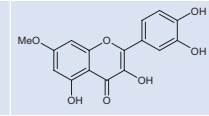
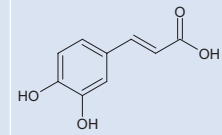
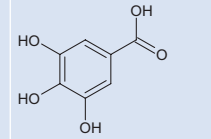
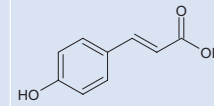
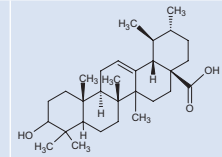
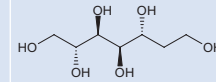
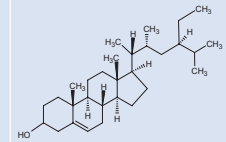
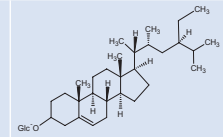
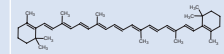
**Table 19.1** (continued)

| Chemical compound | Plant part | Compound's name | Structure | References |
|---|---|---|---|---|
| Flavonoids | Leaves, flowers | Rutin |  | Kostova and Iossifova (2007), Shammas et al. (1990) |
| | | Quercetin |  | |
| | | Quercetrin |  | |
| | | Isoquercetrin |  | |
| | | Hyperoside |  | |
| | | Apigenin |  | |
| | | Quercetin-3-glucoside |  | |
| | | Quercetin-3-galactoside |  | |
| | | Quercetin-3,7-galactoside |  | |
| | | Rhamnetin |  | |

(continued)

| Chemical compound | Plant part | Compound's name | Structure | References |
|---|---|---|---|---|
| Organic acids | Bark, leaves, and flowers | Caffeic acid |  | Kostova (2001) |
| | | Gallic acid |  | |
| | | *p*-coumaric acid |  | |
| | | Ursolic acid |  | |
| Other compounds | Manna, bark, flowers | Mannitol |  | |
| | Flower | Sitosterol |  | |
| | Bark | Sitosterol glucoside |  | |
| | Leaves | Carotene |  | |
| | Bark | 1-hydroxypinoresinol-4′-β-D-glucoside | | |

### 19.3.3 Antiviral Activity

Antiviral activity of hydroxycoumarins isolated from *F. ornus* bark and their acetate derivatives investigated against Newcastle virus, poliovirus 1, and influenza virus A, among the tested compounds, esculetin and esculin displayed antiviral activity against NDV with the toxicity inhibition zone of 19.6 mm and 16.2 mm, respectively (Galabov et al. 1996).

### 19.3.4 Anti-inflammatory Activity

The ethanol extract of stem barks of *Fraxinus ornus* and its constituent esculin inhibited both classical and alternative inflammatory pathways with zymosan- and carrageenan-induced paw edema (Sarfraz et al. 2017). The crude ethanol extract prepared from *F. ornus* stem barks and its main constituent esculin were evaluated for anti-inflammatory activity on paw edema induced by

carrageenan and zymosan in mice. The study results showed that both the extract ($AP_{50}$ = 44.4 Unit/mL) and esculin ($AP_{50}$ = 28.2 Unit/mL) reduced the zymosan-induced edema and only extract ($AP_{50}$ = 38.5 Unit/mL) reduced the carrageenan-induced paw edema, while esculin did not (Stefanova et al. 1995).

### 19.3.5 Skin-Regenerating Activity

Previous studies have reported that the ethanol extract from *F. ornus* bark and the isolated pure compound esculin had moderate skin regenerative effects, but no toxicity or local irritation. (Kostova and Iossifova 2002a, b). In another study, total methanol extract, ethyl acetate, petroleum, and methanol-water fractions obtained from *F. ornus* bark were investigated by Lazorova et al. for their photodynamic protective activity. Ethyl acetate extract and the isolated compound esculetin and fraxetin showed highest photodynamic protective activity on fungus cell membrane (Lazarova et al. 1993).

### 19.3.6 Anticoccidial Activity

Potential protective effects of *F. ornus* were investigated by Papazahariadou et al. on broiler chickens infected with *Eimeria tenella* coccidian strains; results showed that *F. ornus*, which was included in the broiler diet at a level of 2%, decreased the number of oocysts excreted in the feces of chickens infected with *E. tenella* (Papazahariadou et al. 2010).

### 19.3.7 Hypoglycemic Activity

Antidiabetic activity was investigated by using nicotinamide-streptozotocin-induced type-2 diabetic model on 16 plants and 4 algae species used against diabetes in Egypt. Hydroethanolic extract prepared from *F. ornus* showed highest antihyperglycemic activity at the oral administration dose of 10 or 50 mg/kg for one week (AbouZid et al. 2014).

## 19.4 Clinical and Toxicological Studies

### 19.4.1 Clinical Study

No relevant data available for clinical study on the *F. ornus*.

### 19.4.2 Toxicological Study

The ethanol extract and its main constituent esculin obtained from *F. ornus* stem bark were investigated for acute toxicity on *Swiss albino* mice by oral administration of 50–8000 mg/kg and were found to be practically nontoxic (Kostova and Iossifova 2002a, b).

In the presence of ileus, the medication should not be used. There are no known health risks or side effects associated with the proper administration of prescribed therapeutic dosages. Flatulence and nausea can occur in those who are susceptible (Company 2004).

## 19.5 Available Commercial Products

The drug is approved by Commission E for the treatment of constipation. There is a food supplement called *Fricol kids*® produced by NTC pharma, prepared in 6 sachets of 5 g, which is used to support gastrointestinal health and cleanse the intestines based on Manna and its active constituent mannitol, which is classified as osmotic laxatives, obtained from *Fraxinus ornus* L. *Vado syrup*®, produced from figs and manna by Promo pharma, is used for physiological functions of the intestinal transit. *Pronatura* Swedish Bitters™ is a soft gel herbal dietary supplement produced from different plants extract mixture including *F. ornus* L. Another syrup product is *Manna-feigen sirup* prepared from *F. ornus* and fig extract. *Physiomanna, physiomana LaxDepur, physiomanna Baby, and* physiomanna Fibra are natural dietary supplements based on pure *Fraxinus* manna dedicated to the gastrointestinal health and transit. There is also tinctures and

Manna di Sicilia soups prepared from *F. ornus* or manna.

## 19.6 Conclusions and Future Perspectives

This review reveals that *F. ornus* is a valuable medicinal plant which is used in Turkey and other countries with its different biological potentials. Biological activity studies were carried out on the plant extracts obtained from the *F. ornus* and its isolated compounds. However, there are not more clinical or toxicological studies. Here, the toxicity of coumarin derivative compounds should be investigated in a dose-dependent manner. In addition, we anticipate that the active substances obtained from this plant should be carried out with future studies depending on the molecular mechanism or protein/enzyme targets.

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# *Fumaria officinalis* L.

20

Fatma Ayaz

**Abstract**

*Fumaria officinalis* L. (Fumariaceae family), annual herbaceous plant, grows naturally throughout the world and is traditionally used in many countries. The dried aerial parts of *F. officinalis* (fumitory) at flowering period, Fumariae herba, has been accepted by numerous monographs, including Com E and EMA. The digestive and gallbladder-biliary systems have been the subject of the traditional uses of *F. officinalis*. It is also known that the plant is used to treat conjunctivitis, arteriosclerosis, bladder infections, constipation, skin disorders, as well as anti-rheumatism, and is cleaner of blood in folk medicine. The herbal medicinal products of *F. officinalis* have been available as comminuted in tea or powdered, and dry water extract in various pharmaceutical forms on the markets for more than 30 years. It is also reported that liquid extract, tincture, and juice of the plant are included in the components of the herbal preparations. Phytochemical constituents of *F. officinalis* have frequently been characterized as isoquinoline alkaloids, flavonoids, and phenolic acids. It is demonstrated that various experimental studies on *F. officinalis*, such as in vitro, in vivo, and clinical trials, have been proceeded, in which therapeutic effects of the plant are exhibited due to the above-mentioned bioactive contituents. In the literature, it is seen that biological activities of *F. officinalis* extracts such as antimicrobial, cytotoxic, antioxidant, hepatoprotective, amphocholeretic, and analgesic were examined. Otherwise, there has been no detailed evaluation of *F. officinalis* in pharmacognosic aspects until now. The aim of this work is to present *F. officinalis* description, and ethnobotany, phytochemistry, as well as its biological potentials by highlighting the connection between its ethnomedicinal uses and scientific or clinical proof. Additionally, the medicinal administrations and posology of *F. officinalis* were summarized, as well as herbal medicinal products available on the market. According to a review of the literature, certain medical applications of *F. officinalis*, such as dermatological conditions, infections, hypertension, and constipation, have not been adequately supported by research. Based on the current reports, it is clear that it is necessary to investigate *F. officinalis* more in terms of different biological activities and bioactive phytochemical components.

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**Keywords**

Herbal preparation · Digestive system · Gallbladder-biliary system · Alkaloids · *Fumaria officinalis*

## 20.1 Introduction

The genus *Fumaria* L., derived from Latin "*fumus terrae*", was described with the grayish green color of these plants, giving the appearance of smoke rising from the soil and the juice makes the eyes tear as smoke does (Mitich 1997; De Bray 1978). The genus is also considered as invasive weeds susceptible of damaging whole agricultural crops (Holm et al. 1997). For these reasons, *F. officinalis* L. is known as "fumitory, fume of the earth, fumus, fumusterre, hedge, God's fingers and thumbs, fuminity, fumiterre, wax dolls, earth smoke, snapdragon, vapor, and beggary" in English (Mitich 1997; Holm et al. 1997; Gruenwald et al. 2007). In addition, it is generally called as "şahtere, sedef otu, şahtere otu" in Turkey (Şener 1982).

Since the fifth century AD, *Fumaria* species have been linked to magic and superstitious nonsense in Europe. The smoke from the leaves on fire is thought to have the ability to remove and defend against bad forces and illusions (Le Strange 1977; Allan 1978). *Fumaria* species, generally small annual herbaceous plants, have long been traditionally used as antihypertensive, blood purifier, antiallergic, and diuretic, as well as for the cure of rheumatism, hepatobiliary and skin diseases, diarrhea, fever, abdominal and stomach cramps, syphilis, and leprosy as herbal medicines (Sener 2002; Maiza-Benabdesselam et al. 2007; De Bray 1978; Brenchley 1910; Erdoğan 2018).

Among one of the medicinal *Fumaria* species, *F. officinalis* is the most popular and has frequently been a significant subject of scientific research nowadays. Previously, *F. officinalis* has also been used in different fields such as cutting milk and producing a yellow wool dye (Le Strange 1977). However, *F. officinalis*, known with principal bioactive constituents as isoquinoline alkaloids, has been the subject of many printed and online publications in pharmacognosy diciplinary, as well as regulatory controls. It was also included in the Pharmacopoeial and Other Monographs, such as British Pharmacopoeia 2009, European Pharmacopoeia ninth Edition, Complete German Commission E (Com E), European Scientific Cooperative on Phytotherapy (ESCOP), Martindale 35th edition, and Committee on Herbal Medicinal Products (HMPC) in European Medicines Agency (EMA) (Barnes et al. 2007).

According to literature, there has been no current inclusive publishment on *F. officinalis* up to date. In this paper, a comprehensive knowledge about *F. officinalis* has been compiled in the hopes of being helpful to guide scientists in the future. Therefore, it is revealed that this work evaluates the description, and ethnobotany and medicinal administration doses, phytochemical components, and medicinal herbal products of *F. officinalis*, as well as its therapeutic potentials using in vitro, in vivo, and clinical assays by focusing on the comparison of the scientific or clinical evidences with ethnomedicinal uses.

## 20.2 Distribution and Status of Species

*Fumaria* genus, belonging to Papaveraceae, is represented by around 72 taxa and 57 species and has been extensively investigated in terms of phytochemical components, bioactivity potentials, ethnobotanical research, and traditional medicine (Lidén 1986; Murphy 2009; Pérez-Gutiérrez et al. 2012; Webpage). The genus is naturally distributed in Europe, Africa northern, and the Middle Asia, especially the most various in the Mediterranean range, and expanded to Australia and America (Mitich 1997; Suau et al. 2002; Samundeeswari et al. 2013; Iwasa et al. 1996).

*F. officinalis*, an annual herbaceous plant, is semi-erect and slender, branching with a climbing height at 10–50 cm. The leaves, grey-green and alternate, are divided into 2–4 segments with lanceolate-linear. Inflorescence is dense with 20–40 flowers. Sepals are lanceolate with

0.5–1 mm broad, and Corolla is pink and 7–9 mm, with spur 1.5 mm, curved. Fruit is 2–2.5 mm long and broad, truncate, and retuse. Flowering period is april-may (Cullen 1965; Gruenwald et al. 2007; Demirezer et al. 2017).

## 20.3 Comparison of Traditional/ Ethnomedicinal/Local Uses

Fumariae herba, the dried material as the aerial parts of *F. officinalis* at flowering period, approved by Com E and HMPC in EMA to use liver, gallbladder, bile ducts, and gastrointestinal tract symptoms, such as stomach ache, flatulence, sensation of fullness, vomiting, slow digestion, and nausea due to antispasmodic and amphicholeretic effects (EMA Monographs 2011; ESCOP Monographs 2018; Gruenwald et al. 2007; Barnes et al. 2007). Moreover, it was reported that the plant had weak diuretic and laxative effects and was also used to cure conjunctivitis, skin diseases, such as chronic eczema, and cutaneous eruptions, as well as constipation, infections (cystitis and arthritis), arteriosclerosis, as cleaner of blood, anti-rheumatism, and hypoglycemia in folk medicine (Gruenwald et al. 2007; Barnes et al. 2007). The plant's homeopathic uses were established for chronic, itchy eczema caused by liver disease (Gruenwald et al. 2007).

Fumitory has been used in many countries, such as France, Spain, Iran, Portugal, Morocco, Austria, Germany, Turkey, and Cyprus, as well as regions, including Europe, North America, Sicily, and Britain (Demirezer et al. 2017; Zhang et al. 2020; Al-Snafi 2020). Despite the fact that *F. officinalis* has been well known since ancient, it was first used as a medicine in Europe in the early Medieval Period. It was thought to be healthy for the eyes in seventeenth century Europe and used to cure conjunctivitis as an eye drop in folk medicine (EMA Reports 2011; Barnes et al. 2007). The juice obtained from leaves of *F. officinalis* was used to treat liver disorders and ailments of skin, such as cutaneous eruptions, specifically, chronic eczema in folk medicine (Le Strange 1977; Barnes et al. 2007). In addition, the dried leaves were smoked like tobacco to treat head disorders. Otherwise, for melancholia, dried powder of seed from *Fumaria*, together with water, mixed with honey from roses was used. Fumariae Herba, mentioned in the EMA, and its preparations were used to treat gastrointestinal and biliary tract disorders (EMA Reports 2011). There are unproven experimental uses, mentioned in folk medicine, such as for the treatment of skin diseases, constipation, bladder infections, arteriosclerosis, rheumatism, arthritis, and infections, as well as a blood purifier, and hypoglycaemia (Gruenwald et al. 2007; Duke 2002; EMA Reports 2011). Traditional uses of *F. officinalis* were summarized in Table 20.1.

## 20.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques

Phytochemical investigations on *Fumaria* species have showed their secondary metabolites, especially four groups, alkaloids, flavonoids, phenolic acids, and other constituents (Fig. 20.1). *Fumaria* belongs to the Papaveraceae family and is known for its various and distinct alkaloids, primarily isoquinoline groups (Barnes et al. 2007; ESCOP Monographs 2018; Zhang et al. 2020).

*F. officinalis* mainly contains isoquinoline alkaloids as characteristic constituents (0.3–1%), protopine (fumarine) and cryptopine. The European Pharmacopoeia specifies protopine as a minimum of 0.40% of total alkaloids is contained in the dried aerial parts of *F. officinalis,* cultivated in full flower (EMA Reports 2011). The secondary metabolites of *F. officinalis* were classified as alkaloids, flavonoids, phenolic acids, and others, as shown in Table 20.2.

The medicinal administrations of *F. officinalis* were also summarized in Table 20.3, comparing with their doses and references below.

**Table 20.1** Traditional uses of *F. officinalis*

| Countries/ regions | Traditional uses | Reference |
|---|---|---|
| Northern Portugal | As tea, against hepatic problems, and gallbladder disorders | Neves et al. (2009) |
| Italy | For treatment of hypotension, spasms, and arteriosclerosis; as respiratory stimulant, and cholagogue | Lokar and Poldini (1988) |
| | As tonic, depurative by preparing fresh juice of the plant diluted in water | De Natale and Pollio (2007) |
| Morocco | Against hypertension and cardiac disease | Eddouks et al. (2002) |
| Iran | Against skin diseases, scabies, anti-scorbite, anti-bronchite | Amin (1991) |
| | For treatment of diabetes | Goodarzi et al. (2013) |
| France | To promote urinary and digestive elimination functions | EMA Reports (2011) |
| | Maceration of flowers and tops in wine for the treatment of dyspepsia | EMA Reports (2011); Zhang et al. (2020) |
| Spain | For symptomatic healing of gastrointestinal problems, including dyspepsia and flatulence | EMA Reports (2011) |
| Cyprus | For constipation, liver detoxification; as antispasmodic, and hypotensive | Zhang et al. (2020) |
| Europe | As a cleaner of blood, it can help with arteriosclerosis, inflammation, as well as constipation, bladder infections, low blood sugar, rheumatoid arthritis, and infections | EMA Reports (2011); Zhang et al. (2020) |
| Britain | To cure conjunctivitis, use as an eye drop | |
| Sicily | To treat imperfections on the skin | |
| North America | As tonic | Le Strange (1977); Zhang et al. (2020) |
| Turkey | Against gallbladder diseases, as a blood purifier, and diuretic | Sarı et al. (2010); Demirezer et al. (2017) |

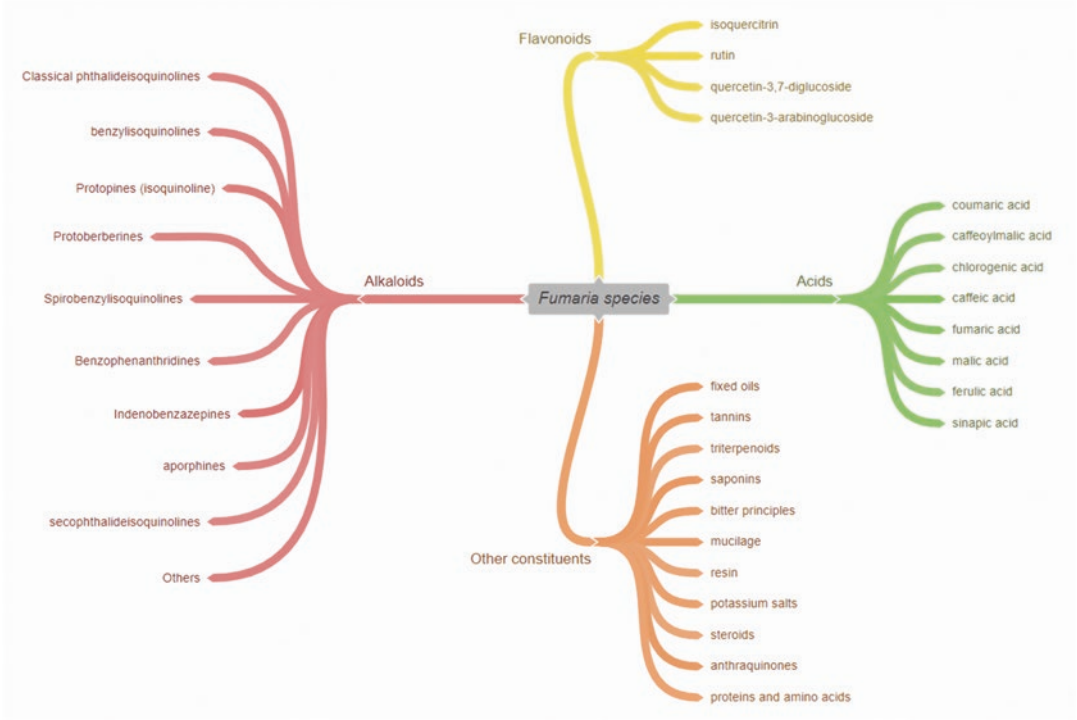


**Fig. 20.1** Constituents of *Fumaria* species

**Table 20.2** Chemical components of *Fumaria officinalis*

| Secondary metabolite group | Chemical components | Reference |
|---|---|---|
| Alkaloids | Protopines: Protopine (fumarine), cryptopine (cryptocavine) | Manske (1938); Hermansson and Sandberg (1973); Sener (1985); Soušek et al. (1999); Suau et al. (2002) |
| | Protoberberines: Aurotensine, stylopine, N-methylstylopine, scoulerine, sinactine, N-methylsinactine, coptisine, and others | MacLean et al. (1969); Mardirossian et al. (1983); Soušek et al. (1999); Seger et al. (2004) |
| | Spirobenzylisoquinolines: Fumaritine, fumaritine N-oxide, fumaricine, fumarilicine (parfumine), fumariline, dihydrofumariline, fumarophycine, O-methylfumarophycine, fumaranine, fumarostrejdine, and others | Saunders et al. (1968); MacLean et al. (1969); Murav'eva et al. (1974); Mardirossian et al. (1983); Soušek et al. (1999); Suau et al. (2002); Chlebek et al. (2016) |
| | Benzophenanthridines: Sanguinarine, dihydrosanguinarine, and corydamine | Forgacs et al. (1986); Suau et al. (2002); Seger et al. (2004); Sturm et al. (2006) |
| | Indenobenzazepines: Fumaritrididine, fumaritridine, fumaritrine, fumarofine (fumarostelline), bulgaramine | Preisner and Shamma (1980); Kiriakov et al. (1980); Blaskó et al. (1981); Forgacs et al. (1982); Mardirossian et al. (1983); Yakimov et al. (1984); Forgacs et al. (1986) |
| | Others: Adlumine, N-methylhydrastine, adlumidiceine, adlumiceine, corytuberine, | Mardirossian et al. (1983); Soušek et al. (1999); Seger et al. (2004); Sturm et al. (2006) |
| Flavonoids | Quercitrin, isoquercitrin, rutin, quercetin 3,7-diglucoside, quercetin 3-arabinoglucoside, and their aglycones | Torck et al. (1971); Massa et al. (1971); Păltinean et al. (2017) |
| Phenolic acids | Chlorogenic, caffeic, fumaric, malic, caffeoylmalic, coumaric, sinapic, ferulic, S-hydroxybenzoic, protocatechuic acids, and other aliphatic acids | Massa et al. (1971); Hahn and Nahrstedt (1993); Boegge et al. (1995); Soušek et al. (1999); Ivanov et al. (2014) |
| Other components | Bitter principles, terpenoids, polysaccharides (mucilage), resin from latex, carbohydrates, phytosterols, protein derivatives, saponins, fixed oils, tannins, and potassium salts | Barnes et al. (2007); Al-Snafi (2020) |

## 20.5 Scientific Evidences

*F. officinalis* was known to have most abundant bioactive alkaloids having several medicinal properties, such as antibacterial (Preininger 1975), hypotensive, bradycardic, sedative (Goetz et al. 2009), antispasmodic (Hiller et al. 1998), cytotoxic (Saglam and Arar 2003), choleretic (Bisset and Wichtl 2001), amphocholytic (Fiegel 1971), antiacetyl- and butyryl-cholinesterase (Chlebek et al. 2016) effects, as well as depressive effect of the nervous system (Kumar et al. 1986). The extracts of *F. officinalis* were investigated on antimicrobial (Dulger and Gonuz 2004; Sengul et al. 2009), amphocholeretic, antispasmodic, laxative (Boucard and Laubenheimer 1966; Reynier et al. 1977a; Lagrange and Aurousseau 1973), antiallergic and choleretic activity (Zacharewicz et al. 1979; Boucard and Laubenheimer 1966; Denden et al. 2010), hepatoprotective, analgesic (Sharma et al. 2012; Sharma et al. 2014), antiacetylcholinesterase (Vrancheva et al. 2016), antioxidant (Sengul et al. 2009; Ivanov et al. 2014), antidiabetic (Goodarzi et al. 2013), and cytotoxic (Erdoğan 2018) activities, as listed in Table 20.4.

**Table 20.3** Posology and administration of *F. officinalis*

| Usage | Preparation and Daily Dosage | Reference |
|---|---|---|
| Oral | An infusion is taken 30 minutes before meals; 2–3 g drug are mixed with boiling water and after 20 minutes are filtered. (6 g drug/daily) | Gruenwald et al. (2007) |
| | Juice is prepared by pressed (cold or hot infusion); 2–3 teaspoons/daily (2.4 to 3.5 g drug) | |
| | Grated fresh plant; 1 teaspoon-3 times/daily | |
| Oral and parenteral | Homeopathic medicine:<br>Acute; 5 drops, 1 tablet or 10 globules every 30–60 minutes.<br>Chronic; 1–3 times/daily (oral)<br>Acute; 1–2 ml sc, 3 times/daily. Chronic: 1/daily (parenterally) | |
| Oral | An infusion; herb 2–4 g, 3 times/daily | Barnes et al. (2007) |
| | Extract with ethanol (25%), liquid extract (1:1);<br>2–4 mL, 3 times/daily | |
| | Extract with ethanol (45%), tincture (1:5);<br>1–4 mL, 3 times/daily | |
| Oral | Herbal tea (infusion) is taken 30 min before meals; 2 g of the comminuted herbal substance in 250 ml of boiling water. (1–2 times daily, 2–4 g daily dose) | EMA Monographs (2011); EMA Reports (2011); |
| | Powdered herbal substance; 220 mg/single<br>(up to 1100 mg/daily) | |
| | Extract with water, dry extract (3.5–4.5:1);<br>250 mg/single (up to 4 times/daily) | |
| | Extract with ethanol (25% V/V), liquid extract (1:1) before meals;<br>0.5–2 ml/single (2–4 ml/daily) | |
| | Tincture (1:5) with ethanol (45% V/V) is taken before meals;<br>0.5–1 ml/single (1–4 ml/daily) | |
| | Juice of the fresh plant;<br>Daily dose: 3.5–4 g<br>The use in children and adolescents under 18 | |
| Oral | 4–6 g of the drug as an aqueous dry extract | ESCOP Monographs (2018) |
| | Infusion; other equivalent preparations, e.g. extract with ethanol (25% V/V), liquid (1:1); extract with ethanol (45% V/V), tincture (1:5) | |

**Table 20.4** The detailed investigation on bioactivity of *Fumaria officinalis*

| Experiments | Activity/Effect | Extract/Constituents | Reference |
|---|---|---|---|
| **In vitro** | Effects on smooth muscle; in isolated rabbit jejunum and in isolated rat duodenum | An alkaloid-rich dry extract | Reynier et al. (1977a) |
| | Effects on smooth muscle; on isolated bile duct and Oddi's sphincter from pigs | An aqueous dry extract | Kimura and Matsui (1973) |
| | Neuroprotective effects; the inhibition of acetyl- and butyryl-cholinesterase, propyl oligopeptidase | An alkaloid-rich extract (ethyl acetate), and the isolated alkaloids parfumidine and sinactine | Chlebek et al. (2016) |
| | Neuroprotective effects; the inhibition of acetylcholinesterase | An alkaloid-rich extract (ethanol) | Vrancheva et al. (2016) |
| | Antioxidant activity; DPPH, ABTS, FRAP, and CUPRAC | Ethanolic extract (70%) | Ivanov et al. (2014) |
| | Antioxidant potency; total phenolic content (TPC), total Flavonoid content (TFC) and total phenolic acid content (TPAC), ABTS scavenging activity, and by *Saccharomyces cerevisiae* cell assays | Decoction | Chanaj-Kaczmarek et al. (2015) |
| | Antioxidant activities; DPPH and ABTS methods, TPC, TFC | Extracts with petroleum<br>Ether, ethyl acetate, chloroform, and methanol | Edziri et al. (2020) |
| | Antioxidant activitiy by DPPH | Extracts with n-hexane, chloroform, methanol, and water | Fatima et al. (2019) |
| | Antioxidant activities; ABTS assay using Trolox equivalents (TEAC) and electron spin resonance (EPR) spectrometry, TPC, TFC, total hydroxycinnamic content (THC) | An ethanolic extract (70%) | Păltinean et al. (2017) |
| | Antioxidant activity; β-carotene-linoleic acid assay, TPC | Methanol, and aqueous extracts | Sengul et al. (2009) |
| | Antioxidant activity; DPPH and ABTS, total antioxidant capacity, lipid peroxidation inhibition, and ferric reduction | Ethanolic extract (95%) | Khamtache-Abderrahim et al. (2016) |
| | Antibacterial activity | | |
| | Antimicrobial activity | Methanol, and aqueous extracts | Sengul et al. (2009) |
| | Antimicrobial activity | Silver nanoparticles using aqueous extract | Elumalai and Velmurugan (2015) |
| | Antimicrobial activity | An ethanolic extract (80%) | Dulger and Gonuz (2004) |
| | *Agrobacterium tumefaciens*-induced potato disk tumour assay | An aqueous extract | Pehlivan Karakaş et al. (2012) |
| | Cytotoxicity and apoptosis induction in Leukemia and multiple myeloma cell lines | A methanol extract giving hexane, chloroform, ethyl acetate, and butanol | Adham et al. (2021) |
| | Cytotoxic activity of extracts on FaDu, SCC-25, MCF-7, and MDA-MB-231 cancer cell lines | An ethanol extract | Petruczynik et al. (2019) |
| | Cytotoxicity by brine shrimp lethality bioassay | Extracts with n-hexane,<br>Ethyl acetate, ethanol, methanol, and aqueous (infusion) | Erdoğan (2018) |

(continued)

**Table 20.4** (continued)

| Experiments | Activity/Effect | Extract/Constituents | Reference |
|---|---|---|---|
| | Expression of CYP1A enzymes in human hepatocytes And HepG2 cells | Protopine and allocryptopine | Vrba et al. (2011) |
| | Alpha-amylase inhibitory activity | Extracts with n-hexane, chloroform, methanol, and water | Fatima et al. (2019) |
| | Toxic and genotoxic activity; neutral red uptake test, the Vitotox test, and the alkaline comet assay | Extracts with petroleum Ether, ethyl acetate, chloroform, and methanol | Edziri et al. (2020) |
| | Anticoagulant activity; prothrombin time (PT) test, and activated partial thromboplastin time (aPTT) test | Extracts with petroleum Ether, ethyl acetate, chloroform, and methanol | Edziri et al. (2020) |
| | Anthelmintic activity | Methanol, and aqueous extracts | Váradyová et al. (2018) |
| | Trematocidal effects | A methanol extract | Ferreira et al. (2011) |
| | Against hepatitis B infection | Isoquinoline alkaloids isolated from plants | Aljofan et al. (2014) |
| | Hepatoprotective effects in hepatocytes | Methanol extract, and phenolic fraction, as well as the isolated alkaloids, such as Protopine, cryptopine, and parfumine | Táborská et al. (1996) |

| Experiments | Activity/Effect | Extract/Constituents | Reference |
|---|---|---|---|
| **In vivo** | Hepatobiliary effects to rats; an increase in bile flow, biliary-excreted bilirubin, and cholesterol | An alkaloid-rich dry extract | Reynier et al. (1977b) |
| | Hepatobiliary effects to rats | An aqueous dry extract | Boucard and Laubenheimer (1966); Boucard et al. (1966) |
| | Hepatobiliary effects to dogs | An aqueous dry extract | Giroux et al. (1966) |
| | Hepatobiliary effects; choleretic activity in rats | An aqueous dry extract | Kimura and Matsui (1973) |
| | Hepatobiliary effects to mice | An aqueous dry extract | Lagrange and Aurousseau (1973) |
| | Hepatoprotective effects to rats | An aqueous dry extract | Guesnier et al. (1974) |
| | Hepatoprotective activity in rats | An ethanolic extract | Sharma et al. (2012) |
| | Cardiac effects to mice | Fumitory alkaloids | Gorbunov et al. (1977) |
| | Cardiac effects to dog | Fumitory alkaloids | Gorbunov et al. (1980) |
| | Diuretic activities in rats | An ethanolic extract (70%) | Păltinean et al. (2017) |
| | Neuropharmacological activities in mice (analgesic effect) | An ethanolic extract | Sharma et al. (2014) |
| | Neuropharmacological activity in mice on muscle relaxation and motor coordination | An ethanolic extract | Sharma et al. (2015) |
| | Haematological activity in rabbits | Hydroethanolic extract (70% ethanol) | Khoshvaghti et al. (2014) |
| | The quantities of blood urea nitrogen (BUN) and creatinine were determined by enzyme-mediated methods in rabbits | Hydroethanolic extract | Khoshvaghti et al. (2013) |
| | Wound healing activity in induced hypertrophic scar of rabbits | Ethanol extract (90%), and phytosterol fraction | Noori and Abu-Raghif (2019) |
| | Antidiabetic effects in type 2 diabetic rats | An aqueous extracts (10%) | Goodarzi et al. (2013) |
| | Antidiabetic activity against Alloxan induced diabetes, and Oral glucose tolerance test (OGTT) in normoglycemic Rats | Extracts with methanol and water | Fatima et al. (2019) |
| | Antineuropathic and anti-inflammatory potentials in mice; acute, subchronic, and chronic alloxan-induced diabetes and diabetic-neuropathy, and carrageenan-induced acute Inflammatory-pain and chronic-inflammatory edema. | Standardized ethanol extract (80%), alkaloid-rich Fraction, niosome formulations, Stylopine, Sanguinarine | Raafat and El-Zahaby (2020) |
| | Protective effects against the testicular toxicity of Fluoxetine in rat | Ethanol extract (70%) | Sharef et al. (2020) |
| | Immunosuppressive and antioxidant activity in rats | Ethanol extract | Wasu and Muley (2009) |

## 20.6 Clinical Studies

At the start of the new millennium, contraindications, potential risks, or adverse effects of fumitory with the standard application of prescribed therapeutic medications were not well known (Gruenwald et al. 2007; Barnes et al. 2007). However, in cases of hypersensitivity to the active substances, and gallstones, cholangitis, biliary obstruction, as well as any other biliary diseases and hepatitis fumitory should not be used without medical advice by doctor (EMA Monographs 2011; ESCOP Monographs 2018). According to animal experiments, it was shown that hypotensive effects, haematological alterations, and renal function parameters variations can be observed. It is unknown whether fumitory is safe to use during pregnancy or lactation. Due to the absence of pharmacological and toxicity proof, fumitory should not be used throughout pregnancy or lactation (Hoffmann 1996). The clinical reports and pharmacological studies in humans were presented in Table 20.5.

## 20.7 Toxicological Studies

According to the literature, the $LD_{50}$ limit value of the ethanol extract from *F. officinalis* leaves was 2000 mg/kg body weight in an acute toxicity analysis. (Sharma et al. 2015). The acute intraperitoneal $LD_{50}$ of an aqueous dry extract of *F. officinalis* was detected as 1.91 g/kg in mice; 1.88 g/kg in rats for single dose toxicity. Repeated dose toxicity of an aqueous dry extract (2.4 g/kg/day) following 3 months of oral treatment in rats caused no delayed progress, differences in major organs, or anomalies in the blood (Cahen et al. 1964). In a study on kidney functions of rabbits for the hydroethanolic extract of *F. officinalis*, substantial increases in BUN and serum creatinine levels in small doses are observed, whereas decreases in BUN and increases in serum creatinine levels were reported in high doses (Khoshvaghti et al. 2013). In addition, haematological study on the hydroethanolic extract of *F. Officinalis* reported remarkable declines in complete blood count test including packed cell volume (PCV), haemoglobin (Hb), mean corpuscular volume (MCV), red blood cell (RBC), total white blood cells (WBC), and neutrophil ratios, as well as increases in lymphocyte, eosinophil, and monocyte percentages (Khoshvaghti et al. 2014). Another study demonstrated that $LC_{50}$ value of *n*-hexane extract of *F. officinalis* was <1000 μg/mL, whereas the aqueous extract had no cytotoxicity (Erdoğan 2018).

As for clinically safety, over 500 people have taken part in experimental trials with *F. officinalis* aqueous dry extracts for up to 6 months at doses ranging from 750 to 1500 mg daily. It was explained that the treatments were very well tolerated, and in a small number of cases, minor side effects such as gastrointestinal complaints and/or an allergic response with pruritis occurred (ESCOP Monographs 2018).

## 20.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies

*F. officinalis* has mostly been investigated in terms of biological activities of the extracts obtained from different parts of the plant with organic solvents such as petroleum ether, ethyl acetate, chloroform and methanol, as well as ethanol, and water. In addition, there are several herbal products including the extracts or herbal substances of *F. officinalis* as single and in combinations with other plant materials for the relief of colicky symptoms in various digestive and biliary system disorders in the markets of France, Spain, and Austria. *F. officinalis* is also sold as an herbal tea in Germany (Zhang et al. 2020; Al-Snafi 2020; EMA Reports 2011). According to EMA, *F. officinalis* has been used by mouth as herbal preparations in European market and has been served in the form of solid or liquid with comminuted plant materials as herbal tea, and powdered plant materials, as well as dry water extract (3.5–5:1) at least 30 years. Moreover, the herbal medicines of the plant extracts, such as liquid ethanol extract (1:1, 25% V/V), and tincture with ethanol (1:5, 45% V/V), as well as juice

**Table 20.5** The clinical evaluation on bioactivity of *Fumaria officinalis*

| Experiments | Treatment Group for Clinical study | Extract/Constituents | Reference |
|---|---|---|---|
| ***Clinical study*** | Various biliary disorders including dyskinesia, cholecystitis, and post-cholecystectomy syndrome | An aqueous dry extract | Zacharewicz et al. (1979) |
| | Biliary disorders of various origin (dyskinesia, hepatomegaly, gallstone complaints, and post-cholecystectomy symptoms) | An aqueous dry extract | Fiegel (1971) |
| | Biliary dyskinesia, biliary lithiasis, migraine (frequently Associated with concomitant nausea or vomiting), Hepatobiliary insufficiency, post-cholecystectomy Symptoms, and jaundice following viral hepatitis | An aqueous dry extract | Fablet et al. (1963); Colson and Jauneau (1967); Roux (1977); Warembourg and Ducloux (1967); Dornier (1968) |
| | Amphocholeretic effects; diarrhoea or chronic constipation of biliary origin | An aqueous dry extract | Roux (1977) |
| | Effect on irritable bowel syndrome (IBS); 1500 mg daily and placebo (3 times a day, 18 weeks), IBS-related pain, and distension | Herbal remedy | Brinkhaus et al. (2005) |
| ***In human pharmacological studies*** | Amphocholeretic effect;after choledochostomy in 25 patients, a single dose (1500 mg, oral) | An aqueous dry extract | Salembier (1967) |
| | Amphocholeretic effect; to 20 post-choledochostomy patients for an average of 12 days, oral (4 × 250 mg, daily) | An aqueous dry extract | Devin and Villani (1969) |
| | Amphocholeretic effect; in 20 healthy volunteers, 500 mg (in physiological serum) by an intraduodenal probe | An aqueous dry extract | Heully et al. (1969) |

of the fresh plant have been shown for more than 30 years in many literature providing the consistent knowledge with the traditional usage (Gruenwald et al. 2007; Goetz et al. 2009; EMA Reports 2011). Monograph and List Working Party (MLWP)- Committee on Herbal Medicinal Products (HMPC) has approved the traditional medicinal usage of *F. officinalis* as enhancing bile flow for the cure of indigestion complaints such as fullness, bloating, and poor digestion (EMA Reports 2011). Herbal medicines of *F. officinalis* were presented in Table 20.6 below.

## 20.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

*F. officinalis*, also known as fumitory, is a medicinal plant that has long been used in traditional medicine for the treatment of digestive complaints and liver diseases, as well as dermatological problems in a lot of different countries. There are many herbal products on the market that include *F. officinalis* extracts or substances as single or in combinations with other medicinal plants for the relief of colicky symptoms in various digestive and biliary system disorders. It was recorded as an approved usage of traditional herbal medicine to increase bile flow and treat indigestion symptoms including fullness, bloating, and weak digestion without safety problems. There were no high gap between ethnomedicinal and scientific and clinical evidences.

## 20.10 Challenges and Future Recommendations as Potential Drug Candidate

In the previous studies on *F. officinalis,* it was shown that the plant extracts had antioxidant, antimicrobial, amphocholeretic, hepatoprotective,

**Table 20.6** Preparations of *Fumaria officinalis*

| | Country | Product name | Reference |
|---|---|---|---|
| Multi-ingredient preparations | Hungary | Hepabene | Barnes et al. (2007); Goetz et al. (2009) |
| | Germany | Lymphomyosot | |
| | Austria | Hepabene; Oddispasmol | |
| | Czech Republic | Hepabene | |
| | France | Actibil; Bolcitol; Depuratif Parnel; Depuratum; Schoum; Phytelia digestion; Azema; Boribel nº 7 biliaire; Boribel nº 10 depurative; tisane de sante | |
| | Italy | Soluzione Schoum | |
| | Russia | Hepabene (Гепабене) | |
| | Spain | Natusor Hepavesical; Odisor; Solucion Schoum | |
| | UK | Echinacea; skin cleansing | |
| Single-ingredient preparations | Austria | Bilobene; Oddibil | |
| | Germany | Bilobene | |
| | Hungary | Bilobene | |
| | Brazil | Oddibil | |
| | France | Oddibil; Elusanes fumeterre; Septiline | |

analgesic, cytotoxic, antidiabetic, neuroprotective, cardiac effects, etc. It was also revealed that the plant has medicinal properties due to the major components, isoquinoline alkaloids and polyphenols. A survey of literature shows that although the plant is also used for cutaneous symptoms, constipation, hypertension, bladder infections, conjunctivitis, and infections as well as a diuretic, sedative, and laxative, there is no enough experimental evidence. It is concluded that there is still a need to conduct biological tests and clinical trials for confirming the traditional uses of *F. officinalis*. Moreover, it is suggested that more investigation on the usage of the plant to specific group, children, and old people, as well as during pregnancy and lactation, is needed.

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# *Helichrysum plicatum* DC.

# 21

Erkan Yılmaz

**Abstract**

*Helichrysum* genus, known as everlasting flowers or immortelles worlwide, is a member of the Asteraceae family represented by about 600 species over the world. *Helichrysum plicatum* DC., which is part of this genus, is an important figure in Turkey, Balkan Penunsula, and Iran because it is traditionally used for treatment of many diseases, especially diabetes, kidney stone, jaundice, and wounds. It is of great importance for Turkey due to hosting four subspecies of *Helichrysum plicatum* DC., which are *Helichrysum plicatum* DC. subsp. *plicatum* DC., *Helichrysum plicatum* DC. subsp. *pseudoplicatum* (Nab.) Davis & Kubicha, *Helichrysum plicatum* DC. subsp. *polyphyllum* (Lebed) Davis & Kubicha, and *Helichrysum plicatum* DC. subsp. *isauricum* Parolly. Flavonoids, pyrones, phloroglucinols, terpenoid, phtalides, and phenolic acids were detected in *Helichrysum plicatum* with a small number of studies. Likewise, monoterpenes, fatty acids, and sesquiterpenes were found in essential oil with limited number of phytochemical investigations. In recent year, the several pharmacological activities such as antioxidant, antimicrobial, antifungal, antiinflammaory, antidiabetic, antiurolithiatic, insecticidal, and anticancer activity have been confirmed by researchers. In this chapter, it is aimed that its traditional uses, phytochemistry and pharmacological properties of *Helichrysum plicatum* until date will be summarized and highlighted to explore the gaps and to contribute to future potential.

**Keywords**

*Helichrysum plicatum* · Asteraceae · *Helichrysum plicatum* subsp. *polyphyllum* · *Helichrysum plicatum* subsp. *plicatum* · *Helichrysum plicatum* subsp. *isauricum* · *Helichrysum plicatum* subsp. *pseudoplicatum* · Pharmacognosy · Phytoconstituents · Ethnopharmacology

## 21.1 Introduction

*Helichrysum plicatum* is part of the habitat in Turkey, Balkan Penunsula, and Iran (Davis and Kupicha 1975; Erik 2000; Bigović et al. 2017). In Turkey, *Helichrysum* genus is represented by 24 species and 30 taxa, 17 of these are endemic to Turkey. Flora of Turkey hosts four subspecies of *H. plicatum*. These are *H. plicatum* subsp. *plicatum*, *H. plicatum* subsp. *pseudoplicatum, H. plicatum* subsp. *polyphyllum,* and *H. plicatum* subsp. *isauricum*. *H. plicatum* subsp. *isauricum*

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is endemic to Turkey (Aksoy 2012). There are many vencular names in Turkey. Amel otu (Özdemir and Alpinar 2015), Sarılık çiçeği (Fujita et al. 1995), Yayla çiçeği (Fujita et al. 1995; Yeşilada et al. 1995; Özdemir and Alpinar 2015), Sesum (Polat et al. 2013; Karakaya et al. 2019; Polat 2019), Şahkak (Tetik et al. 2013), Altın çiçeği (Karaman and Kocabaş 2001; Tetik et al. 2013; Mükemre et al. 2015), Altın otu (Özdemir and Alpinar 2015; Sargin 2015), Sarıbaş (Özdemir and Alpinar 2015), Arı çiçeği (Yeşilada et al. 1995), Yılan çiçeği (Yeşilada et al. 1995), Sarı çiçek (Yeşilada et al. 1995), Yayla gülü (Yeşilada et al. 1995), Sevgül (Yeşilada et al. 1995), Herdemtaze (Sezik et al. 1991), Herdemgüzel (Sezik et al. 1991), and Bozoğlan (Yeşilada et al. 1993) are the names used for *H. plicatum*. Yayla çiçeği (Fujita et al. 1995; Sezik et al. 2001; Korkmaz and Karakurt 2015; Mart and Türkmen 2018), Ölmez otu (Mart and Türkmen 2018), Ölmez ot (Dalar et al. 2018), Ölmez sarıçiçek (Güneş and Özhatay 2011), Düvenci çiçeği (Arı et al. 2018), Altın otu (Doğan and Bağcı 2011; Kilic and Bagci 2013; Korkmaz and Karakurt 2015; Arı et al. 2018), Yılan otu (Arı et al. 2018), Mantuvar (Demirci and Özhatay 2012; Güneş et al. 2017), Solmaz çiçek (Cakilcioglu et al. 2010), Gülülga zer (Kaval et al. 2014), Sarı çiçek (Yeşil and Akalin 2009; Özüdoğru et al. 2011), Geyikmisi (Bulut et al. 2017), Ölmez çiçek (Korkmaz and Karakurt 2015), Herdemcan (Dalar 2018), Gündöndü (Tatlı et al. 2009), and Altın çiçeği (Mükemre et al. 2015) are the names used for *H. plicatum* subsp. *plicatum* in Turkey. *H. plicatum* subsp. *polyphyllum* is known by names such as Yayla çiçeği (Mart and Türkmen 2018), Ölmez otu (Mart and Türkmen 2018), Günendi (Honda et al. 1996), Gündoğdu (Honda et al. 1996) and Kaymak çiçeği (Sezik et al. 1997). Herdemcan (Dalar et al. 2018) and Altın çiçeği (Mükemre et al. 2015) are vencular names of *H. plicatum* subsp. *pseudoplicatum* in Turkey. Apart from these, *H. plicatum* is known as Borsillok i verdhë among Albanians and as Свилен among Macedonians (Pieroni et al. 2014).

General morphological properties of ***H. plicatum*** DC. are naturally spread in flora of Turkey; *Helichrysum plicatum* is glandular, subglabrous to lanate-tomentose indumentum. Flowering stems are erect or (rarely) procumbent. Resting buds are absent usually. Basal leaves are linear-oblanceolate; cauline leaves subamplexicaul, linear-oblanceolate to linear. Capitula subglobose to hemispherical. Phyllaries obtuse to acute, ± irregularly and loosely imbricate, yellow or cream (Davis and Kupicha 1975). *H. plicatum* includes four subspecies (subsp. ***isauricum*****,** subsp. ***plicatum*****,** subsp. ***polyphyllum***, subsp. ***pseudoplicatum***) in Flora of Turkey (Davis and Kupicha 1975; Erik 2000). General morphologial properties of subpecies of *Helichrysum plicatum are* as follows;

***Helichrysum plicatum*** DC. subsp. ***plicatum*** DC. (Synonymous: *H. anatolicum* Boiss.) is thinly to densely lanate-tomentose; cauline leaves whitish- or greyish-green, herbaceaus perennial plant. Leaves are villose or rare lanate, in large quantities of capitula. Basal leaves are linear-oblanceolate. Flowers are in capitula. Flower number of capitulum about 5–9. Phyllaries are yellow (Fig. 21.1) (Davis and Kupicha 1975; Elkıran 2012).

***Helichrysum plicatum*** DC. subsp. ***polyphyllum*** (Ledeb.) Davis & Kubicha (Synonymous: *H. polyphillum* Ledeb.) is subglabrous, herbaceaus perennial. Cauline leaves are yellowish green. Phyllaries are yellowish green, leaves villous or sparsely lanatus, plants cluster, upper stem unbranched, capitula numerous, 4–9 mm long, margins of capitulum female, stems and leaves not clearly glandular, solid, branched, woody bodied, stem leaves are 1–20 x 17–70 mm (Fig. 21.2) (Davis and Kupicha 1975; Elkıran 2012).

***Helichrysum plicatum*** DC. subsp. ***pseudoplicatum*** (Nab.) Davis & Kubicha (Synonymous: *H. plicatum* var. *lancetum* Boiss., *H. pseudoplicatum* Nab.) is thinly to densely lanate-tomentose; cauline leaves are whitish- or greyish green. Involucre cream. Generally subglabrous, with straight stems, narrowly linear leaves, and small capitula (4–6 mm) (Davis and Kupicha 1975).

***Helichrysum plicatum*** DC. subsp. ***isauricum*** Parolly is a perennial plant. Stem erect arising from woody caudex, densely hairy with many

**Fig. 21.1** *Helichrysum plicatum* DC. subsp. *pilicatum* DC. in its habitat. (Photo: Ömer Kılıç)

glandular hairs. Rosulate basal leaves, oblong-sparhulate, obtuse, 3-veined. Lower cauline leaves soon wither, narrowly oblong-spathulate, margine undulate; upper cauline leaves are smaller, finally passing over into bracts. Inflorescence corymbose. Involucre broadly campanulate to hemispherical. Pappus yellowish. It is an endemic plant and Mediterranean element (Erik 2000).

There are some taxonomic uncertainties on *H. plicatum* and subspecies (Aksoy et al. 2011; Aksoy 2012; Anonymus 2021). In order to avoid confusion about these taxonomic problems, it was decided to evaluate the plants as mentioned in the publications.

## 21.2 Distribution and Status of Species

*H. plicatum* subsp. *plicatum* is widespread in Anatolia, except in the west part. *H. plicatum* subsp. *polyphillum is* ditributed mainly in South and East Anatolia. However, *H. plicatum* subsp. *pseudoplicatum* grows Southeast part of Anatolia. External distribution of these species includes countries such as Balkans, Lebanon, North Iraq, Iran, and Caucasia (Davis and Kupicha 1975). *H. plicatum* subsp. *isauricum* is an endemic and Mediterranean element. It can only be seen in Karaman and Antalya (Fig. 21.3) (Erik 2000).

**Fig. 21.2** *Helichrysum plicatum* DC. subsp. *polyphyllum* (Ledeb.) Davis et Kubicha in its habitat. (Photo: Ömer Kılıç)

## 21.3 Comparison of Traditional/ Ethnomedicinal/Local Uses

Many ethnopharmacological surveys conducted in different regions in Turkey show that *H. plicatum*, particularly subspecies of it, *H. plicatum* subsp. *plicatum*, have been very important medicinal plant used for hundreds of years (Fujita et al. 1995; Yeşilada et al. 1995; Sezik et al. 2001; Korkmaz and Karakurt 2015; Mükemre et al. 2015; Dalar et al. 2018; Mart and Türkmen 2018; Karakaya et al. 2019). Ethnobotanical uses regarding *H. plicatum* in Turkey with the region where the plant is used, its medicinal uses, plant parts used, type of preparation, and utilization methods are summarized in Tables 21.1 and 21.2. Data collected from these surveys show that the most frequently reported traditional uses are internal as herbal teas for kidney stone (Fujita et al. 1995; Yeşilada et al. 1995; Korkmaz and Karakurt 2015; Mükemre et al. 2015), diabetes (Cakilcioglu et al. 2010; Polat et al. 2013; Mükemre et al. 2015; Dalar et al. 2018), and diuretic (Özüdoğru et al. 2011; Sargin 2015; Mart and Türkmen 2018) and externally against wounds (Sezik et al. 1991; Fujita et al. 1995; Sezik et al. 2001). Another important usage among the public is jaundice. Internal (Fujita et al. 1995; Yeşilada et al. 1995) and external usage (Korkmaz and Karakurt 2015; Karakaya et al. 2019) for this purpose are encountered in different regions of Turkey. *H. plicatum* subsp. *plicatum* is added to bath water to treat jaundice in babies (Korkmaz and Karakurt 2015). As well as being medicinally valuable species, they are used as ornamental plants in the home due to the everlasting flowers (Mart and Türkmen 2018). Based on these data, the mostly used plant parts of *H. plicatum* are the flowers and aerial parts (Yeşilada et al. 1995; Kilic and Bagci 2013; Kaval et al. 2014; Polat 2019). Flowers and herbs of *H. plicatum* are used to keep a snake away from house by putting under the bed (Yeşilada et al. 1995). Plenty of capitula of *H. plicatum* subsp. *plicatum* collected are kept in home and stable so as to prevent nearing snake and scorpions (Arı et al. 2018). The common modes of preparation of these species are infusion and decoction internally (Yeşilada et al. 1995; Sezik et al. 2001; Özüdoğru et al. 2011; Polat 2019). Administration of inhalation for earache in baby was reported only by Demirci and Özhatay (2012). There are a few ethnobotanical data other than Turkey. In the neighbouring country, Azerbaijan (Nakhchivan), *H. plicatum* is used for

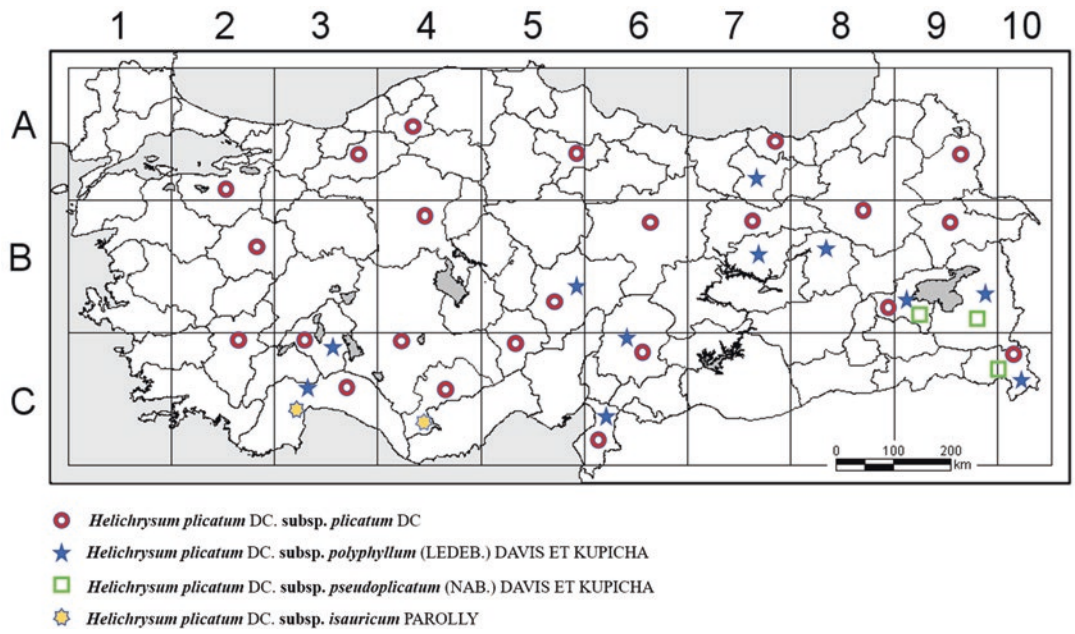


**Fig. 21.3** Geographical distribution of *H. pilicatum* subsp. *pilicatum, H. pilicatum* subsp. *polyphyllum, H. pilicatum* subsp. *pseudoplicatum,* and *H. pilicatum* subsp. *isauricum* in Turkey (Davis and Kupicha 1975; Erik 2000)

digestive (Ozturk et al. 2018), and in another neighbouring country, Georgia, the tea prepared from *H. plicatum* is widely used to decrease high blood pressure and treat kidney-related ailments (Kazancı et al. 2020). Infusion of flowering aerial parts *H. plicatum* which is well known in the local Macedonian folk medicine is used for stomachaches, as a digestive, appetizing, cardiotonic, anti-diarrheal, diuretic, and anti-moths (Pieroni et al. 2014).

## 21.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques

Phytochemistry of *H. plicatum*, especially collected from Turkey and Balkan peninsula including Macedonia, Albania, and Serbia, were carried out (Kulevanova et al. 2000; Demir et al. 2009; Bigović et al. 2011; Öztürk et al. 2014; Bigović et al. 2017; Acet et al. 2020; Aydin 2020; Vujić et al. 2020). *H. plicatum* and subspecies are the rich source of phenolic compounds including flavonoids and phenolic acids (Kulevanova et al. 2000; Albayrak et al. 2010b; Kolaylı et al. 2010; Acet et al. 2020; Aydin 2020; Vujić et al. 2020). Essential oil studies on these species exist, but are limited (Sezik and Aslan 1997; Öztürk et al. 2014). Compounds which are isolated or identified from extracts and essential oil of these plants are summarized in Table 21.3. The presence of flavonoids, such as apigenin, luteolin, and naringenin, and phenolic acids such as chlorogenic acid and caffeic acid are widespread (Kulevanova et al. 2000; Albayrak et al. 2010a, b; Bigović et al. 2011; Vujić et al. 2020). 2R-enantiomer and 2R, S-enantiomers of naringenin-5-β-D-glucoside which were called helichrysin A and helichrysin B, respectively, were isolated from *H. plicatum* subsp. *plicatum* (Demir et al. 2009; Akbaş et al. 2016; Aydin 2020). The most comprehensive study done so far was conducted by Vujić et al. (2020). In this study, 142 compounds were identified in the aerial parts of *H. plicatum*. A wide variety of secondary metabolites, including terpenoids and numerous (poly)phenolic compounds, phenolic acids, flavonoids, pyrones, phthalides, phloroglucinols, acetophenones, and

**Table 21.1** Ethnobotanical uses regarding *Helichrysum pilicatum, Helichrysum pilicatum* subsp. *polyphyllum,* and *Helichrysum pilicatum* subsp. *pseudoplicatum* in Turkey with region, their medicinal uses, plant parts used, type of preparation, and utilization methods

| Region | Medicinal uses | Plant part | Preparation/ Utilization method | References |
|---|---|---|---|---|
| ***Helichrysum pilicatum*** | | | | |
| **Amasya** | Kidney stone<br>Wounds | Flowers<br>Herbs | Infusion/internal<br>Burned/Ash is applied on wounds | (Fujita et al. 1995) |
| **Bilecik (Söğüt)** | Jaundice | Flowers | Decoction/internal | (Fujita et al. 1995) |
| **Bingöl** | Diabetes, hepatitis, kidney stones | Flowers | Infusion/drinking one tea glass before meal | (Polat 2019) |
| **Bingöl (Solhan)** | Diabetes, hepatits, kidney stone | Flowers | Infusion/drinking one tea glass before meal | (Polat et al. 2013) |
| **Erzurum (south part)** | Kidney stone<br>Wounds, scar<br>Hemostatic<br>Constipation<br>Jaundice in babies | Capitulum<br>Leaves, capitulum<br>Leaves, capitulum<br>Leaves<br>Capitulum | Infusion/internal<br>Crushing and mixing with olive oil/external<br>Decoction/external<br>Raw/internal<br>Decoction/external | (Karakaya et al. 2019) |
| **Gümüşhane (Şiran)** | Wounds, burns | Flowers | Infusion/external | (Sezik et al. 1991) |
| **Iğdır** | Digestive | – | – | (Ozturk et al. 2018) |
| **Isparta (Sütçüler)** | Kidney stone | Flowers | Infusion/internal | (Yeşilada et al. 1995) |
| **Kahramanmaraş** | Urinary dysfunction, antifungal | Flowers | – | (Karaman and Kocabaş 2001) |
| **Karaman (Sarıvelliler)** | Jaundice | Flowers + herbs | Decoction/internal | (Yeşilada et al. 1995) |
| **Karaman (Sarıvelliler and Ermenek)** | To keep a snake away from house | Flowers + herbs | Putting under the bed | (Yeşilada et al. 1995) |
| **Malatya** | Wounds | Flowers | Pomade/external | (Tetik et al. 2013) |
| **Mersin (Bozyazı)** | Nephralgia, kidney stones, diuretic, pleasure, medicinal tea | Flowering branches, aerial parts (with/without flower) | Infusion, leaf powder, spice/drinking a teacup 3 times a day for 3–4 weeks | (Sargin 2015) |
| **Mersin (Erdemli)** | Kidney stone or sand | Flowers | Decoction/internal | (Yeşilada et al. 1993) |
| **Nigde (Aladağlar)** | Abdominal pain, diabetes, kidney stones, diarrhea, stomach ache | Aerial parts | Infusion/internal | (Özdemir and Alpinar 2015) |
| **Osmaniye** | Dysurea | Flowers + herbs | Infusion/internal | (Yeşilada et al. 1995) |
| ***Helichrysum pilicatum*** subsp. ***polyphyllum*** | | | | |
| **Afyonkarahisar (Şuhut)** | Stomachache | Flowers | Infusion/internal | (Honda et al. 1996) |
| **Ardahan (Ölçek)** | Diarrhoea, intestinal diseases | Flowers | Decoction/drinking one glass daily for 2–3 days | (Sezik et al. 1997) |
| **Osmaniye (Bahçe and Hasanbeyli districts)** | Diuretic, bile secretion | Flowers | Infusion | (Mart and Türkmen 2018) |

(continued)

**Table 21.1** (continued)

| Region | Medicinal uses | Plant part | Preparation/ Utilization method | References |
|---|---|---|---|---|
| ***Helichrysum pilicatum*** subsp**. *pseudoplicatum*** | | | | |
| **Ağrı** | Diabetes | Leaves, flowers | Infusion/ drinking one tea glass in the evening | (Dalar et al. 2018) |
| **Van (Çatak)** | Diabetes, cholesterol, kidney stone | Aerial parts | Decoction/drinking one glass before meal in the morning | (Mükemre et al. 2015) |

other phenolic derivatives have been detected in this research. In a study on essential oils, *H. plicatum* subsp. *polyphyllum*, *H. plicatum* subsp. *İsauricum,* and *H. plicatum* subsp. *plicatum* were investigated and 199 compounds were identified. The fatty acids and their esters were detected as main compounds of aerial parts. The inflorescences of *Helichrysum* subspecies displayed richness in monoterpenes, fatty acids, and sesquiterpenes. Fenchene (88.3%), a monoterpen hydrocarbon, was noted as the main component found in essential oil of *H. plicatum* subsp. *isauricum* inflorescences (Ozturk et al. 2018).

## 21.5 Scientific Evidences: Pharmacological Activities

### 21.5.1 Antioxidant Activity

The antioxidant potential of the different extracts derived from *H. plicatum* flowers, stems, and leaves was evaluated by using different model systems including inhibition of DPPH radical (1,1-diphenyl-2-picrylhydrazyl), protection of β-carotene-linoleic acid, and inhibition of hydroxyl radicals. BHA, BHT, luteolin, quercetin, and sylimarin were used as reference. Although the methanol extract obtained from the leaves displayed the highest inhibition, it was found to show lower inhibition than the reference substances. All extracts of *H. plicatum* were found to inhibit the production of $OH^{\bullet}$ radicals. The ethyl acetate extract hydrolysis with HCI derived from leaves and stems was found to exhibit higher inhibition than all reference substances, including BHT. Methanol extract derived from flowers possessed the highest value, but it did not show as high a value as BHA in terms of the inhibitory activity on β-carotene bleaching. Its extracts were found to exhibit potent hydroxyl radical scavenging, free radical scavenging, and antioxidant activity in vitro (Panovska and Kulevanova 2005). In a different study investigating antioxidant potential of *H. plicatum*, aerial parts collected at the full blooming stage were extracted separately with different solvents. Ethanol, dichloromethane, and acetonitrile extracts were found to have notable DPPH scavenging activity. The dichloromethane extract was detected to show higher antioxidant potential than BHT, while ethanol extract was found to exhibit slightly lower activity than Trolox and BHT (Vujić et al. 2020). In other research, the antioxidant properties of ethyl acetate, methanol, and ethanol extracts derived from stem, flower, and root parts of *H. plicatum* subsp. *plicatum* were determined by using ABTS and DPPH assays. In ABTS assay, the highest activity was detected in the ethyl acetate extract of stem parts (IC50 = 31.6 μg/mL). Moreover, in DPPH assay, the highest activity was observed in the ethanol extract of the flower parts (IC50 = 234.8 μg/mL) (Acet et al. 2020). In different study conducted by Tatlı et al. (2009), assessing the antioxidant activities of methanol extract derived from aerial parts of *H. plicatum* subsp. *plicatum,* the extract displayed radical scavenging activity dose-dependently against DPPH with ED50 (39.0 mg/L) and the reference compound (7.4 mg/L) as chlorogenic acid. The extract had strong antioxidant and scavenging activities studied in a cell-free system versus $O2^{\bullet-}$ and $H_2O_2$, ED50 varying from 305.2 mg/L to 301.6 mg/L against $O2^{\bullet-}$ and H2O2, respectively. it also inhibited $Cu^{2+}$-induced LDL oxidation dose-dependently with ED50

**Table 21.2** Ethnobotanical uses regarding *Helichrysum pilicatum* subsp. *plicatum* in Turkey with region, its medicinal uses, plant parts used, type of preparation, and utilization methods

| Region | Medicinal uses | Plant part | Preparation/ Utilization method | References |
|---|---|---|---|---|
| ***Helichrysum plicatum*** subsp**. *plicatum*** | | | | |
| **Adana (Karaisalı)** | Cholesterol, cancer | Flowers | Infusion/drinking one glass after meal | (Güneş et al. 2017) |
| **Antalya** | Preventing nearing snake and scorpions | Capitulum | Placed into home | (Arı et al. 2018) |
| **Ağrı** | Kidney pains, cholesterol, diabetes | Flowers, leaves | Decoction, infusion/ drinking one glass before meal in the morning; drinking one teacup after meal | (Dalar et al. 2018) |
| **Denizli (Acipayam)** | Urinary system diseases | Aerial parts | Infusion/internal | (Bulut et al. 2017) |
| **Hakkari (Geçitli)** | Kidney stone | Aerial parts | Decoction/drinking one tea glass three times a day | (Kaval et al. 2014) |
| **Elazığ** | Hemostatic, kidney stone | Aerial parts | Decoction/internal | (Doğan and Bağcı 2011) |
| **Elazığ (Keban)** | Kidney stone | Aerial parts | Decoction | (Kilic and Bagci 2013) |
| **Elazığ (Sivrice)** | Cholagogue, diabetes, diuretic | Flowers | Infusion, decoction/ drinking a teacup after meal | (Cakilcioglu and Turkoglu 2010) |
| **Elazığ (Yazıkonak and Yurtbaşı districts)** | Diabetes | – | Decoction | (Cakilcioglu et al. 2010) |
| **Gümüşhane (Kelkit)** | Asthma, bronchitis, diuretic, kidney stone, urinary tract infection, eczema, varicose veins, prostate, jaundice, cholesterol, antibiotic<br>Jaundice in babies | Whole plant | Tea, honey is added<br>Added to the bath water<br>Added to the bath water of babies | (Korkmaz and Karakurt 2015) |
| **Kahramanmaraş (Andırın)** | Earache for baby<br>Kidney stone | Aerial parts | Inhalation (ear)<br>Decoction/internal | (Demirci and Özhatay 2012) |
| **Kars (eastern part)** | Rheumatism, jaundice, clean intestine | All parts | Decoction | (Güneş and Özhatay 2011) |
| **Van** | Diabetes | Aerial parts | Decoction/drinking three tea glasses after meal | (Dalar 2018) |
| **Yozgat (Akdağmadeni)** | Diuretic, kidney stone | Whole plant | Infusion/internal | (Özüdoğru et al. 2011) |
| **Tokat** | Piles on the hand and foot | Flowers | Decoction, cooled for overnight/internal | (Fujita et al. 1995) |
| **Malatya (Akçadağ)** | Kidney stone, kidney and stomach ailments<br>Deprecioatory | Aerial parts | Infusion, decoction/ internal<br>Tea/internal | (Yeşil and Akalin 2009) |
| **Niğde (Çamardı)** | Wounds | Flowers | Poultice/applied on wounds, to obtain poultice, decoction is mixed with barely flour. | (Sezik et al. 2001) |
| **Osmaniye (Bahçe and Hasanbeyli districts)** | Diuretic, bile secretion | Flowers | Infusion | (Mart and Türkmen 2018) |

(continued)

**Table 21.2** (continued)

| Region | Medicinal uses | Plant part | Preparation/ Utilization method | References |
|---|---|---|---|---|
| **Sivas (Şarkışla)** | Stomach ulcer | Whole plant | Infusion/internal | (Özüdoğru et al. 2011) |
| **Van (Çatak)** | Diabetes, cholesterol | Aerial parts | Decoction/drinking one glass before meal in the morning, drinking one tea glass three times a day | (Mükemre et al. 2015) |

(36.5 mg/L). The plant was found to be effective on ROS in a non-cellular system. In another study, the hydro-alcoholic extract derived from capitulum of *H. plicatum* subsp. *plicatum* was found to exhibit strong ABTS radical cation scavenging activity (98.4%) at 3000 μg/ml. There was a positive correlation between ABTS radical scavenging activity and total phenol contents (Orhan et al. 2014). In other research, the antioxidant activities of different extracts of aerial parts derived from *H. plicatum* subsp. *plicatum* were determined. The methanol extracts were detected to exhibit the highest value, but lower than ascorbic acid. Moreover, the methanol extracts were found to show stronger ABTS radical cation scavenging activity and ferric reducing activity than other extracts. The Soxhlet methanol extraction technique has been identified as the most suitable method besides having the highest flavonoid content (Taşkın et al. 2020). In another study conducted on methanol extracts of *H. plicatum* subsp. *plicatum* by using DPPH assay and β-carotene/linoleic acid systems, when compared with BHT, polar sub-fractions were found to show better activity. In the β-carotene/linoleic acid test system, the inhibition rate of BHT was found to be 96% and *H. plicatum* subsp. *plicatum* was between 50–60% (Tepe et al. 2005). In a different study using ferric reducing antioxidant power (FRAP) method, all methanolic extracts from three parts (Flowers, leaves and stem-barks) of *H. plicatum* subsp. *plicatum* were found to show high antioxidant activity. The highest FRAP value was observed at leaves, flowers, and stem-bark in the decreasing order (Kolaylı et al. 2010). In another study, the methanolic extracts of *H. plicatum* subsp. *polyphyllum* and *H. plicatum* subsp. *plicatum* were determined to exhibit strong antioxidant and radical scavenging activity. The total antioxidant capacity as ascorbic acid equivalents of 152.64 mg/g and 163.47 mg/g dry extract was determined for *H. plicatum* subsp. *polyphyllum* and *H. plicatum* subsp. *plicatum*, respectively, in the phosphomolybdenum assay (Albayrak et al. 2010b). In another study conducted on the methanolic extract of aerial parts obtained from *H. plicatum* subsp. *pseudoplicatum,* the total antioxidant activity (161.79 ± 0.3 mg ascorbic acid equivalent/g extract), was determined in the phosphomolybdenum assay. The free radical scavenging activity of the plant (79.59%) was found to be near that of BHT (92.15%) (Albayrak et al. 2010a).

### 21.5.2 Anti-inflammatory Activity

In a study, anti-inflammatory activity was tested on paw of rats using methanol extracts of aerial parts obtained from *H. plicatum* subsp. *plicatum* by using different extraction techniques. Indomethacin inhibition, which was 34.04% at first hour, increased to 85.01% at second hour and reached 89.73% at fourth hour after carrageenan injection. Maceration methanol extract performed the highest inhibition with 62.06% at first hour. It produced 67.02% inhibition at the second hour and 66.58% inhibition at the fourth hour. The maceration method was found to be more effective, except for the 77.94% inhibition created by the extract prepared with Soxlet method at the time when both of them signifi-

**Table 21.3** Main chemical compounds present in extracts and essential oil obtained from different parts of *Helichrysum plicatum* and subspecies

| Taxa | Compound (s) | Plant parts | References |
|---|---|---|---|
| *H. plicatum* | Apigenin, naringenin, glycosides of apigenin, kaempferol, naringenin, quercetin<br>Luteolin, glycosides of quercetin, luteolin | Flowers<br>Stems and leaves | (Kulevanova et al. 2000) |
| *H. plicatum* | Chlorogenic acid, chalcone derivate, apigenin, naringenin, kaempferol, glycosides of apigenin, naringenin, quercetin, kaempferol | Flowers | (Bigović et al. 2011, 2017) |
| *H. plicatum* | Pyrones (micropyrone, helipyrone C, bisnorhelipyrone, helipyrone B, arenol, arzanol, heliarzanol, auricepyrone, etc.)<br>Flavonoids (luteolin, naringenin, apigenin, quercetin, kaempferol glucosides of naringenin, apigenin and kaempferol, helichrysoside, tomoroside A, isosalipurposide, etc.)<br>Terpenoid (sesquiterpene derivative, diterpene derivative, athrolide C, ainsliaside E, gymnospermin, etc.)<br>Phloroglucinols (2,3-dihydro-4,5-dimethoxy-2,2-dimethyl-6-benzofuranon, [2,6-dihydroxy-4-[(3-methyl-2-buten-1-yl) oxy]phenyl] phenyl-methanone, etc.)<br>Phthalides (5,7-dihydroxyphthalide, 4-(4-hydroxy-3-methylbutyl)-5,7-dimethoxy-1(3H)-isobenzofuranone, etc.)<br>Phenolic acids (derivative) (chlorogenic acid, caffeic acid, everlastoside M, syringic acid, etc.)<br>Acetophenone (4′-hydroxy-3′-(3-methyl-2-butenyl)-acetophenone, etc.)<br>Other (inositol, tetrahydrojacarone, pinellic acid, etc.)<br>Unclassified (helinivene A, piperitol, etc.) | Aerial parts | (Vujić et al. 2020) |
| *H. plicatum subsp. plicatum* | Caffeic acid, gallic acid, chlorogenic acid, ferulic acid, syringic acid, trans-cinnamic acid, vanillic acid, hesperidin, apigenin, luteolin, kaempferol<br>Saturated fatty acids (lauric acid, capric acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid)<br>Monounsaturated fatty acids (myristoleic acid, oncobic acid, palmitoleic, heptadecenoic acid, oleic acid)<br>Polyunsaturated fatty acids (linolenic acid, linoleic acid) | Aerial parts<br>Flowers, stems | (Acet et al. 2020) |
| *H. plicatum* subsp. *plicatum* | Naringenin, helichrysin A, helichrysin B | Flowers | (Demir et al. 2009) |
| *H. plicatum* subsp. *plicatum* | Apigenin, β-cytosterol 3-O-β-D-glycopyranoside, helichrysin A, helichrysin B, astragalin, isosalipurposide | – | (Akbaş et al. 2016) |
| *H. plicatum* subsp. *plicatum* | Caffeic acid, benzoic acid, gallic acid, ferulic acid, vanillic acid, proto-catechuic acid, p-OH benzoic acid, chlorogenic acid, syringic acid, p-coumaric acid, o-coumaric acid, trans-cinnamic acid, quercetin, catechin, epicatechin, rutin | Flowers, leaves, stem-barks | (Kolaylı et al. 2010) |
| *H. plicatum* subsp. *plicatum* | β-sitosterol, nonacosanoic acid, apigenin, astragalin, β-sitosterol-3-O-β-D-glucopyranoside, helichrysin A, helichrysin B, isosalipurposide | Flowers | (Aydin 2020) |
| *H. plicatum* subsp. *plicatum* | Hexadecanoic acid (21.3%), T-cadinol (7.9%), β-eudesmol (3.3%)<br>α-fenchene (18.2%), α-pinene (10.4%), decanoic acid (6.4%) | Aerial parts<br>Infloresence | (Öztürk et al. 2014) |
| *H. plicatum* subsp. *plicatum* | Caffeic acid, chlorogenic acid, p-coumaric acid, p-hydroxybenzoic acid, apigenin, hesperidin, luteolin, naringenin, apigenin-7-glucoside | Aerial parts | (Albayrak et al. 2010b) |
| *H. plicatum* subsp. *plicatum* | Palmitic acid (11.76%), tetradecanoic acid (9.30%), decanoic acid (6.72%) | Capitulum | (Sezik and Aslan 1997) |

(continued)

**Table 21.3** (continued)

| Taxa | Compound (s) | Plant parts | References |
|---|---|---|---|
| *H. plicatum* subsp. *plicatum* | Dicaffeoylquinic acid, chlorogenic acid, luteolin, isoquercitrin, luteolin-7-O-glucoside, naringenin-O-hexoside | Aerial parts | (Taşkın et al. 2020) |
| *H. plicatum subsp. plicatum* | α-copaene (11.03%), δ-cadinene (10.14%), caryophyllene (7.86%) | Aerial parts | (Dolarslan and Gurkok 2018) |
| *H. pilicatum* subsp. *polyphyllum* | Hexadecanoic acid (28.0%), tetradecanoic acid (27.8%), dodecanoic acid (9.6%)<br>Hexadecanoic acid (15.2%), dodecanoic acid (9.6%), α-pinene (8.4%) | Aerial parts<br>Infloresence | (Öztürk et al. 2014) |
| *H. pilicatum* subsp. *polyphyllum* | Chlorogenic acid, caffeic acid, ferulic acid, p-hydroxybenzoic acid, syringic acid, p-coumaric acid, epicatechin, apigenin, hesperidin, naringenin, luteolin, apigenin-7-glucoside | Aerial parts | (Albayrak et al. 2010b) |
| *H. pilicatum* subsp. *isauricum* | Tetradecanoic acid (37.9%), hexadecanoic acid (15.4%), dodecanoic acid (10.4%)<br>α-fenchene (88.3%), limonene (1.5%), 2-hexanol (1.1%) | Aerial parts<br>Infloresence | (Öztürk et al. 2014) |
| *H. plicatum* subsp. *pseudoplicatum* | Caffeic acid, chlorogenic acid, ferulic acid, p-hydroxybenzoic acid, syringic acid, p-coumaric acid, epicatechin, apigenin, hesperidin, naringenin, luteolin, apigenin-7-glucoside | Aerial parts | (Albayrak et al. 2010a) |

cantly reduced volume of paw edema at the second hour (Taşkın et al. 2020).

### 21.5.3 Antiurolithiatic Activity

In order to examine the protective agent of *H. plicatum* subsp. *plicatum* flowers ethanol:water (1:1) extract against kidney stones, urolithiasic rat model induced by 1% ethylene glycol and 1% ammonium chloride was used. Three doses of 125, 250, and 500 mg/kg body weight were studied. There was a parallelism between decrease in pH level and production of calcium oxalate crystal. Higher urine pH level was seen in flower extract. Increased calcium oxalate crystal in urine and biochemical parameters in both urine and serum were decreased with extract. It was found that the decreasing weight of the rats with the disease was higher in the rats treated with the extract. Histopathological results showed that *H. plicatum* subsp. *plicatum* extract has both preventive effect on intratubular crystal deposition and protective effect on tubular structures. In addition, administration of 500 mg/kg body weight dose, the highest dose given, did not change biochemical parameters of urine and serum, urine pH level, and general architectures of the kidney in rats without urolithiasis (Bayir et al. 2011).

### 21.5.4 Insecticidal Activity

The essential oil of *H. plicatum* was studied on *Dendroctonus micans* (Kugelann) causing the death of trees in high levels. The essential oil showed an insecticidal effect against the larvae, in comparison with controls. It has been found that the mortality of the larvae increased significantly after treatment with the essential oil. The mortality rate of after 72 hours of administration of essential oils of *H. plicatum* to 1–2 larval stages of insects was detected to be 56.6%. However, the mortality rate was found to be 24.4% for 3–4 larval stages. The researchers suggested that essential oil of *H. plicatum* might be a new and effective biological control agent against *Dendroctonus micans* larvae (Gokturk et al. 2011).

### 21.5.5 Central Nervous System Activity

In a study using *H. plicatum* flower extract to test antineurodegenerative activity, the extract was found to exhibit better acetylcholinesterase inhibitory activity (AChE) compared to tyrosinase inhibitory activity. When 100, 200, and 500 mg/mL doses were tested, AChE inhibitory activity was found to be 39.53% at a dose of

100 mg/mL and 41.15%, the strongest activity observed at a dose of 500 mg/mL. This inhibition values were found to be low when compared to galantamin standart (57.11%) (Jovanović et al. 2020). In different study, the enzyme inhibitory effects of different part of *H. plicatum* subsp. *plicatum* extracted with different solvent on butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) were assesed. BChE inhibitory activities were found to be higher than the AChE inhibitory activities. The ethyl acetate extract of flowers was found to display the highest AChE inhibition with 17.75% and stem's ethanol extract showed BChE inhibition with 35.12% (Acet et al. 2020). In another study four different extracts of *H. plicatum* subsp. *plicatum,* prepared with different solvents and technics, were examined. The Soxhlet method showed the strongest anticolinesterase activity (58.51%). However, no effect was observed in petroleum ether extract using Soxlet method. All the extracts were found to possess lower anticholinesterase activity than galantamine used as reference (88.14%) (Taşkın et al. 2020).

### 21.5.6 Anticancer Activity

The effect of the methanol (%70) extract prepared from flowering tops of *H. plicatum* subsp. *plicatum* was tested on mammalian DNA topoisomerase I via in vitro supercoil relaxation assays using plasmid substrate. The extract was found to manifest a remarkable inhibition on this enzyme, making it a potential anticancer agent (Kucukoglu et al. 2006). In a different study, several concentrations of ethanol and different mixtures of ethyl acetate-ethanol were used for extraction and re-extraction of *H. plicatum* flowers, respectively. The degree of comminution varied was also taken into account. Some extracts and some flavone agylcones were chosen for investigation of cytotoxic activity on three human cancer cell lines, prostate cancer cells (PC3), human cervix adenocarcinoma cells (HeLa), and myelogenous leukemia cells (K562). Sample with the following features, such as degree of comminution (710 μm), extraction with 50% ethanol, and re-extraction with 100% ethyl acetate was found to be the most active against PC3 and K562 cell lines with IC50 values of 39.2 and 25.9 μg/mL, respectively. All samples tested were found to display moderate activity against HeLa cells. In this study in which cisplatin was used as a positive control, no extract or substance was found to be as effective as cisplatin. Flavone aglycone, kaemphferol was found to have the highest effect among all extracts and other aglycones (Bigović et al. 2011).

### 21.5.7 Antidiabetic Activity

In a study, it was found that *H. plicatum* subsp. *plicatum* extracts obtained from different parts of the plant extracted with different solvents exhibited a high level of inhibitory activity against α-amylase and α-glucosidase. The highest inhibitory activities were found in the flower ethyl acetate extract (197.12 mmol acarbose equivalents/g extract) for α-amylase and (22.33 mmol acarbose equivalents/g extract) for α-glucosidase (Acet et al. 2020). In another study conducted on enzymes mentioned above, the inhibitory effects of aqueous and hydro-alcoholic extracts of *H. plicatum* subsp. *plicatum* capitulum were investigated. Aqueous extract was found to be more effective (12.7%) than hydro-alcoholic extract (5.4%), but both extracts were far from the effectiveness of acarbos (73.7%) at 3000 μg/ml in terms of inhibitory effect on α-amylase enzyme. All the extracts were found to show inhibitory effects on α-glucosidase enzyme dose dependently. IC50 value of acarbose used as reference drug was 0.0009 mg/ml. Hydro-alcoholic extract was determined to display a better result (IC50 = 0.8570 mg/ml) than aqueous (IC50 = 5.0933 mg/ml) (Orhan et al. 2014). In another study conducted on streptozotocin-induced diabetic (STZ) and normal animals to understand the hypoglycaemic potential, water and ethanolic extracts derived from capitulums of *H. plicatum* subsp. *plicatum* were tested on rats. Tolbutamide was used at a dose of 100 mg/kg as a reference drug and extract doses given to

rats were 500 mg/kg for body weight. Investigation of the immediate effects showed that ethanol extract caused a significant decrease in blood glucose levels which lasted longer than that of tolbutamide in STZ-induced diabetic rats. Additionally, tolbutamide was found to reduce the blood glucose level to low levels bordering on hypoglycaemic shock in normoglycaemic rats. On subacute administration to STZ-diabetic rats, the activity of both extracts were found to be more effective than tolbutamide. During subacute study, not any significant change was seen between the group treated with extracts and the group treated with tolbutamide throughout eight days in diabetic animals regarding the body weight. In the oral glucose tolerance test, extracts exhibited a weak inhibitory effect compared to the potent effect of tolbutamide on blood glucose levels. In addition, increasing MDA levels and decreasing GSH levels in tissues, associated with diabetes, were restored with the extracts. The ethanol extract was found to be more potent in acute and subacute tests compared to water extract (Aslan et al. 2007). In a study carried out by Sezik et al. (2010), they presented the first study evaluating the efficacy of herbal extract in a pregnant animal model in 2010. Hypoglycaemic effect of extract obtained from *H. plicatum* subsp. *plicatum* was invesigated in the streptozotocin-induced type 1 diabetes rat model during pregnancy. Ethanol (80%) extract prepared from capitulums was given at a dose 250 mg/kg body weight orally to rats for 15 days, starting three days before mating. By administration of the extract, a glucose-lowering effect with increased serum insulin and decreased serum triglyceride levels were seen in both pregnant and non-pregnant rats. There was a correlation between the administration of the plant extract and increased pup number. Pregnant diabetic rats treated with the extract were shown to gain similar body weight when compared with non-diabetic and pregnant control group. In addition, liver thiobarbituric acid reactive substances and reduced glutathione measurements in treated diabetic pregnant animals were found to be similar to non-diabetic pregnant control group.

### 21.5.8 Antimicrobial and Antifungal Activity

Ethanolic extract prepared from *H. plicatum* flowers was evaluated against various bacteria, fungi, and yeast using microdilution method. The MIC values against bacteria ranged from 0.01 to 0.055 mg/mL. Gram-positive bacteria (*Bacillus subtilis*, *Listeria monocytogenes*, *Micrococcus flavus*, *Micrococcus luteus*) were found to be more susceptible to the ethanolic extract than Gram-negative bacteria. It was reported to inhibit completely their growth at the lowest concentrations. *Bacillus subtilis* was found to be the most sensitive bacteria to the plant extract. It has been shown that for the inhibition of growth of Gram-negative bacteria, growth higher concentrations of extract were required and the most resistant strain was found as *Escherichia coli*. Regarding pathogenic fungi, they were found to be more susceptible to the extract than bacteria. The majority of the fungi were sensitive to the extract when compared to commercial fungicide, fluconazole. *Fusarium solani, Fusarium equiseti, Fusarium verticillioides, Alternaria alternata,* and *Penicillium* sp. were detected to exhibit the highest sensitivity to the extract with MIC value of 0.005 mg/mL. However, *Fusarium subglutinans*, *Aspergillus flavus,* and *Chaetomium* sp. displayed higher resistance to the extract. It has been determined that inhibition of fungal growth, which are producers of various mycotoxins, including aflatoxins (*Aspergillus flavus),* was sensitive at low concentrations of the extract (Bigović et al. 2017). In another study investigating the antimicrobial activity of *H. plicatum,* aerial parts at the full blooming stage were extracted with different polarity solvents against five Gram-negative bacteria (*Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli*, *Proteus hauseri*, *Salmonella enterica* subsp. *enterica*), three Gram-positive bacteria (*Clostridium sporogenes, Staphylococcus aureus*, *Bacillus subtilis*), two yeasts (*Candida albicans*, *Saccharomyces cerevisiae*), and *Aspergillus brasiliensis* as fungal strain. In this study in which the broth microdilution method was used, all the extracts were found to display considerable

antibacterial activity in the range of 0.157–2.5 mg/mL. Dichloromethane extract was found to be more active against *Pseudomonas aeruginosa* than the chloramphenicol. The extracts tested were found to show better or the equal activity against fungi compared to nystatin used as positive control (Vujić et al. 2020). In a different study, the antimicrobial activity of the ethanol, methanol, and ethyl acetate solvent extracts of the flower and stem parts of *H. plicatum* subsp. *plicatum* was investigated by using four Gram-negative bacteria (*Yersinia enterocolitica*, *Klebsiella pneumoniae*, *Vibrio parahaemolyticus*, *Salmonella typhimurium*), seven Gram-positive bacteria (*Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus epidermidis*, *Bacillus cereus*, *Enterococcus hirae*, *Listeria monocytogenes*, MRSA) and one yeast (*Candida albicans*) using disc diffusion and MIC tests. All extracts obtained from stem and flower were found to exhibit poor activity against Gram-negative bacteria. No inhibition was seen in ethyl acetate extracts. The extracts were detected to show equal or higher activity than novobiocin. In addition, the plant extracts except ethyl acetate extracts showed strong activity against all Gram-positive bacteria. Furthermore, only the ethanol extracts from flowers and stem were found to have strong activity against *Candida albicans* (Acet et al. 2020). In a different study conducted on the extracts of *H. plicatum* subsp. *plicatum* leaves, stem, and flowers extracted with different solvent, it has been shown that the extracts exhibited various inhibitory effects against 15 different bacterial species and strains (7–31 mm 50 $\mu l^{-1}$ inhibition zone). All the plant parts tested were detected to show no inhibitory effect against *Corynebacterium xerosis*. The ethyl acetate extracts of flowers, stem, and leaves were found to have better antibacterial efficiency than other extract. Chloroform extracts follow the ethyl acetate extracts in terms of effect. The lowest effects were detected in acetone flower extract and methanol stem and leaves extract. *Bacillus subtilis* var. *niger* is the *Bacillus* affected by all extracts (Erdoğrul et al. 2001). In another study conducted on a dangerous food pathogen *Escherichia coli* O157:H7 displaying enteroinvasive, enteropathogenic, enterotoxigenic, and enterohemorrhagic properties, the extracts and their fractions derived from either the flowers or the leaves of *H. plicatum* subsp. *plicatum* were studied on inhibition potential of this pathogen. Among the extracts, only ethanol extract of flowers was found to perform a potent inhibitory effect against the pathogen. Then, this promising effect was investigated in their sub-fraction. It was stated that ethanol extract of flowers displayed the greater antibacterial activity than its sub-extracts (Demir et al. 2009). In a different research investigating antimicrobial activities of the methanolic extracts of aerial parts of *H. plicatum* subsp. *plicatum* and *H. plicatum* subsp. *polyphyllum* against 13 bacteria and two yeasts by using the agar diffusion method, among the Gram-negative bacteria tested, the most susceptible bacteria were *Aeromonas hydrophila* and *Pseudomonas aeruginosa* while the most resistant bacteria were detected to be *Yersinia enterocolitica*, *Proteus mirabilis,* and *Morganella morganii*. Both plants showed antibacterial activity against Gram-positive bacteria (*Bacillus brevis*, *Bacillus cereus*, *Staphylococcus aureus* ATCC 25923), but both had no inhibitory effects on *Mycobacterium smegmatis*. Only *H. plicatum* subsp. *plicatum* extracts inhibited the growth of one yeast, *Candida albicans*. Furthermore, both of species did not exhibit any effect against *Saccharomyces cerevisiae* (Albayrak et al. 2010b). In a study emphasizing the importance of extraction procedures and solvents, methanol extract prepared with Soxhlet method was found to exhibit moderate antibacterial and antifungal activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, MRSA, and the yeast *Candida albicans*. No activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa,* and *Proteus mirabilis* was seen for any of the extracts. The petroleum ether extract prepared with Soxhlet method exhibited the significant activity against *Candida albicans*. Chloroform extract prepared with Soxhlet method and methanol

extract prepared with maceration were found to have moderate activity against MRSA and *Candida albicans*. All the extracts were found to show lower antimicrobial activity than standard antibiotics such as clotrimazole, oxacillin cefuroxime-Na, and ceftazidime. As a result, the Soxhlet method was found to be more effective than the maceration method in terms of obtaining the significant antibacterial activity (Taşkın et al. 2020). In a study conducted on *H. plicatum* subsp. *pseudoplicatum* to reveal antibacterial potential using the agar-well diffusion method, it has been shown the methanol extract of aerial parts possessed antibacterial activity against *Klebsiella pneumoniae, Aeromonas hydrophila*, *Pseudomonas aeruginosa, Bacillus brevis*, *Bacillus cereus,* and *Staphylococcus aureus* ATCC 29213, but no activity was detected against *Mycobacterium smegmatis, Escherichia coli, Bacillus* subtilis, *Morganella morganii*, *Staphylococcus aureus* ATCC 25923, *Yersinia enterocolitica, Proteus mirabilis*, *Saccharomyces cerevisiae,* and *Candida albicans* (Albayrak et al. 2010a).

### 21.5.9 Protective of Liver and Kidney

In a study conducted by Yildirim et al. (2017), with the help of biochemical results and histopathological evidence, administration of *H. plicatum* subsp. *plicatum* dose at a dose of 100 mg/kg was found to prevent the gentamicin-induced nephrotoxicity. It was shown that normalization of serum creatinine and blood urea nitrogen was observed as well as beneficial effects in decreasing the elevated malondialdehyde levels of liver and kidney levels. Morover, it was found to increase the activity of antioxidant enzymes such as glutathione peroxidase, catalase, and superoxide dismutase in nephrotoxic rats induced by gentamicin. Histopathological analysis showed that the damage to the liver and kidneys was reduced with plant extract. Co-administration of *H. plicatum* subsp. *plicatum* with gentamicin was found to possess a renoprotective and hepatoprotective effect, showing that only mild infiltrations had normal glomeruli and alleviated tubular degeneration.

### 21.5.10 Other Activities

Methanol extract of *H. plicatum* subsp. p*licatum* and two compounds, helichrysin A and astragalin purified from extract, were applied to MCF-7 breast cancer cells to determine the relationship with the immune system. The effects on stimulatory of interferon genes (STING) and IFNβ gene expressions were determined. All of them did not have toxicity on MCF-7 breast cancer cell lines. On the other hand, it was observed that the extract increased STING activation; helichrysin A and astragalin did not show a significant effect on STING. Furthermore, interferon expression increased significantly with administration of extract and helichrysin A, but astragalin showed no effect (Akbaş et al. 2016).

The lifespan extension effects of water extract prepared by infusion from *H. plicatum* subsp. *plicatum* flowers were tested on *Caenorhabditis elegans*, an advantageous organism for age-related diseases and longevity research. Age-synchronized wild-type *Caenorhabditis elegans* specimens were treated with different concentrations of the extract, in lifespan assays. The extract was found to be not toxic to worms. Morover, the plant was found to provide lifespan-extending effects in worms in both median and maximum lifespan (Ergen et al. 2018).

In a study investigating the spasmolytic activity of *H. plicatum*, the ethanol extract of flowers was found to display a relaxant effect on isolated rat intestine. The extract was able to inhibit spontaneous ileum contractions and contractions induced by histamine, acetylcholine, potassium, and barium ions (Bigovic et al. 2010).

In another study examining the possible antimutagenic potential of *H. plicatum* subsp. *plicatum* by AMES-salmonella analysis using *Salmonella typhimurium* against direct acting mutagens, the methanol extract of the leaves was detected to show antimutagenic activity (Ozbek et al. 2009).

## 21.6 Clinical Studies

No information available.

## 21.7 Toxicological Studies

In a study conducted on human lymphocyte cultures to understand the genotoxic and antimitotic effects of aqueous extracts of *H. plicatum* subsp. *plicatum* prepared by decoction, the recommendation was reached that it should not be used freely in high amount because of causing chromosomal damage (an increase in micronucleus) and delaying in the cell division (decrease in mitotic and replication indexes). Otherwise, it should be taken into account that its antiproliferative activities may suggest anticarcinogenic properties (Erhan et al. 2010). The same results were obtained in both studies with the increasing dose of methanol extract of the same species (Eroğlu et al. 2009) and metanol extract of *H. plicatum* subsp. *polyphyllum* and *H. plicatum* subsp. *pseudoplicatum* (Eroğlu et al. 2010).

## 21.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies

No information available.

## 21.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

*H. plicatum* DC. is well-known medicinal plant with everlasting flowers. Studies show that a large number of traditional uses have been documented in region where *H. plicatum* grow wild, but these data are limited except from Turkey. The fact that Turkey hosts four subspecies is perhaps a result of this. Many ethnobotanic data especially from Turkey have been found to shed light on biological and phytocemical studies. Although there are many reports from ethnobotanic surveys, biological activity studies are not too much to validate the whole data from these surveys. There seems to be a close relationship between ethnobotanical usage and pharmacological data. However, many traditional usages have not been validated by pharmacological studies, e.g. treatment of wounds, scars, constipation, piles on the hand and foot, jaundice, asthm, varicose veins, and eczema; and activities of diuretic, bile secretion, and cholagogue. Morover, the treatment of earache and jaundice in babies and to keep snakes away from houses are interesting usage methods which are waiting to be scientifically proven. Many traditional usages of plants even in babies may give an idea about the toxicity, but no toxicity studies and safety testing have been conducted on them apart from some genotoxic and antimitotic effects conducted on *H. plicatum* subsp. *plicatum* (Eroğlu et al. 2009; Erhan et al. 2010), *H. plicatum* subsp. *polyphyllum,* and *H. plicatum* subsp. *pseudoplicatum* (Eroğlu et al. 2010). Several valuable secondary compounds including flavonoids, pyrones, phloroglucinols, terpenoid, phtalides, and phenolic acids were detected in *H. plicatum* and subspecies with few studies, but these studies are not enough to reveal the whole phtochemical profile. Likewise, studies performed on essential oils are very limited. On the other hand, there are some taxonomic uncertainties on *H. plicatum* and subspecies, therefore they need to be examined in more detail and be clarified in some taxonomic problems. Moreover, its clinical effectiveness on humans has not been defined so far.

## 21.10 Challenges and Future Recommendations as Potential Drug Candidate

*H. plicatum* and subspecies have been shown to be an important part of traditional medicine for a long time. Their secondary metabolites with diverse properties seem to possess a curing potential of many diseases. However, further

studies on phytochemical and pharmacological are necessary to reveal the potential of the plants. Several traditional usages claimed have not yet been proven scientifically. Studies about the chemistry of the plants are very promising but not enough to reveal too many active constituents. Lack of studies on toxicological, safety, and effectiveness are other challenges that need to be addressed. Additionally, no clinical studies have been conducted on these plants. However, *H. plicatum* and subspecies have very promising effects with potent antioxidant effect, and antibacterial and antifungal activities in terms of food technologies. The inhibition of fungal growth has been determined, which are producers of various mycotoxins, including aflatoxins. Moreover, the plants appear to be an important resource for the treatment of many diseases such as kidney stones, where there is a lack of safe and effective medication.

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# *Hyoscyamus niger* L.

22

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**Abstract**

The aim of this chapter is to review the ethnobotanical uses, chemical composition, and biological effects of *Hyoscyamus niger*. The plant has been known since the ancient era and the ethnobotanical records have indicated different uses including toothache, asthma, and gastrointestinal problems, as a sedative, hallucinogenic. Observed ethnobotanical uses could be explained by the presence of alkaloids, especially hyoscyamine, scopolamine, and atropine. In recent studies, some new compounds have been isolated as well as the alkaloids. In biological activity studies, we have observed different actions including antifungal, antibacterial, antidiarrheal, antisecretory, bronchodilator, and urinary bladder relaxant abilities. However, the plant is known as a toxic plant and different cases have been reported on poisoning with the plant. At this point, human beings have to be more careful with the applications of this plant. The review could be a new starting point for designing further studies with this plant.

**Keywords**

*Hyoscyamus niger* · Seeds · Hyoscyamine · Sedative · Toxic effects

## 22.1 Introduction

Since the prehistoric era, plants are considered as a big treasure for managing health problems. For example, Hippocrates said "Let food be thy medicine and medicine be thy food" and he pointed at the plants in this sentence. Since the industrial revolution, human beings are seeking to find new raw materials for designing effective drugs (Khan et al. 2021). In this sense, many raw materials from nature for drugs have been discovered and they have been marketed in the pharmacy shelf. However, because the fact has been restricted by several reasons such as increasing population, high cost, or short shelf life, synthetics have been still popular in the applications. Recent studies have shown that the utilization of synthetics is linked to several health problems in the long term and human beings have to find alternative raw materials to replace synthetic ones. Taken together, in the twenty-first century, scientists

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have focused on novel and effective compounds from nature, especially plants to find potential compounds (Atanasov et al. 2021; Mathur and Hoskins 2017; Newman and Cragg 2016). In this sense, the discovery of artemisinin is considered as a cornerstone and this case is encouraging the scientist to more focus on nature (Su and Miller 2015).

The *Hyoscyamus* genus is an important genus of the family *Solanaceae* and the genus is represented by 17 species worldwide, especially Asia, Europe, and North Africa (Akbar 2020). The name of *Hyoscyamus* (Henbane) is derived from the Anglo-Saxon Hen (chicken) and Bana (murderer); when fowls consumed the plants (especially seeds), they got paralyzed and died (Haas 1995). Generally, the members of *Hyoscyamus* are known as toxic plants and even small levels can lead to significant anticholinergic effects such as dizziness and delirium (Akbar 2020). In Greek ancient times, the plants were known as narcotic plants. In this sense, more attention need to be given while consuming the plants or their preparations. *H. niger* is the most known species in the genus and it is 30–80 cm tall with 15–20 cm alternate leaves (Fig. 22.1). Flowers have lurid yellow corolla and densely hairy calyx. The plants have flowering time from April to August (Akbar 2020). In ethnobotanical views, the members of *Hyocysamus,* especially *H. niger,* have been widely used as traditional purposes such as stomachache, asthma, neuralgia, and sedative. Phytochemical studies have indicated that alkaloids especially tropane alkaloids (hyoscyamine and scopolamine) are the main secondary metabolites in the *Hyoscyamus* genus and the above-mentioned effects could be attributed to the presence of alkaloids (A Sajeli Begum et al. 2009; S. Begum et al. 2010; Sengupta et al. 2011). This chapter gives a quick overview of medicinal and nutraceutical properties of *H. niger.* Furthermore, current information and applications with *H. niger* have been explored. This chapter will provide a new scientific starting point on *H. niger.*

## 22.2 Origin, Distribution, and Local Names

It is believed that *Hyoscyamus niger* is originated in northern hemisphere, especially Asia, Europe, and north Africa. This distribution is shown in Fig. 22.2. The plant has a large distribution in different environment such as wayside, waste places, sandy or arid soils, and high altitude (as 3000 m above of sea level). Some records have


**Fig. 22.1** *Hyoscyamus niger* in the flowering season

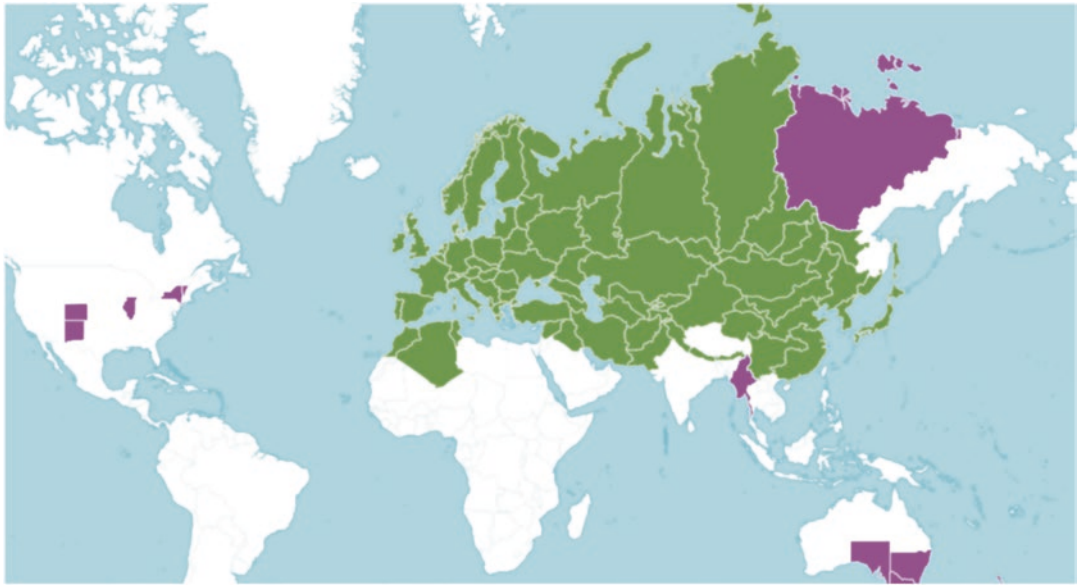

**Fig. 22.2** Distribution of *Hyoscyamus niger* in the world. (Green: Native; Purple: Cultivated) (http://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:815932-1#source-KBD)

indicated that the plants have been distributed from Europe to other continents, namely Asia and north Africa (Akbar 2020).

The plant is known by different names in the worldwide. Henbane is the most common name and other names from different language are listed below (Akbar 2020):

Arabic name: **Bazrul-banj**
Czech name: **Blin cerny**
Finish name: **Hullulkaali**
Germanic name: **Schwarzes bilsenkraut**
Italian name: **Alterco**
French name: **Hannebane**
Russian name: **Belena ernaja**
Turkish name: **Ban otu**

## 22.3 Ethnobotanical Uses

The *Hyoscyamus* genus has great potential in terms of ethnobotanical and traditional uses. Since the ancient Greek era, *H. niger* has been used to alleviate toothache and manage sleep disorders, including insomnia. Also, the plant is known as an important anesthetic for the respiratory systems and mental disorders. Because of the anesthetic effects, the plant was usually used in religious rites in the ancient area (Fatur 2020). Ethnobotanical studies have reported different uses for *H. niger* and they are summarized in Table 22.1. The uses have been indicated as a large variation from heavy coughs to manic psychosis. In addition, the plant has been also recommended by several researchers for urinary problems, rheumatoid, and dental pains. The above-mentioned large ethnobotanical uses of *H. niger* could be explained by its analgesic, antispasmodic, sedative, anticonvulsant, antimuscarinic, and contraceptive effects. As can be seen in Table 22.1, seeds of *H. niger* are the most used parts and followed by flowers and leaves. Kunwar et al. (2021) have reviewed the ethnobotanical uses and phytochemical composition of *H. niger* in Himalayas and they have reported several uses including diphtheria, spams of bladder, some tumors (cervix, rectum, or urethra), Parkinson disease, and diarrhea.

nm: not mentioned.

**Table 22.1** Ethnobotanical uses of *Hyoscyamus niger*

| Ethnobotanical uses | Plant parts | References |
|---|---|---|
| Toothaches | Seed | (Polat 2019) |
| | Flowers, seeds, and leaves | (Vitalini et al. 2015) |
| | Leaves and seeds | (Polat and Satıl 2012) |
| | Seeds | (Polat et al. 2013) |
| | Seeds | (Altundag and Ozturk 2011) |
| | Seeds | (Sezik et al. 2001) |
| | Whole plant | (Rivera et al. 2019) |
| | Fruits, seed, and leaves | (Kültür 2007) |
| | Flowers and leaves | (Gairola et al. 2014) |
| | Leaves and seeds | (Erbay et al. 2018) |
| | Seeds | (Nadiroğlu et al. 2019) |
| | Seeds | (Bulut and Tuzlaci 2015) |
| | Leaves and fruits | (Nejad et al. 2013) |
| Asthma and cough | Leaves, seeds, and fruits | (Kayani et al. 2014) |
| | Leaves, seeds | (Barkatullah et al. 2015) |
| | Flowers | (Šarić-Kundalić et al. 2011) |
| | Flowers and leaves | (Gairola et al. 2014) |
| | Leaves | (Ahmad et al. 2016) |
| | Aerial parts | (Mumcu and Korkmaz 2018) |
| Narcotic, sedative, and antidepressant | Leaves and seeds | (Barkatullah et al. 2015) |
| | Nm | (McClatchey et al. 2009) |
| | Seeds | (Özdemir and Alpınar 2015) |
| | Nm | (Suroowan et al. 2019) |
| | Whole plant | (Dutt et al. 2015) |
| | Flowers and leaves | (Gairola et al. 2014) |
| To expel worms | Seeds | (Özüdoğru et al. 2011) |
| | Seeds | (Sezik et al. 2001) |
| | Flowers, leaves, and seeds | (Kültür 2007) |
| Earache | Seeds | (S. A. Sargın et al. 2013) |
| | Seeds | (Sezik et al. 2001) |
| | Seeds | (S. Sargın and Selvi 2013) |
| | Seeds | (Bulut et al. 2017) |
| Rheumatism | Nm | (Uttra et al. 2018) |
| | Leaves | (El Beyrouthy et al. 2008) |
| | Leaves and fruits | (Nejad et al. 2013) |
| Wounds | Leaves and seeds | (Polat and Satıl 2012) |
| | Flowers, leaves, and seeds | (Kültür 2007) |
| Pain | Leaves | (Teixidor-Toneu et al. 2016) |
| | Fruits and leaves | Sher et al. (2016) |
| | Seeds | (S. Sargın and Selvi 2013) |
| | Leaves and seeds | (Gyawali et al. 2021) |
| | Leaves and fruits | (Nejad et al. 2013) |
| Eczema and skin disorders | Nm | (Benarba et al. 2015) |
| | Leaves | (Bruni et al. 1997) |
| Ophthalmological purposes | Leaves | (Teixidor-Toneu et al. 2016) |
| | Seed | (Sezik et al. 2001) |
| Antispasmodic | Leaves and seeds | (Gyawali et al. 2021) |
| | Leaves | (Jaradat et al. 2016) |
| Sinusitis | Seed | (S. A. Sargın et al. 2013) |
| Antihaemorhoidal | Nm | (Gras et al. 2017) |
| Antipiretic | Nm | (Noronha et al. 2020) |
| Stomach craps | Leaves and fruits | (Nejad et al. 2013) |

## 22.4 Phytochemistry

In the phytochemical studies, the *Hyoscyamus* genus is rich in terms of alkaloids, especially hyoscyamine and scopolamine. Most of pharmacological effects of the members of this genus can be linked to the presence of these compounds. These compounds are shown in Fig. 22.3. The leaves of *H. niger* contain different levels of alkaloids (0.012–0.161% dry weight) and several studies have been performed to increase the levels of alkaloids. In addition to alkaloids, several compounds, including rutin, vanillic acid, β-sitosterol, withanolides, or lignanamides, are isolated from *H. niger* seeds. Bahmanzadegan et al. (2009) investigated hyoscyamine and scopolamine levels of four *Hyoscyamus* species and their levels were the highest in seeds when compared with leaf, stem, and roots. In addition, atropine content in the seeds of *H. niger* was found to be 0.004% w/w in an earlier paper (Pundarikakshudu et al. 2019). Jan, Kamili, Parray, Bedi, and Ahmad et al. (2016) investigated the levels of tropane alkaloids of *H. niger* at two different sites and hyoscyamine was the main component (4.7–5.6 mg/g extract) in these locations (Table 22.2).

## 22.5 Biological Activities

*H. niger* exhibits different biological activities such as spasmolytic, hallucinogenic, sedative, and antidiarrheal properties (Ghorbanpour et al. 2010; Gilani et al. 2008). *H. niger* extracts or compounds could competitively inhibit acetylcholine and generally muscarinic receptors are more sensitive than nicotinic or ganglionic ones.

Sengupta et al. (2011) investigated antiparkinsonian effect of *H. niger* seed as well as monoamine oxidase inhibitory (MAO) and hydroxyl radical scavenging potential. Especially, the aqueous methanol extract administration significantly improved motor functions. Also, the extract had promising MAO inhibition and quenching hydroxyl radical scavenging abilities.

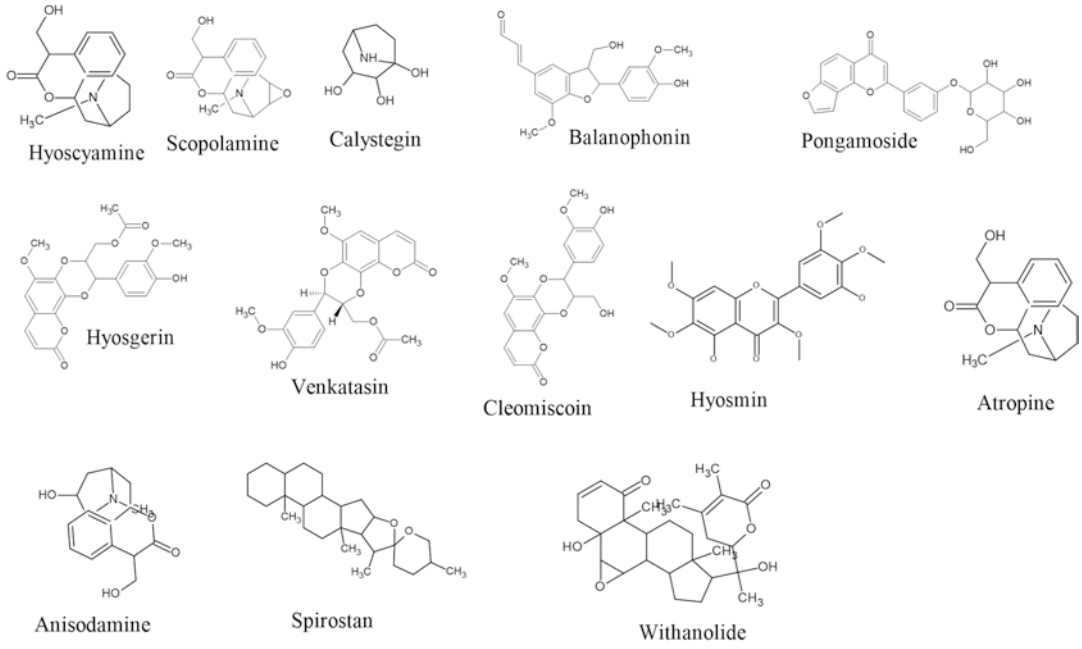


**Fig. 22.3** Several compounds isolated from *H. niger*

**Table 22.2** Several compounds isolated from *H. niger*

| Compounds | Plant parts | References |
|---|---|---|
| Seven calystegins (A3, A5, A6, B1, B2, B3, and N1) | Whole plant | (Asano et al. 1996) |
| Hyoscyamal, Balanophonin, pangamoside C, pangamoside D | Seeds | (A Sajeli Begum et al. 2009) |
| Hyosgenin, venkatasin, cleomiscoin A, cleomiscoin B | Seeds | (Sajeli et al. 2006) |
| Hyosmin | Seeds | (Ahil Sajeli Begum et al. 2006) |
| Lignanamides | Seeds | (Zhang et al. 2012) |
| Spirostane saponins | Seeds | (Lunga et al. 2008) |
| Cleomiscoin derivatives | Seeds | (S. Begum et al. 2010) |
| Withanolides (daturalactone-4, hyosyamilactol, 16α-acetxyhyoscyamilactol) | Seeds | (Ma et al. 1999) |

In the study, the extract was characterized by using HPLC and the presence of hyoscyamine, scopolamine, cleomicosin B, venkatasin, daturalactone4, hyoscyamal, balanophonin, and hyoscyamide was reported. The observed activities might be explained with these compounds.

Reza et al. (2009) tested the methanol extract of *H. niger* as anticonvulsant activity against picrotaxin-induced mice. In the study, different concentration (12.5–400 mg/kg) extracts were applied and 300 mg/kg dose was noted most active. The extract exhibited remarkable anticonvulsant ability.

Gilani et al. (2008) investigated the spasmolytic, antidiarrheal, antisecretary, branchodilatory, and urinary bladder relaxant abilities of *H. niger* seed extracts. The extract exhibited remarkable relaxation of spontaneous contractions of rabbit jejunum. Also, the extract displayed a $Ca^{2+}$ channel blocking mechanism in addition to anticholinergic effect. The extract had antidiarrheal and antisecretory effects in mice. Altogether, the ethnobotanical uses of *H. niger* were confirmed by this study.

S. Begum et al. (2010) tested anti-inflammatory, antipyretic, and analgesic activities of *H. niger*. The methanol extract exhibited remarkable analgesic effects in hot plate. In acute and chronic inflammation process, the extract had great potential. In this study, several compounds were isolated from this extract and cleomiscoin A was noted as an anti-inflammatory compound.

Dulger et al. (2010b) tested antifungal abilities of *H. niger* seed extract against *Candida albicans*, *C. tropicalis, C. guilliermandii, C. krusei*, *C. glabrata*, *C. parapsilosis,* and two *Cryptococus* (*C. neoformans* and *C. laurentii*). The extract displayed strong antifungal abilities. Giordani et al. (2020) also confirmed the antifungal effects of *H. niger*. In addition, Dulger et al. (2010a) examined the antibacterial activities of *H. niger* seed extract against *Bacillus subtilis, B. cereus, Staphylococcus aureus, Escherichia coli, Proteous vulgaris, Salmonella typhimurium,* and *Pseudomonas aeruginosa*. The extracts displayed significant antibacterial activity on *S. aureus*. Other bacteria were not affected by the extract. Similar to this study, Turker et al. (2018) reported that *H. niger* extracts did not exhibit any antibacterial effects.

Zhang et al. (2012) tested phytotoxic effect of lignanamides from *H. niger* seeds. All lignanamides exhibited remarkable inhibition and germination and radical elongation of *Allium fistulosum*, especially lignanamide 3 was the most active at $10^{-4}$ M concentration.

Deniz et al. (2017) investigated cytotoxic effects of some medicinal plants and one of them was *H. niger*. The leaves and seeds exhibited moderate cytotoxic effects on A-549, CCC-221, K-562, MCF-7, and PC-3 cell lines. The extract ability ranged from 10% to 30%.

Küpeli Akkol et al. (2020) investigated the insecticidal effect of *H. niger* on *Lucilia sericata* and the extract obtained from seed exhibited remarkable activities with those values of 8.04, 8.49, and 7.96 μg/ml in first, second, and third instar, respectively. The authors observed also weak cuticle and small damaged larvae. In their study, hyoscyamine and scopolamine were detected as main compounds and they might be responsible for the observed insecticidal effects.

In a recent study, Kosari et al. (2021) investigated anti-COVID-19 effect of *H. niger* with

propolis. One syrup was prepared and it contained 1.6 g methanolic extract with 450 mg propolis in 10 ml. The syrup decreased COVID-19 clinical symptoms and the authors suggested that *H. niger* could be a potential agent for designing anti-COVID-19 formulations.

## 22.6 Toxic Effects

Because of high concentrations of tropane alkaloids, the high concentration of *H. niger* may result in poisoning. Generally, the central nervous system is affected by these alkaloids and these effects are restlessness, hallucinations, delirium, and manic-depressive attacks. Because all parts of this plant contain significant levels of these alkaloids, especially scopolamine, all parts could be poisoned (Verstraete 2010). In addition, any drying or boiling process could not reduce the alkaloid concentrations and thus the uses of the plant have to be more careful. Animals don't prefer the leaves of this plant, because the leaves don't have a good odor, but humans could use the root accidentally and this could result in poisoning (Grieve 1913).

When higher concentration of the plant parts was administered, symptoms including tachycardia, arrhythmia, agitation, convulsion, and coma could be observed (Vidović et al. 2005). In addition, dry mouth, headache, vomiting, blurred vision, and urinary problems could be observed with the administration of toxic levels of the plants.

For example, in Canada, a married couple consumed mistakenly the plant as cooked roots and then they were hospitalized. They had serious effects including mydriasis, urinary problems, hallucinations, and tachycardia and were discharged on day 2 (women) and 3 (men) (Shams et al. 2017). As another example in Croatia, an 18-year-old male consumed the seeds as swallowed and euphoric effects were observed. The man was hospitalized and agitation, vision problems, hallucinations, dry oral mucosa, and incoherent speech were observed. The man was discharged on fourth day (Vidović et al. 2005). In Turkey, an elderly male consumed the leaves as tea and hallucinations and speech problems were observed. The elderly male was hospitalized in intensive care and discharged on the same day (Erkal et al. 2006). Daneshvar et al. (1992) reported 900 patients in a case study and most of them were children. In the study, most of the patients had hallucinations and convulsion as intoxication signs.

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# *Juglans regia* L.

23

Derya Çiçek Polat

**Abstract**

Walnut (*Juglans regia* L.) is grown in temperate regions of the world. It is cultured around the world due to the consumption of its fruits as food. In addition to being used as food, walnuts are used in the treatment of varied diseases from past to present. It is known that oil, seeds, bark, leaves, and seeds green husks are used in traditional treatment. Walnut is known to reduce blood sugar, as well as LDL, triglyceride, and cholesterol levels. Numerous biological activity studies have been performed on it. Preparations containing walnut oil are available in the market. However, more studies are needed in terms of toxicological studies and clinical studies.

**Keywords**

*Juglans* · *Juglans regia* · Juglandaceae · Walnut

## 23.1 Introduction

Walnut (*Juglans regia* L.) (Fig. 23.1), as a botanical classification, is located in Dicotyledoneae class, Juglandaceae family, and Juglans genus. There are 21 species in *Juglans* genus. There are 21 species in the genus *Juglans* and *Juglans regia* is one of the most important species. *J. regia* has 16 synonym names (*J. asplenifolia, J. dissecta, J. duclouxiana, J. fallax, J. fertilis, J. frutescens, J. fruticose, J. heterophylla, J. kamaonia, J. longirostris, J. orientis, J. quercifolia, J. regia var. laciniata, J. regia subsp. sinensis, J. salicifolia, J. sinensis*). The names of walnuts around the world are as follows: Turkish: Ceviz; Arabic: Joz; Chinese: Hu tao; English: Walnut, Carpathian walnut, Circassian walnut, English walnut, Madeira walnut, Persian walnut; French: Noyer commun; German: Echte Walnuß; India: Akhort; Portuguese: Nogueira-comum, Nogueira-européia; Spanish: Nogal común, Nogal europeo, Nogal inglés; Swedish: Valnöt (Gençler Özkan 2011; Al-Snafi 2018; Catanzaro et al. 2018; Plants of the World online 2021).

Due to the high quality of fruit among the *Juglans* species, the only species grown for its fruit in the world is *J. regia*. In addition, it is the most common species among *Juglans* species. Walnut species are grown in temperate regions. Walnut trees are sensitive to very hot temperatures in summer and very cold in winter (Manning 1978; Bernard et al. 2018; Delaviz et al. 2017).

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**Fig. 23.1** *Juglans regia* L. (Photo: Derya Çiçek Polat – 03.07.2020)

The walnut tree is 10–25 m tall. Short and thick stem is very branched and forms a wide crown, bark is grayish in color. Its leaves are imparipinnate, with 5–9 foliol, foliol is approximately 10–15 cm. The flowers are separate as male flower and female flower. Fruit type is drupe, approximately 4–5 cm (Tanker et al. 2016). It is among the plants used in traditional medicine because of its fruit, fruit peel, and leaves. The parts used are oil, seeds, bark, leaves, and seeds green husks (Delaviz et al. 2017). In this section, an overview of *J. regia* has been made and the studies have been compiled.

## 23.2 Distribution and Status of Species

Origin of walnut trees can be traced to especially Turkey, the Balkans, Eastern Himalayas and extends from Southwestern China. It has commercial importance due to the quality of its fruit and its consumption as food. For this reason, it is cultured in many parts of the world. Today it is grown in many parts of the world, including Asia (Himalayas, Iran, China, and Japan), Southern and Eastern Europe, and North and South America (Fig. 23.2). Temperature is important for walnut trees; it is susceptible to very hot in summer and very cold in winter (Delaviz et al. 2017).

## 23.3 Comparison of Traditional/Ethnomedicinal/Local Uses: In Turkey and throughout the World (Asia and Europe)

Archeological evidence, c.a. 7300-year BP shows that walnuts are collected and consumed by people in regions near to the Mediterranean. Oil, seeds, bark, leaves, and seeds green husks are known to be used in traditional medicine. Seeds are consumed as food (Al-Snafi 2018). According to studies, walnut leaves contain compounds that are efficient for health, and because of these compounds, they are used in traditional medicine in the treatment of venous deficiency, hemorrhoid


**Fig. 23.2** Geographical distribution of *Juglans regia* (Plants of the World online 2021)

symptoms, antidiarrhea, and antiparasitic. In addition, walnut roots are used to treat diabetes, leaves to treat rheumatic pains, fever, diabetes, and skin diseases, and flowers to treat malaria and rheumatic pains (Delaviz et al. 2017).

In Turkey, walnut is used in diseases such as diabetes, rheumatism, eczema, hair problems such as hair loss and hair care, hyperlipidemia, and hemorrhoids. Its leaves are mostly used for medicinal purposes. Walnut leaves are prepared and consumed as infusion (2%) if used internally, and as decoction (5%) if used topically. Walnut leaves are used for their appetizing, constipated, blood sugar lowering, and strengthening effects. In addition, its leaves are used externally as an antipyretic and antiseptic in skin diseases. Apart from leaves, the most commonly used drugs are fruit and fruit peels. Besides, the fixed oil obtained from walnuts is used in the treatment of constipation, the shell of the green walnut in the treatment of skin diseases, and the roots are used in the treatment of diabetes and rheumatism (Baytop 1999; Bellikci Koyu 2020).

In Iranian traditional medicine, walnuts are used to lower blood sugar and to treat inflammatory bowel disease (Taha and Al-wadaan 2011; Moravej et al. 2016; Delaviz et al. 2017). In Kashmir Himalaya, walnut leaves are used as itching, chronic dysentery, mosquito repellent and lice repellent; fruits for memory enhancer, aphrodisiac, constipation, and rheumatism treatment; oils relieve dandruff, muscle pain, sharpen eyesight, memory booster; roots are used in hair loss, against tooth decay, as an antiseptic, and wound healing (Al-Snafi 2018). In Palestine, it is used in the treatment of prostate, vascular diseases, diabetes, and asthma (Taha and Al-wadaan 2011). In China, the green fruit husk and branches of walnuts are used in stomach, liver, and lung cancer. In Mexico, the fruits of walnuts are used against liver damage and their skins are used for dental cleaning. In Nepal, the fruits of walnuts are used for healing wounds, while walnut shells are used for skin diseases, arthritis, and dental cleaning. In Calabrian folk medicine, walnut peel is used in the treatment of malaria (Taha and Al-wadaan 2011; Al-Snafi 2018). Considering its use in the world in general, walnut leaves are used for the treatment of skin inflammation, venous insufficiency, hyperhidrosis hemorrhoidal symptoms, ulcers, for diarrheic, as antihelmintic, depurative, antioxidants, antiseptic, anti chem-

bacterial, astringent, and preventive purposes. In addition to the use of fruits as food, it is used as a liver protect. Stem bark and root are used as anthelmintic, astringent, and cleaner. In addition, dried stem bark is used as a tooth cleaner and tooth whitener (NirmlaDevi et al. 2011). Apart from its medicinal uses, walnut is used in furniture making due to its high quality of wood, while green fruit shell and leaves are used in fabric dyeing and hair coloring (Al-Snafi 2018).

## 23.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques

In researches, it has been determined that the same species in different locations can vary in terms of compound type and amount (Van Vuuren et al. 2007; Polat and Coskun 2016; Polat et al. 2018). Depending on the geographical location, temperature, time, and other factors, the type and amount of compounds contained in walnuts can also vary. The seeds of the walnut are a valuable food source. Approximately 70% of seeds are composed of oils, while 15% of them are composed of proteins. Aspartic acid, serine, threonine, proline, glycine, glutamic acid, valine, methionine, alanine, isoleucine, leucine, tyrosine, histidine, lysine phenylalanine, and arginine are the amino acids it contains (Al-Snafi 2018; Delaviz et al. 2017). The energy of 100 grams of walnut seeds is approximately 654 kcal. Vitamins in 100 gr walnuts: Vitamin A (20 IU), Thiamine (0.341 mg), Riboflavin (0.15 mg), Niacin (1.125 mg), Pantothenic acid (0.570 mg), Vitamin B6 (0.537 mg), Vitamin C (1.3 mg), Vitamin E (0.7 mg), and Vitamin K (2.7 mg) (Şen and Karadeniz 2015). It is rich in polyunsaturated fatty acids (palmitoleic acid, oleic acid, gadoleic acid, linoliec acid, lineliec acid), saturated fatty acids (myristic acid, palmitic acid, stearci acid, and archidic acid), phenolic compounds (ellagic acid, gallic acid, syringic acid, caffeic acid, p-coumaric acid, ferulic acid, synaptic acid), and tannins (glansrins A, B and C, casuarinini, and stenophyllarin) (Al-Snafi 2018; Delaviz et al. 2017). Studies on walnut leaves have found that it contains phenolic acids, tannins, essential fatty acids, carbohydrates, cardiac glycosides, ascorbic acid, flavonoids, caffeic acid, paracomaric acid, alkaloids, and protein. Among the most important flavonoids, it contains quercetin galactoside and quercetin pantocid derivatives, quercetin arabinoside, quercetin xyloside, and quercetin rhamnoside. Quercetin 3-galactoside is the main component among the compounds (Zhao et al. 2014; Delaviz et al. 2017). In addition, walnut leaves contain naphthalene derivatives. Juglone (5-hydroxy-1,4-naphthoquinone) is the important naphthaquinone derivative found in walnuts. Juglone, a toxic compound, is found only in fresh and green walnuts, but not in dried leaves (Cosmulescu et al. 2010; Delaviz et al. 2017).

## 23.5 Scientific Evidences: Pharmacological Activities

### 23.5.1 Antioxidant Activity

In biological systems, oxidative stress is reasoned by the instability between the production of reactive oxygen species (ROS) and antioxidant defense systems. Excessive oxidative stress can cause some diseases to occur (Valko et al. 2007). Studies have shown that walnut seeds, green peels, and leaves have significant antioxidant effects. It has been observed that the antioxidant potential of the walnut varies according to the region where it is grown (Pereira et al. 2007; Oliveira et al. 2008). In the study conducted on the hydroalcoholic extract of walnut peel, it was determined that 0.2 μg ml-1 extract reduced serum LDL oxidation by 87% (Ahmadvand et al. 2011). In different study, the antioxidant activity of the methanol extract of walnut peel was examined by DPPH method and it was found to be active. (DPPH 0.19 mg mL-1). In another study, antioxidant activity was examined with 3 different in vitro methods and it was found to be as effective as leaves. (DPPH 0,035 mg mL-1; β-Carotene bleaching 0,127 mg mL-1; Reducing power 0,05 mg mL-1) (Oliveira et al. 2008). In another study, antioxidant activities were exam-

ined on different extracts of walnut peels (aqueous, hydroalcoholic, chloroform, and petroleum ether) and their aqueous and hydroalcoholic extracts were found to be more active (Al-Snafi 2018). The antioxidant activity of walnut leaves was found to be higher in 2 different in vitro methods which were performed comparatively with methanol extracts of walnut leaves and olive leaves. (DPPH: 0.0530 mg mL-1; ABTS: 0.0421 mg mL-1) (Polat et al. 2019). In another study, the antioxidant activity of walnut leaves was examined with 2 different in vitro methods (O2-: IC50 0,047 mg mL-1; H2O2: IC50, 0,0383 mg mL-1) (Almeida et al. 2008). In an antioxidant study with methanol extracts of walnut flowers, it was found that it is effective against H2O2 radials (0,311 mg mL-1) (Al-Snafi 2018).

### 23.5.2 Anti-inflammatory Activity

It was found that methanol leaf extract inhibited the edema caused by carrageenan in a statistically significant way at almost all doses (250–1000 mg/kg ip) compared to control groups. The highest activity was seen at 1000 mg/kg ip (Nabavi et al. 2011). Walnut methanol extract was found to induce internalization of the LPS receptor, toll-like receptor 4, and it has been determined that the anti-inflammatory effects of walnuts are due to the functional activation of phospholipase D2 (Willis et al. 2010). In a comparative study of methanol extracts of walnut leaves and olive leaves, it was found that the anti-inflammatory activity of walnut leaves was higher (0.3959 mg mL-1) (Polat et al. 2019).

### 23.5.3 Cardiovascular Activity

In a study conducted on rats with diabetes, it was found that in rats given 200 and 400 mg/kg of ethanol leaf extract for 28 days, it lowered blood sugar as well as LDL, triglyceride, and cholesterol levels (Mohammadi et al. 2011). It has been noticed that diets containing walnuts cause a small change in the total amount of fat. It is thought that this small amount of change may be an additional process in preventing vascular plaque formation (Delaviz et al. 2017). In a study with rats with hypertension, seed methanol extract (100 and 200 mg/kg) was administered orally, and after 16 days, it was found to have similar effects to Captopril (Joukar et al. 2017). In a study conducted with 19 male rats, hydroalcoholic leaf extracts were given and it was found to reduce mean arterial pressure and systolic and diastolic pressure (Ebrahimiyan et al. 2016). The antihemolytic activities of methanol extracts of Juglans regia flowers were evaluated by various in vitro experiments and it was determined that they showed antihemolytic activity against hemolysis caused by H2O2 and CuOH (Ebrahimzadeh et al. 2013).

### 23.5.4 Central Nervous System Activity

In a study with 98 male rats, walnut seed methanol extract (50, 100, 200, and 500 mg/kg) was administered orally. As a result of the study, it was determined that the extracts cause an anticonvulsant effect (Asadi-Shekaari et al. 2014). In a different study, walnut fruit extract (100 and 150 mg/kg) was administered orally to animal groups in which 2 different depression models (forced swimming test and tail suspension test) were created. Antidepressant effects were detected in both doses. This effect has been attributed to the omega 3 contained in walnuts (Nabavi et al. 2011; Al-Snafi 2018). Dichloromethane, ethyl acetate, acetone, methanol, and distilled water extracts of walnut leaf and fruit were obtained, and no significant effect was found in the in vitro butyryl cholinesterase and acetyl cholinesterase inhibitor activity study (Orhan et al. 2011). Due to the omega 3 it contains, walnuts have been found to improve cognition and nerve function in rats due to age. In a study conducted with 45 male rats supplemented with walnuts in their diets, it was found that it significantly reduced pro-inflammatory tumor necrosis factor alpha, cyclooxygenase-2, and inducible nitric oxide synthase in rats (Fisher et al. 2017).

### 23.5.5 Anticancer Activity

Many studies have shown that plant components especially flavonoids can be effective and protective against oxidative damage (Yalçın et al. 2020; Karakaş et al. 2021). Walnut is the main source of flavonoids, and due to the flavonoids it contains, it has antioxidant properties that play a role in the regulation of immune function and increase the body's anticancer activities (Delaviz et al. 2017). In a study conducted with rats, the effects of juglone on colon cancer cells were examined, and it was shown that it has an anticancer role in preventing the formation of benign or malignant intestinal tumors (Sugie et al. 1998; Zhang et al. 2012). In an in vitro study performed with hexane extracts of walnut leaves on the prostate cancer cell line, it has been determined that it inhibits the growth of cancer cells (Li et al. 2015). In a study conducted on NCI-H322 and A549 lung cancer cell lines, it was determined that juglone isolated from walnut roots showed cytotoxic effects (Zhang et al. 2015). In another study conducted on MDA-MB-231, MCF7, and HeLa cells lines, it was determined that methanol extracts of walnut showed cytotoxic effects. Its mechanism has been reported to be impaired mitochondrial function and apoptosis (Le et al. 2014).

### 23.5.6 Antidiabetic Activity

Diabetes mellitus is one of the major diseases due to its fatal complications. Although the most common way of treatment is the use of insulin, the diet is also effective. Some plants are known to be effective in diabetes, and one of them is walnut (Fallah Huseini et al. 2006; Said et al. 2008). In Iranian traditional medicine, walnut leaves and fruits are among the natural remedies recommended for diabetics. Green walnut peel has also been reported to reduce complications of diabetes. In previous studies, it has been determined that walnut and olive leaf infusion has a blood sugar lowering effect in diabetic patients (Delaviz et al. 2017). In a study with diabetic rats, the extract was applied to rats at doses of 125, 250, 500, 1000 mg/kg twice a day, and it was found that diabetic rats lowered blood sugar after 24 hours. It was found to have no hypoglycemic effects in normal rats (Fathiazad et al. 2006). In different study, 200 and 400 mg/kg leaf extract was applied to diabetic rats and it was found to be effective against hyperglycemia (Mohammadi et al. 2011). It has been found that in combination with the extracts of leaves (*Juglans regia*, *Olea europea*, *Urtica dioica,* and *Atriplex halimus*), they act synergistically and regulate glucose homeostasis (Said et al. 2008). In another study, alcohol extracts of walnut leaf were applied to rats with diabetes (750 mg/kg and 500 mg/kg). It has been reported to cause a decrease in cholesterol, triglyceride, hemoglobin A1c (HbA1c), and LDL and an increase in HDL and hyperinsulinemia in rats with diabetes (Majidi et al. 2015). In a study conducted with walnut peel and leaf methanol extracts, it was found that it reduced glucose levels in rats with diabetes (Javidanpour et al. 2012).

### 23.5.7 Antimicrobial and Antifungal Activity

An inhibitory effect on *Propionibacterium acnes* was detected in a study conducted on ethanol extracts of walnut leaves. It has been shown that it can be an alternative method to acne treatment (Sharafatichaleshtori et al. 2010). In another study, it was stated that walnut leaf extracts may be beneficial against bacteria responsible for human gastrointestinal infections (Amaral et al. 2004). In addition, walnut leaf methanol extracts were detected to be effective in studies on *Candida albicans* (Sytykiewicz et al. 2015). The effect of walnut shell hydroalcoholic extract on *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus* spp., *Pasteurella multocida,* and *Mannheimia haemolytica* pathogens was investigated. The minimum inhibitory concentration was 62.5 mg/ml against *S. aureus*, *P. multocida*, *M. haemolytica,* and *Streptococcus* spp. No significant response was found on *S. aureus*, *Streptococcus spp*., *P. multocida,* and *M. haemolytica* at concentrations below 100 mg/disc (Moori Bakhtiari and Khalafi 2015).

The antifungal effects of walnut leaf extracts fractions were studied against *Ascosphaera apis*. It is thought to have antifungal effects due to juglone and eugenol substances (Al-Snafi 2018). The antifungal effects of walnut leaf extract fractions (methanolic, ethyl acetate, alkaloid, and hydrolyzed methanolic) on Candida albicans were studied. It has been found that methanol extracts have high antifungal activity, while ethyl acetate fractions have lower antifungal activity (Al-Snafi 2018).

### 23.5.8 Protective of Liver and Kidney

In the study, 36 male rats with liver oxidative damage were applied 50, 100, 200, and 400 mg/kg of walnut leaf ethanol extract for 28 days. Walnut leaf extract has been determined to have strong hepatoprotective effect (Eidi et al. 2011). In different study, it was found that walnut leaf extracts given to rabbits with acute kidney failure had important effects in treatment (Ahn et al. 2002).

### 23.5.9 Other Activities

In Iranian Traditional Medicine, walnut consumption is used in the treatment of inflammatory bowel disease (Delaviz et al. 2017). In different study, walnut leaf ethanol extract (0.5, 1, 1.5 mg/kg) was given to 70 male rats and it was found that it caused an important reduction in pain when administered in acute pain (Mokhtari et al. 2008).

The anthelmintic activity of different extracts of walnut leaf against *Pheretima posthuma* was tested. While the water extract showed significant activity, the petroleum ether extract was the least active. The acaricidal activities of walnut extracts (chloroform, petroleum ether, ethyl acetate, and methanol) on *Tetranychus cinnabarinus* and *Tetranychus viennensis* were evaluated under laboratory conditions. It was determined that petroleum ether extract ($LC_{50}$ 0.73–0.04 mg/ml) caused the highest mite mortality (Al-Snafi 2018).

## 23.6 Clinical Studies

### 23.6.1 Cardiovascular Activity

In the study conducted with 18 healthy male patients, two different diets were followed and followed for 8 weeks. It was found that LDL and HDL values decreased in the group with walnuts in their diets (Sabate et al. 1993). In another study, the diets of 793 patients were examined, and it was found that HDL and total cholesterol in the blood decreased in those who consumed walnuts (Lavedrine et al. 1999). In the study conducted with 13 women and 5 men aged 60 years in the postmenopausal period, walnuts were added to the diets of the patients for 4 weeks. It has been found that patients regulate lipid levels. (Almario et al. 2001). In Iran, in a study conducted, walnut oil capsules were given to patients for 45 days (Zibaeenezhad et al. 2003). In another study with walnut oil capsules, a decrease in LDL levels was found in patients with type II diabetes (Zibaeenezhad et al. 2017).

### 23.6.2 Antidiabetic Activity

In a study conducted on patients (61 patients) with type II diabetes, a group of walnut leaf water extract capsules (100 mg) were administered twice a day for 2 months. The other group was given a placebo capsule. The normal treatment of the patients (metformin and glibenclamide) continued. As a result of the study, it was determined that insulin, HbA1C, total cholesterol, and triglyceride levels were significantly decreased in Type II diabetes patients treated with walnut leaf extract (Hosseini et al. 2014a). Iranian patients with type II diabetes were included in the clinical study. Walnut leaf extract was given to the patients for 2 months. As a result of the research, it was found that HbA1c and blood sugar levels were significantly reduced (Hosseini et al. 2014b). In a different study, eight patients with Type I diabetes were advised to drink 250 ml of walnut hydrosol (walnut hydrosol) twice a day after meals. In seven people, the average daily blood sugar level and insulin dose decreased.

Two patients developed a generalized itchy erythematous skin rash. One patient fell into a hypoglycemic coma (Moravej et al. 2016).

## 23.7 Toxicological Studies

Methanol leaf extracts up to 4 g/kg were found to exhibit no toxicity when ip injected into mice (Nabavi et al. 2011). No liver, kidney, and other adverse effects were observed in Type II diabetic patients using 100 mg leaf extract capsules for 3 months, except for a GI event (especially a mild diarrhea) (Hosseini et al. 2014b).

Rats were given 2 g/kg of walnut polyphenols orally and were observed for 14 days. No toxic events or abnormal changes were observed when compared with the control group (Al-Snafi 2018).

Juglone: while studies with rats show that it can cause irritation and hyperpigmentation of the skin, it has been found to be very rare in humans (Al-Snafi 2018).

## 23.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies

Especially walnut oil preparations are available in the market. It is recommended as an alternative to fish oil due to the high amount of Alpha linolenic acid it contains. It is also used to protect the blood cholesterol level. These products are available in glass bottles or capsule form (ZadeVital 2021).

## 23.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidence

In addition to being used as food, walnuts have been used in the treatment of various diseases from past to present (Al-Snafi 2018). Traditionally, walnut leaves are known to be used in the treatment of hemorrhoids, as an antidiarrhea, antiparasitic appetizer, and blood sugar lowering, externally as an antipyretic and antiseptic in skin diseases (Baytop 1999; Delaviz et al. 2017; Al-Snafi 2018; Bellikci Koyu 2020). In studies conducted with rats, walnut leaf extracts were found to lower LDL, triglyceride, and cholesterol levels as well as lower blood sugar (Fathiazad et al. 2006; Mohammadi et al. 2011; Delaviz et al. 2017). In addition, the anthelmintic and antibacterial effect of the leaf extracts has also been determined. This is supported by clinical studies, and it has been determined that leaf extracts reduce the levels of insulin, HbA1C, total cholesterol, and triglycerides in the blood (Hosseini et al. 2014a; Hosseini et al. 2014b; Majidi et al. 2015; Moravej et al. 2016).

The seeds, which are the eaten part of the walnut, are used in memory enhancer, aphrodisiac, constipation, and rheumatism treatment. The oil obtained from these seeds has traditional use in removing dandruff, muscle pain, sharpening the eyesight, liver damage, and memory enhancer (Baytop 1999; Bellikci Koyu 2020; Taha and Al-wadaan 2011; Al-Snafi 2018). Studies with rats have shown that walnuts have anticonvulsant effects and are also effective against depression. In clinical studies, it has been determined that walnuts and walnut oil capsules added to diets regulate blood cholesterol levels (Sabate et al. 1993; Lavedrine et al. 1999; Zibaeenezhad et al. 2003; Zibaeenezhad et al. 2017). The green shell of walnut is used in skin diseases and stomach, liver, and lung cancer (Taha and Al-wadaan 2011; Al-Snafi 2018).

## 23.10 Challenges and Future Recommendations as Potential Drug Candidate

Studies have shown that plants belonging to the Juglandaceae family contain monoterpenes, coumarin, flavonoids, tannins, saponins, and alkaloids. For many years, walnuts have been used in the treatment of various diseases. It has been suggested that walnut reduces the risk of

hypertension, diabetes mellitus, cancer, and microbial activity due to its active ingredients. However, since they contain too many active ingredients, more studies are needed in terms of toxicology. In addition, more clinical studies need to be done on walnuts. Thus, it can be a plant suitable for use in drug formulation for the treatment of certain diseases.

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# *Laurus nobilis* L.

24

Gülsen Kendir

**Abstract**

*Laurus nobilis* L. is evergreen aromatic shrubs or trees, belongs to Lauraceae family, and is cultivated because of its aromatic leaves and ornamental interest. This chapter first summarized the description and distribution of the plant. Its chemical composition and traditional use were demonstrated in detail. The biological activities of its extracts, fractions, and pure compounds have been highlighted for further studies of the researchers. Besides, its toxicity and allergenicity properties were indicated.

**Keywords**

*Laurus nobilis* · Traditional use · Chemical composition · Biological activities

## 24.1 Introduction

*L. nobilis* belongs to Lauraceae family and is dioecious, evergreen aromatic shrubs or trees that can grow till 2–15 m. The leaves are simple, alternate, oblong-lanceolate to ovate, apex acute, or acuminate, entry or wavy with margins, coriaceous, short-stalked, 3–10 (11) cm height, and 2–4 (5) cm wide. The upper surface is bright, dark green to brown, glabrous and the lower surface is matte, lighter green to brown with marked midrib and veins. The flowers are small and yellow in small clusters. The male flowers have 8–12 stamens and the female flowers have 2–4 staminodes. The perianth is 4- to 6-lobed. The ovary is superior with l-celled, a short style, and a triangular obtuse stigma. The fruit is a berry, 10–15 mm, with a single seed, globular to ellipsoid, black when ripe (Demiriz 1982; Sharma et al. 2012). *Laurus nobilis* is known by different names such as bay leaf, laurel, or sweet bay in English; defne, har, or tehnel in Turkish; alloro or lauro in Italian; waraq ghaar in Arabic; lorbeer in German; dafni in Greek; teejpatta in Hindi; Laurier D'apollon in French; and Gekkeiju in Japanese (Batool et al. 2020). It is a Mediterranean element and most likely originated in South Asia. Also, the plant is grown in varied ecological and climatic circumstances. It is reproduced by seeds or by cuttings. Moist, sandy soils or moist atmospheric circumstances imminent in the ocean coast are the best circumstances for growing the plant, and also the plants should be protected from winter winds (Patrakar et al. 2012; Batool et al. 2020). It is a respected plant since ancient times. It was used as a symbol of peace and victory. The crown of laurels on the crown of kings and the heads of the winners in the old Olympics is an indication of its use as a symbol of victory

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(Conforti et al. 2006). Its leaves are especially used as a spice and have industrial importance as dried leaves. They are used in powdered form, especially for soups and condiments. Turkey, Spain, Portugal, and Iran are the largest dried exporters. While the leaves and fruits are used for medicinal purposes, the essential and fixed oils obtained from them are used especially in the food, perfumery, soap, and pharmaceutical sectors. It is used as a food preservative in the food industry due to its antimicrobial and insecticidal effects. Most of the evergreen laurels grown as hedges are used by florists because of their beautiful leaves (Chahal et al. 2017; Petkova et al. 2019). Based on the idea of the discovery of new drugs with traditional herbal medicines, the plant, which is used for both medicinal and food purposes and has an important field of use in the industry, has been tried to be examined from various aspects such as its traditional use, chemical structure, and biological activities.

## 24.2 Distribution and Status of Species

It is native to the Mediterranean region and grows naturally in Europe and California. The plant is widely cultivated in many warm regions of the world, especially in India, Pakistan, other Southeast Asian countries, some Pacific islands, Australia, around the coast of the Mediterranean and Southern Europe, Greece, Portugal, France, Turkey, Spain, Algeria, Morocco, Belgium, Central America, Mexico, Southern United States, and the Canary Islands (Parthasarathy et al. 2008; Sharma et al. 2012).

## 24.3 Comparison of Traditional/Ethnomedicinal/Local Uses

**Italy** The leaves are utilized as an ingredient in "Ricotto", and as an aromatic herb, with meat or *Castanea sativa* Mill. fruits. It also is employed to repel moths. The leaf infusion is used as digestive, sedative, antiemetic, cough sedative, tonic stimulant, and antidiaphoretic. The leaf decoction is taken orally for airway inflammation, cold, cough, sore stomach, abdominal pains, menstrual pains, intestinal pain, dysmenorrhea, antidiarrheal, carminative, and as a diuretic (Ballero et al. 2001; Maxia et al. 2008; Motti et al. 2009; Leto et al. 2013; Motti and Motti 2017; Mautone et al. 2019). The leaf decoction is applied in the form of a foot-bath as stimulating blood circulation and also used against cold and hemorrhoid. The fruit decoction is consumed for gastrointestinal disorders (Vitalini et al. 2013). The leaf infusion was commonly used by women who just gave birth as a galactagogue in the past (Guarrera and Leporatti 2007). A poultice prepared from the leaf is used for insect bites (Ross 2001). The fruit macerated in oil is used for rheumatic pains, and the wine prepared from its fruits is utilized for contusions (Ballero et al. 2001; Leto et al. 2013).

**Spain** The leaf infusion is taken orally as an antispasmodic, expectorant, mucolytic, and emmenagogue (Gonzalez et al. 2010). The leaf is employed as antiecchymotic in the form of liniment or lotion (Rigat et al. 2015).

**India** The leaf is applied directly on the skin in crushed form for treatment of prickly heat (Saikia et al. 2006). The fruit is consumed as an emmenagogue (Ross 2001).

**Algeria** Decoction of the leaf is used in the treatment of hypertension (Benderradji et al. 2014). The decoctions of leaves and roots are employed for respiratory, genital organ, and bronchopulmonary infections (Bouasla and Bouasla 2017). For hair loss, decoction or infusion of the leaves is applied in the form of a massage (Senouci et al. 2019).

**Morocco** Decoction of the leaves is used for mouth ulcers, gingivitis, and halitosis as a gargle (Najem et al. 2020). Decoctions of the leaves and fruits are taken orally for rheumatism and also

their infusions are drunk for the liver, pancreas, and digestive pains. Oil of the leaf and fruit are used externally for face care (Abouri et al. 2012).

**Israel** The fruit is used for arthritis and sugar in the blood (Lev and Amar 2000). The fruit essential oil is employed externally on wounds and also for rheumatic and neuralgic pains (Ross 2001).

**Serbia** The leaf decoction is consumed for bronchitis and as part of a person's diet (Jarić et al. 2015).

**Greece** Hot water extract of the leaf is drunk as a contraceptive (Ross 2001).

**Turkey** The leaf infusion is taken orally for abdominal pain, asthma, and sore throat (Bulut and Tuzlaci 2013; Ecevit Genç and Özhatay 2006). The infusion of the leaves is drunk in the form of one teacup 2–3 times a day for 3–5 days for antipyretic and analgesic purposes and also in the form of one teacup 2–3 times a day before meal for 5–7 days for the treatment of hemorrhoid (Ugulu et al. 2009). Four glasses of boiled water are poured over 1–2 teaspoons of dried leaves and infused for 10–15 minutes; then it is applied to areas with psoriasis and eczema (Korkmaz et al. 2016). Decoction of the leaves is drunk for sterility by women as one teacup two times a day for a week (Polat and Satıl 2012). The leaf decoction is taken orally for diabetes, kidney, and stomach diseases. Infusion of the flowers and leaves is consumed for cardiac diseases (Ecevit Genç and Özhatay 2006). The leaf is crushed and used externally for a toothache (Bulut and Tuzlaci 2013).

The fruit decoction is taken orally as antidiabetic. The fruit oil is applied externally to the skin for treatment of hemorrhoid, eczema, itching, and scabies. Besides, it is applied topically for parasitic diseases in animals (Güzel et al. 2015). The fruit is crushed and used as an antiseptic (Ugulu et al. 2009). The fatty oil obtained from the seeds is applied to the dorsal area in the form of massage for a herniated disk. The soap prepared with its fatty oil is used through washing the skin for skincare and cleaning. The fatty oil is applied for rheumatoid pain and cracked skin on the affected area with rubbing (Akaydın et al. 2013).

## 24.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques

### 24.4.1 Essential Oil

The essential leaf oil was analyzed and 6-terpinylacetate was characterized for the first time in nature (Braun et al. 2001). 1,8-Cineole was determined as the major compound in the fresh leaves, together with α-terpinyl acetate, sabinene, α-pinene, β-pinene, β-elemene, α-terpineol, linalool, and eugenol. Besides that, 1,8-cineole, pinenes, α-eudesmol, β-elemene, and β-caryophyllene were the main components in the flowers, (*E*)-β-ocimene and bicyclogermacrene in the fruits, and β-ocimene and germacrene D in the buds. The key odorants of leaves were detected through aroma extract dilution analysis and (*Z*)-3-hexenal (fresh green), 1,8-cineole (eucalyptus), linalool (flowery), eugenol (clove), (E)-isoeugenol (flowery), and an unidentified compound (black pepper) were determined (Kılıc et al. 2004). Also, 1,8-cineole, α-pinene, β-longipinene, linalool acetate, cadinene, β-pinene, α-terpinyl acetate, and α-bulnesene were observed as major compounds in the fruit essential oil (Marzouki et al. 2008). 1,8-Cineole, (E)-β-ocimene, α-terpinyl acetate, α-pinene, β-pinene, and β-longipinene were detected as main compounds in the essential oils of the seed and pericarp (Marzouki et al. 2009). Eucalyptol (17.2%), α-terpinyl acetate (9.0%), caryophyllene oxide (6.1%), spathulenol (5.0%), and methyl eugenol (4.2%) were detected as major compounds in the essential oil of seed

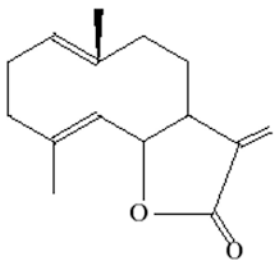
(Elkıran et al. 2018). 1,8-Cineole (51.05%) and α-terpinyl acetate (13.94%) were found as the main components from the essential oil of the stem (Chalchat et al. 2011).

### 24.4.2 Fixed Oils

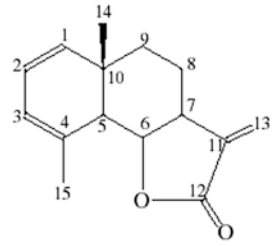
Palmitic acid was detected as the major fatty acid in the commercial leaves, while linolenic acid in the wild leaves was found (Dias et al. 2014). The fixed oils from dried berries obtained by supercritical fractioned extraction with carbon dioxide 12:0 (27.6%), 18:1 n-9 (27.1%), 18:2 n-6 (21.4%), and 16:0 (17,1%), with the 18:1 n-9 and 18:2 n-6 unsaturated fatty acids were found as the most represented fatty acids (Marzouki et al. 2008). Fatty acids composition of the fruit and seed was analyzed with combined techniques of HPLC and GC. The fruit had high level of unsaturated fatty acids (especially polyunsaturated fatty acids), while the seed had higher level of saturated fatty acids (Marzouki et al. 2009). The seed oil was analyzed by using supercritical $CO_2$ extraction and lauric acid was found as a major constituent (Beis and Dunford 2006). Oleic, linoleic acid, lauric, and palmitic acids were dominant in the pericarp, whereas oleic, palmitic, and linoleic acids were found as the main fatty acids in the seed (Petkova et al. 2019).

### 24.4.3 Sesquiterpenoids

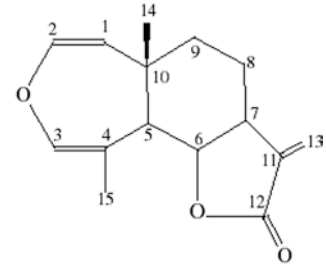
Sesquiterpene lactones, 10-epigazaniolide, gazaniolide, spirafolide, artremorin, costunolide, zaluzanin D, reynosin, santamarine, 5a,9-dimethyl-3-methylene-3,3a,4,5,5a,6,7,8-octahydro-1-oxacyclopenta[c]azulen-2-one, dehydrocostus lactone, 3β-chlorodehydrocostuslactone, deacetyl laurenobiolide, laurenobiolide, (5*S*,6*R*,7*S*,8*S*,10*R*)-6,8-dihydroxyeudesma-4(15),11(13)-dien-12-oic acid 12,8-lactone, eudesmane lactones, and their corresponding methyl esters were identified from the leaves (Fang et al. 2005; Dall'Acqua et al. 2006; Fukuyama et al. 2011; Ham et al. 2011; Julianti et al. 2012). Besides, sesquiterpenes, laurupene A, laurupene B, *p*-menthane hydroperoxide, and (1*R*,4*S*)-1-hydroperoxy-*p*-menth-2-en-8-ol acetate were isolated from the leaves (Uchiyama et al. 2002; Chen et al. 2014). Sesquiterpene lactones such as lauroxepine, costunolide, gazaniolide, santamarine, reynosin, 11,13-dehydrosantonin, and spirafolide were isolated from the methanol extract of the fruits (Barla et al. 2007).




Contunolide




Spirafolide




Gazaniolide

### 24.4.4 Norisoprenoids

Megastigmane and megastigmane glucosides (laurosides A-E, ampelopsisionoside, alangioside A, dendranthemoside A, icariside B1, citroside A) were isolated from the methanolic extract of the leaves (De Marino et al. 2004).

### 24.4.5 Tocopherols

α -tocopherol was determined as 17.62 and 12.56 mg/100 g of fresh weight in the branches and roots, respectively. γ -tocopherol was detected in the branches and roots with 7.64 and 0.85 mg/100 g fresh weight, respectively

(Ouchikh et al. 2011). α, β, δ, and γ-tocopherol were detected in the leaves (Dias et al. 2014). α, β, and γ-tocopherol composition of the pericarp and seed was analyzed and content of γ-Tocopherol was observed high. The content of sterols in the seed and pericarp was detected slightly lower (Petkova et al. 2019).

### 24.4.6 Flavonoids

Kaempferol, kaempferol-3-rhamnopyranoside, kaempferol-3,7-dirhamnopyranoside, kaempferol-3-*O*-α-L-(2′′-E-*p*-coumaroyl)-rhamnoside, kaempferol-3-*O*-α-L-(3′′,4′′-di-E-*p*-coumaroyl)-rhamnoside, kaempferol-3-*O*-rutinoside, kaempferol-3-*O*-deoxyhexoside, kaempferol-3-*O*-pentoside, kaempferol-3-*O*-hexoside, quercetin-3-*O*-deoxyhexoside, kaempferol-3-*O*-glucoside, kaempferol-3-*O*-(6″-*O*-deoxyhexosyl)-hexoside, quercetin, quercetin-3-*O*-(6″-*O*-deoxyhexosyl)-hexoside, tetra-methoxy-dihydroquercetin-3-*O*--pentoside, quercetin-3-*O*-hexoside, quercetin-3-*O*-pentoside, rutin, isoquercitrin, naringenin, hesperetin, 8-*C*-hexosyl apigenin, apigenin-6,8-di-*C*-hexoside, apigenin-6-*C*-(2″-*O*-deoxyhexosyl)-hexoside, (iso)rhamnetin-3-*O*-(6″-*O*-deoxyhexosyl)-hexoside, and (iso) rhamnetin-3-*O*-hexoside from the leaves were identified (Kang et al. 2002; De Marino et al. 2004; Emam et al. 2010; Vallverdú-Queralt et al. 2014; Pacifico et al. 2014).

### 24.4.7 Proanthocyanidins

Flavan-3-ols were detected as the major phenolic compounds present in both wild and cultivated leaves, especially the most abundant ones were (−)-epicatechin and a procyanidin trimer with an A-type linkage (Dias et al. 2014). Cinnamtannin B1was identified from the leaves (Pacifico et al. 2014).

### 24.4.8 Other Phenolic Compounds

Phenolic compounds, 2′, *β*-Dihydroxy-*α*,*β*-dihydrochalcone-*α*-*O*-hexoside, 1-(2′-Hydroxyphenyl)-1-hydroxyphenylpropan-*α*-*O*-hexoside, and 2′-Hydroxy-*α*,*β*-dihydrochalcone-*α*-*O*-hexoside, were detected from the leaves (Pacifico et al. 2014). Phenolic acids named as gallic acid, chlorogenic acid, caffeic acid, vanillic acid, coumaric acid, ferulic acid, cryptochlorogenic acid, homovanillic acid, rosmarinic acid, neochlorogenic acid, protocatechuic acid, syringic acid, vanillic acid-*O*-hexoside, caffeic acid-*O*-hexoside, homovanillic acid-*O*-hexoside, *p*-hydroxybenzoic acid, coumaric acid-hexoside, coumaric acid-*O*-hexoside, *m*-hydroxybenzoic acid, *p*-hydroxybenzoic acid, 4-*O*-*p*-coumaroylqunic acid, and 3,4-dihydroxybenzoic acid hexoside were identified from the leaves (Vallverdú-Queralt et al. 2014; Pacifico et al. 2014). The major phenolic acids in the fruits were observed as *p*-coumaric acid, vanillic acid, caffeic acid, and syringic acid (Petkova et al. 2019). The main anthocyanins were detected as cyanidin 3-*O*-glucoside and cyanidin 3-*O*-rutinoside in the fruits. Besides, two minor anthocyanins were detected as 3-*O*-glucoside and 3-*O*-rutinoside derivatives of peonidin (Longo and Vasapollo 2005).

### 24.4.9 Others

Polysaccharides (alginate, fucoidan, and laminaran) were isolated from the leaves (Chmit et al. 2014). Sugars (fructose, sucrose, and glucose) and organic acids (oxalic acid, malic acid, and ascorbic acid) were detected from the leaves (Dias et al. 2014).

## 24.5 Scientific Evidences

### 24.5.1 In vitro Studies

#### Antimicrobial

The antimicrobial activities of the leaf essential oil were evaluated by disc diffusion and minimum inhibitory concentration methods against *Staphylococcus aureus* strains, *Bacillus subtilis*, *Enterococcus gallinarum*, *E. faecium*, *E. faecalis, Listeria monocytogenes, Streptococcus pyogenes, Escherichia coli* strains, *Haemophilus influenza*, *Pseudomonas aeruginosa, Salmonella typhi, and Candida albicans*. The seed oil and the seed oil methanolic extract activities were investigated by agar well method. The seed oil methanolic extract displayed more effective antibacterial activity than the leaf essential oil and seed oil. The seed oil and seed oil methanolic extract did not exhibit effect against Gram-negative bacteria apart from *H. influenzae.* However, they showed considerable antimicrobial effect against Gram-positive bacteria (Ozcan et al. 2010).

Sesquiterpene lactones, laurenobiolide, laurenobiolide, and (5S,6R,7S,8S,10R)-6,8--dihydroxyeudesma-4(15),11(13)-dien-12-oic acid 12,8-lactone isolated from the leaves exhibited growth inhibitory effects against neuropathic pathogens (*Actinomyces viscosus*, *Porphyromonas gingivalis*, *Prevotella intermedia,* and *Actinobacillus actinomycetemcomitans*), opportunistic Gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes*), and fungi (*Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus*) with $IC_{50}$ values ranging from 31 to 1000 $mgL^{-1}$ (Fukuyama et al. 2011).

The antibacterial activities of essential oil, ethanolic, and hot/cold aqueous extracts of the leaf were evaluated against both food spoilage and pathogenic bacteria (*Brochothrix thermosphacta*, *Escherichia coli*, *Listeria innocua*, *L. monocytogenes*, *Pseudomonas putida*, *Salmonella typhimurium,* and *Shewanella putrefaciens*). The essential oil exhibited the highest antibacterial activity against all bacteria. The ethanolic and hot/cold aqueous extracts showed no inhibitory activity against *E. coli, P. putida,* and *S. typhimurium*. The essential oil showed the best inhibitory effect against *P. putida* with MIC value 0.5 mg $mL^{-1}$ (Ramos et al. 2012).

The polysaccharides (alginate and fucoidan) obtained leaves, the essential oil obtained leaves or fruits, and fatty oils showed good antibacterial activity against three Gram-positive bacteria (*Staphylococcus aureus*, *S. epidermidis,* and *Enterococcus faecalis*) and Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). The highest effect was observed with fucoidan against *S. epidermidis* with MIC value ≤60.97 mg/mL and MBC value 60.97 mg/mL. The alginate showed the highest eradication capacity of about 78.0% at the lowest concentration of 46.65 mg/mL against *S. epidermidis* CIP 444 biofilm (Chmit et al. 2014).

The essential oil obtained from the leaves exhibited strong antibacterial activity against the strains Gram-negative *Klebsiella pneumoniae* and *Salmonella enterica* with inhibition diameters 21.93 and 20.47 mm and MIC values 0.2 and 0.11 mg/ml, respectively. However, the essential oil exhibited moderately an antimicrobial effect against *Escherichia coli* and *Proteus* (gram-negative strains) and *Staphylococcus aureus* and *Staphylococcus sp* (gram positive strains) with inhibition diameters (13.73, 12.13, 14.50 and 13.03 mm, respectively) and MIC values (0.5, 0.33, 0.25 and 0.66 mg/ml, respectively) (Goudjil et al. 2015).

The essential oil obtained from fresh leaves exhibited moderate antifungal activity against *Cryptococcus neoformans* with MIC value 0.62 mg/mL and potent antifungal activity against *Cryptococcus gattii* with MIC value 0.31 mg/mL. 1,8-CCineole obtained from the leaves exhibited moderate inhibitory activity against *C. neoformans* with MIC value 0.62 mg/mL and potent inhibitory activity against *C. gattii* with MIC value 0.31 mg/mL. In addition, linalool obtained from the leaves showed moderate inhibitory effect against *C. gattii* and *C. neoformans* with MIC value 0.62 mg/mL (Fernandez-Andrade et al. 2016).

Antibacterial activity of the essential oils obtained from the leaves was investigated against

oral *Staphylococcus aureus* ($n = 21$) strains with broth microdilution method. Besides, antibiofilm activity was evaluated by Crystal Violet staining and MTT tests. The leaves were collected from two Tunisian localities (Gafsa which in the south-west, and Sousse in the central-east of Tunisia). The essential oil from Sousse displayed the best bactericidal activity (MICs values between 3.91 and 15.62 mg/ml). Also, its oil exhibited a strong biofilm inhibitory activity of over 70%, with a low subinhibitor concentration (1/16 MIC). The MTT test showed that both essential oils exhibited strong antibiofilm activity with percentages of eradication between 79.6 ± 2.27 to 95.2 ± 0.56 (Merghni et al. 2016).

The antibacterial activity of the leaf essential oil was evaluated against bacteria isolated from fish and shellfish frequently consumed in Tunisia. The essential oil displayed considerable inhibitory activity against *Aeromonas hydrophila, Enterococcus* spp., *Klebsiella* spp., *Staphylococcus* spp., *Serratia odorifera*, and *Vibrio alginolyticus* with MICs values ranging from 0.05 to 0.2 mg/mL. The lowest MBCs values were observed ranging from 6.25 to 50 mg/mL for *A. hydrophila* strains (Snuossi et al. 2016).

The leaf essential oil displayed an antifungal effect with minimum inhibitory and fungicidal concentrations values ranging from 250 to 500 mg/mL against *Candida* spp. The essential oil may affect cell wall biosynthesis and membrane ionic permeability because the MIC values increased in the presence of sorbitol and ergosterol. The essential oil at concentrations from 1000 mg/mL (2 MIC) inhibited the initial adhesion of *C. albicans* and also displayed activity on mature biofilm formation; no significant difference was found compared to the monodrug nystatin (Peixoto et al. 2017).

Essential oil of the fruit displayed moderate antifungal effect against *Candida albicans* and *Candida albicans* clinical isolates (MIC: 1280 µg/mL) (Petkova et al. 2019).

The leaf essential oil displayed mild antifungal activity against *Aspergillus* sp., *Fusarium* sp., *Penicillium* sp., and *Rhizopus* sp. MIC and MBC values were detected as 1.75 and 2 mg/ml against *Aspergillus flavus*, respectively. The MICs values were determined against the other fungal species varied from 1 and 1.91 mg/ml, while the MFCs values ranged from 1.25 to >2 mg/ml (Belasli et al. 2020).

The antimicrobial activities of essential oils from both cultivated and wild-type leaves and flowers were evaluated against Gram-positive bacteria; *Bacillus cereus*, *Clostridium perfringens*, *Streptococcus pneumoniae*, and Gram-negative bacteria; *Acinetobacter ıwoffii*, *Escherichia coli*, and *Klebsiella pneumoniae,* and yeasts; and *Candida krusei* and *Candida albicans*. All essential oils exhibited significant antimicrobial activities with MICs values varying from 0.1 to 1 µL/mL. However, the leaf essential oil was more potent (Demirbolat et al. 2020).

Antibacterial effects of the leaf essential oil against common food and water-borne pathogenic bacteria (*Escherichia coli* O:157 H:7, *Staphylococcus aureus*, *Salmonella pullorum*, *Enterococcus faecalis*, *Listeria monocytogenes*, *Shigella dysenteriae*, and *Bacillus cereus*) were examined. The essential oil exhibited the highest ($P < 0.05$) effect on *Enterococcus faecalis* (28.0 mm, zone diameter), followed by *Escherichia coli* O:157 H:7 (27.1 mm) and *Salmonella pullorum* (25.2 mm). In terms of MIC/MBC ratios, the essential oil displayed an antibacterial effect against all pathogens apart from *Listeria monocytogenes* (Tomar et al. 2020).

## Antiviral

The fruit oil exhibited strong inhibitory effect against HSV-1 and SARS-CoV replication with $IC_{50}$ values 60 and 120 mg/ml, respectively (Loizzo et al. 2008).

## Antidiabetic

The leaf essential oil and its three major compounds (1,8-cineole, 1-(*S*)-α-pinene, and R-(+)-limonene) were evaluated for α-glucosidase inhibition activity. $IC_{50}$ values were determined for the essential oil, 1,8-cineole, 1-(*S*)-α-pinene, and R-(+)-limonene as 1.748 µL/mL, 1.118 µL/mL, 1.420 µL/mL, and 1.300 µL/mL, respectively. Besides, it was observed that the essential oil and 1, 8-cineole displayed the α-glucosidase

inhibition activity competitively (Sahin Basak and Candan 2013).

## Antioxidant Activity

The EtOH-soluble fraction from leaves showed potent alkyl peroxy radical scavenging activity (Kang et al. 2002).

The antioxidant capacities of the ethanol extracts of the leaves from wild and cultivated plants were evaluated using DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging, bovine brain peroxidation, and β-carotene bleaching assays. The wild plant displayed stronger radical scavenging activity than the cultivated plant ($IC_{50}$ values 22 ± 0.531 and 29 ± 0.634 μg/ml, respectively). The wild plant displayed high antioxidant activity ($IC_{50}$ = 1 μg/ml) in the β-carotene bleaching test. Also, it showed significant effect ($IC_{50}$ = 115 ± 0.831 μg/ml) in the bovine brain peroxidation assay (Conforti et al. 2006).

The lyophilized extracts (both water and ethanol) of the leaves were evaluated for their antioxidant activities with total antioxidant activity, reducing power, free radical scavenging, superoxide anion radical scavenging, hydrogen peroxide scavenging, and metal chelating assays. Both extracts displayed potent total antioxidant activity in the linoleic acid emulsion at 20, 40, and 60 μg $ml^{-1}$ concentrations with percentages of 84.9, 95.7, and 96.8 and 94.2, 97.7, and 98.6% lipid peroxidation inhibition for the water and ethanol extracts, respectively. The high antioxidant activity of the ethanol extract may be because of the phenolic compounds present in the extract (Elmastaş et al. 2006).

The aqueous ethanolic extract of the leaves showed free radical scavenging action against DPPH with $IC_{50}$ value 25.3 μg/mL. Besides, kaempferol, kaempferol-3-rhamnopyranoside, and kaempferol-3,7-dirhamnopyranoside obtained from the leaves displayed free radical scavenging activity with $IC_{50}$ values 7.70, 20.87, and 35.80 μg/mL, respectively (Emam et al. 2010).

Antioxidant activities of the ethanolic extract of leaves, the decoction of leaves, and the essential oil obtained leaves were measured with DPPH and β-carotene-linoleic acid assays. The essential oil exhibited antioxidant activity in the DPPH and β-carotene-linoleic acid tests with 53% and 44% of inhibition, respectively. The ethanolic extract displayed an effect with 67% of inhibition only in the DPPH test. The decoction showed antioxidant effect with 61% and 51% of inhibition in both tests, respectively (Ferreira et al. 2006).

The antioxidant activities of different extracts of the leaves ($Et_2O$, $CHCl_3$, EtOAc, *n*-BuOH, $H_2O$) were evaluated by determining their free radical scavenging capacities (DPPH, NO, $O2^{\bullet-}$, and OH radicals) and inhibitory effect on lipid peroxidation. The ethyl acetate extract showed the highest free radical scavenging capacity on DPPH, $O2^{\bullet-}$ and NO radicals with $IC_{50}$ values 83.24, 163.57, and 158.63 μg/$cm^3$. The highest inhibitory activity was displayed by the ethyl acetate extract on lipid peroxidation (Kaurinovic et al. 2010).

The leaf essential oil displayed an antioxidant activity in DPPH radical scavenging assay with $IC_{50}$ value of 94.655 $mgml^{-1}$, while $IC_{50}$ value of the seed oil methanolic extract was observed unstable. The leaf essential oil and the seed oil methanolic extract showed 64.28 and 88.76% inhibition in the β-carotene/linoleic acid assay, respectively (Ozcan et al. 2010).

The total antioxidant capacities of the leaves, branches, and roots were determined by the phosphomolybdenum method. Total antioxidant capacity was observed higher in the leaves, with significantly lower levels in the root and the stem. The leaves, branches, and roots inhibited the bleaching of β-carotene by scavenging linoleate-derived free radicals. The leaf extract reduced β-carotene ($IC_{50}$: 213.3 mg/mL) higher than the activity of stem and root extracts (Ouchikh et al. 2011).

The essential oils of seed and leaf displayed a radical scavenging effect on DPPH with $IC_{50}$ values of 66.1 and 53.5 mg $mL^{-1}$, respectively. The essential oils of seed and leaf exhibited antioxidant activity in the β-carotene/linoleic acid system, with an $IC_{50}$ value of 41.1 and 35.6 mg $mL^{-1}$ after 30 min of incubation (Saab et al. 2012).

The seed oil showed strong antiradical activity in both the DPPH and ABTS tests with 85.79 and 85.28 mg Trolox/100 g oil, respectively (Uluata and Özdemir 2012).

The antioxidant activities of the leaf essential oil and its three major compounds (1,8-cineole, 1-(S)-α-pinene, and R-(+)-limonene) were investigated with DPPH, inhibition of superoxide radicals, hydroxyl radical scavenging activity, hydrogen peroxide scavenging activity, and lipid peroxidation inhibition assays. The essential oil usually exhibited stronger activity than the three major components of the oil in the assays. $IC_{50}$ values were detected for the essential oil as 0.398 ± 0.028, 0.141 ± 0.004, 2.421 ± 0.136, 0.124 ± 0.003, and 0.575 ± 0.060 μL/mL in the hydroxyl radical scavenging activity, inhibition of superoxide radicals, hydrogen peroxide scavenging activity, lipid peroxidation inhibition, and DPPH assays, respectively (Sahin Basak and Candan 2013).

The methanolic extract and infusions of leaves obtained from the wild and cultivated plant were evaluated in terms of antioxidant activity through DPPH, reducing power, β-carotene bleaching inhibition, and lipid peroxidation inhibition assays. $EC_{50}$ values were observed ranging from 0.01 to 0.20 mg/mL. The infusions of both plants showed usually higher antioxidant activity than the methanolic extracts. The cultivated plant displayed greater DPPH scavenging activity, reducing power, and lipid peroxidation inhibition than the wild plant (Dias et al. 2014).

Antioxidant capacity of the ethanol extract of the leaves was investigated with DPPH radical scavenging, ABTS radical cation scavenging, and lipid oxidation inhibition tests. The leaves displayed an antioxidant capacity of 94.73%, 47.71%, and 76.86% in the DPPH, ABTS, and lipid oxidation inhibition tests, respectively (Muñiz-Márquez et al. 2014).

The essential oil obtained from the leaves exhibited considerable antioxidant activity in the DPPH antiradical test with $IC_{50}$ value 72.78 ± 2.70 μg/ml and the iron-reducing power (FRAP) test with $EC_{50}$ value 14.66 ± 0.96 μg/ml (Goudjil et al. 2015).

The leaf essential oil exhibited antioxidant activity in the DPPH, the β-carotene bleaching, the superoxide radical anion assays with $IC_{50}$ values 135, 3600, and 620 μg/mL, respectively. $EC_{50}$value was observed in the reducing power assay as 1850 μg/mL (Snuossi et al. 2016).

The antioxidant activities of different extracts (hexane, ethyl acetate, ethanol, and water) of the leaves were evaluated with DPPH radical scavenging, β-carotene-linoleic acid bleaching, and ABTS radical cation scavenging tests. The ethyl acetate extract exhibited the strongest activity in ABTS, DPPH, and β-carotene linoleic acid tests (24.98 ± 0.87 μg $mL^{-1}$, 75.65 ± 0.77 μg $mL^{-1}$, and 19.32 ± 1.04 μg $mL^{-1}$). A good correlation between high antioxidant activity and a high amount of phenolic compounds in the extracts was observed (Kıvrak et al. 2017).

The antioxidant activities of essential oils of the leaves and flowers from the cultivated and wild plants were evaluated through DPPH radical scavenging and β-carotene/linoleic acid assays. The leaves and flowers exhibited mild antioxidant activities in the assays. The leaf essential oils showed slightly more activity than the flower essential oils. $IC_{50}$ values were observed ranging from 47.9 ± 0.57 to 65.7 ± 0.48 μg/ml in DPPH assay. Percent inhibition values were obtained ranging from 61.4 ± 1.28 to 68.5 ± 1.28 in the β-carotene/linoleic acid assay (Demirbolat et al. 2020).

## Antiproliferative

The antiproliferative activity of the leaves ethanol extract was evaluated through the sulphorhodamine B assay against the adenocarcinoma of the breast cell line (MCF7). The leaves exhibited antiproliferative activity against MCF7 with $IC_{50}$ value of 24.49 μg/mL (Al-Kalaldeh et al. 2010).

Lauroside B, a megastigmane glycoside from the leaves, prevented the proliferation of three human melanoma cell lines (A375, WM115, and SK-Mel-28). It was indicated that this effect was related to inhibition of IκB-α degradation and constitutive NF-κB DNA-binding activity. Also, it inhibited the expression, regulated by NF-κB, of two antiapoptotic genes (XIAP and c-FLIP) (Panza et al. 2011).

The essential oils of seed and leaf inhibited proliferation of the K562 Human chronic myelogenous leukemia cells with $IC_{50}$ values of 95 and 75 mg $mL^{-1}$, respectively. The seeds essential oil at the concentration of 50 mg $mL^{-1}$ caused 12% erythroide differentiation, while the leaves oil at the concentration of 10 mg $mL^{-1}$ exhibited 15% (Saab et al. 2012).

The antiproliferative activities of the different fractions (ethanol, chloroform, butanol, ethyl acetate, aqueous, and volatile oil) of fruits and leaves were evaluated using sulphorhodamine B assay against breast cancer cell models (MCF7 and T47D). The ethanol fraction displayed pronounced antiproliferative activity for both leaves and fruits with $IC_{50}$ values ranging from 12.3 ± 4.0 to 48.2 ± 5.2 µg/mL. However, the fruits displayed stronger effect against both breast cancer cell models. It was observed that apoptosis mechanism of these extracts was not caspase-8 or Fas Ligand and sFas (Fas/APO-1)-dependent (Abu-Dahab et al. 2014).

## Antinociceptive and Anti-inflammatory

The essential oil obtained from leaf showed antinociceptive and anti-inflammatory activities in mice and rats. The essential oil displayed a pronounced antinociceptive effect in tail-flick and formalin tests. The essential oil significantly displayed an anti-inflammatory effect in the progressive increase in the formalin-induced paw edema, in a dose-dependent manner. Besides, it showed a moderate sedative effect at the anti-inflammatory doses (Sayyah et al. 2003).

Megastigmane glucosides (Lauroside B, Icariside B1, Citroside A) and kaempferol-3-O-α-L-(3″,4″-di-E-p-coumaroyl)-rhamnoside isolated from the leaves inhibited significantly nitric oxide release in lipopolysaccharide-activated murine macrophages (De Marino et al. 2004).

## Anticholinergic Activity

The ethanolic extract of leaves and the essential oil exhibited inhibitory effect against acetylcholinesterase enzyme with 51.3% and 64% of inhibition, respectively (Ferreira et al. 2006).

## Insecticidal

The essential oils obtained from leaves from Tunisia, Algeria, and Morocco were evaluated for their repellent and toxic activities against two stored product beetles *Rhyzopertha dominica* and *Tribolium castaneum*. The essential oils were observed as repellent and toxic to adults of *R. dominica* and *T. castaneum*. The essential oil from Morocco exhibited higher repellent effect compared to Tunisian and Algerian oils in the filter paper tests. $RD_{50}$ values were observed as 0.013 ml/$cm^2$, 0.036 ml/$cm^2$, and 0.033 ml/$cm^2$ for *R. dominica* and 0.045 ml/$cm^2$, 0.139 ml/$cm^2$, and 0.096 ml/$cm^2$ for *T. castaneum*, respectively. The essential oil from Morocco displayed greater fumigant toxicity than that from Algeria and Tunisia against *R. dominica* and *T. castaneum*. The $LC_{50}$ values were detected as 68, 99, and 113 ml/l air for *R. dominica* and 172, 194, and 217 ml/l air for *T. castaneum*, respectively (Jemaa et al. 2012).

The essential oil obtained from the aerial parts exhibited larvicidal activity against *Anopheles stephensi* and *Culex pipiens* larvae with $LC_{50}$ and $LC_{90}$ values 14.9, 22.3 µg/ml and 16.5, 28.6 µg/ml, respectively (Verdian-Rizi 2009).

## Antiprotozoal

The growth inhibition effect of acetonic extract of the leaves was displayed against *Babesia bovis, B. bigemina, B. divergens, B. caballi*, and *Theileria equi* with $IC_{50}$ values 86.6 ± 8.2, 33.3 ± 5.1, 62.2 ± 3.3, 34.5 ± 7.5, and 82.2 ± 9.3 g/mL, respectively (Batiha et al. 2020).

Guaianolides, dehydrocostus lactone, and zaluzanin D with *p*-menthane hydroperoxide, and (1*R*,4*S*)-1-hydroperoxy-*p*-menth-2-en-8-ol acetate isolated from the leaves exhibited considerable activity against epimastigotes of *Trypanosoma cruzi* with minimum lethal concentrations of 6.3 mM, 2.5 mM, and 1.4 mM, respectively (Uchiyama et al. 2002).

## Cytotoxic

The *n*-hexane extract of the leaves displayed cytotoxic activity against Brine shrimp with $LC_{50}$ value with 662.71 ppm (Kıvçak and Mert 2002).

Sesquiterpene lactones (5a,9-dimethyl-3-methylene-3,3a,4,5,5a,6,7,8-octahydro-1-oxacyclopenta[c]azulen-2-one, 3β-chlorodehydrocostuslactone, dehydrocostuslactone, artremorin, costunolide) obtained from the leaves were tested cytotoxic activity against Jurkat (T Lymphoblastoid Leukemia), HL-60 (Promyelocytic Leukemia), and LoVo (Intestinal Adenocarcinoma) cell lines. The compounds except artremorin exhibited significant cytotoxicity especially against the leukemia cell lines with $IC_{50}$ values ranging from 4.1 ± 0.1 to 19.5 ± 2.3 μM (Dall'Acqua et al. 2006).

The methanol extracts of the flowers, leaves, and fruits were investigated for their cytotoxic activity against A2780 human ovarian cancer cell lines and DNA damaging properties against three *Saccharomyces cerevisiae* yeast strains. The fruit extract with 98% inhibition exhibited the most cytotoxic activity and only the fruit extract displayed inhibitory activity (63.2%) against one DNA repair-deficient yeast strain. Sesquiterpene lactones (costunolide, gazaniolide, santamarine, reynosin, 11,13-dehydrosantonin, and spirafolide) isolated from the fruits exhibited highly cytotoxic activity against the A2780 ovarian cancer cell line (Barla et al. 2007).

The leaf essential oil displayed significant cytotoxic activity against five human cancer cell lines: HepG2 (liver cell line), MCF7 (breast cell line), H460 (lung cell line), U-251 (brain cell line), and Hela (cervix cell line) with $IC_{50}$ values 0.6, 0.8, 0.8, 0.9, and 1.8 μg/mL, respectively (El-Sawi et al. 2009).

Sesquiterpenes isolated from the leaves displayed moderate to significant cytotoxicity towards K562 leukemia cells (Julianti et al. 2012).

The $CHCl_3$ parental extract (CHCl3-pe) from the leaves was fractionated to yield $CHCl_3$ (LnC-1), EtOAc (LnC-2), and MeOH (LnC-3) fractions. Each fraction was evaluated in terms of cytotoxic and apoptotic properties versus human neuroblastoma (SK-N-BE(2)-C and SH-SY5Y) and rat glioma (C6) cell lines. LnC-2 (enriched in guaiane and eudesmane terpenes) displayed strong and promising cytotoxic and apoptotic effects (Pacifico et al. 2013).

The cytotoxic activity of the 1,8-cineole and the leaf essential oil was evaluated in human neuroblastoma cell line (SH-SY5Y). The essential oil showed stronger cytotoxicity with $IC_{50}$ value 47.106 μg/mL. Also, administered 1,8-cineole on SH-SY5Y cell line did not exhibit an effect on adenylate cyclase 1 protein (ADCY1) expression, while administered 200 and 100 μg/mL of the essential oil for 24 h significantly decreased ADCY1 expression (Caputo et al. 2017).

The acetonic extract of the leaves displayed cytotoxic activity against the mouse embryonic fibroblast and Madin–Darby bovine kidney cells with $EC_{50}$ values 573.7 ± 12.4 and 831 ± 19.9 μg/mL, respectively. But the human foreskin fibroblasts cell viability was not affected even at 1500 μg/mL (Batiha et al. 2020).

## Neuroprotective Effect

Human neuroblastoma SH-SY5Y cells and brain slices from the rats were exposed to oxygen and glucose deprivation, then reoxygenation with and without the chloroform fraction of leaves. The viabilities of SH-SY5Y cells and brain slices from the rats were observed as 97.2 ± 1.9% at 4 μg/ml in the group treated to the fraction. The leaf's chloroform fraction also considerably inhibited death-associated protein kinase dephosphorylation (Cho et al. 2010).

The spirafolide obtained from the leaves inhibited apoptosis and reactive oxygen species generation in dopamine-treated human neuroblastoma SH-SY5Y cells. Pretreatment for 24 h with spirafolide (0.4, 2, and 10 μM) before treatment to dopamine significantly increased cell survival ($p < 0.01$) and decreased intracellular reactive oxygen species levels ($p < 0.01$). The spirafolide showed neuroprotective effects against dopamine toxicity (Ham et al. 2010).

*n*-hexane fraction from the leaves showed an effect on dopamine-induced apoptosis in human neuroblastoma SH-SY5Y cells with $IC_{50}$ 3 μg/ml. Also, two main compounds of the fraction, costunolide and dehydrocostus lactone, showed an effect with $IC_{50}$ values 7.3 μM and 3.6 μM, respectively. The fraction and two major compounds considerably inhibited reactive oxygen species production in dopamine-induced SH-SY5Y cells

in the range of 0.2–5 μg/ml and 0.4–10 μM, respectively (Ham et al. 2011).

### Other Activities

Magnolialide from the leaves significantly inhibited the mast cell degranulation, IL-4 release ($IC_{50}$ 18.1 μM), and IL-4 mRNA expression levels in the rat basophilic leukemia cells ($IC_{50}$ 15.7 μM) and prevented the proliferation of IL-5-dependent Y16 early B cells ($IC_{50}$ 18.4 μM). It was indicated that magnolialide could be therapeutic potential for immuniglobulin E (IgE)-mediated type I allergic inflammatory disorder such as asthma and atopic dermatitis (Lee et al. 2013).

The leaf essential oil inhibited production of aflatoxin B1 from *Aspergillus flavus* at concentrations between 0.25 (15% decrease) and 1.50 mg/ml (86% decrease). Also, it was totally inhibited above 1.75 mg/ml (Belasli et al. 2020).

## 24.5.2 In vivo Studies

### Anticonvulsant

The leaf essential oil was investigated in terms of anticonvulsant activity against experimental seizures caused by maximal electroshock or pentylenetetrazole in mice. It showed a protective effect against seizures caused by pentylenetetrazole because of methyleugenol, eugenol, and pinene present in the essential oil (Sayyah et al. 2002).

### Antidiabetic

Treatment of diabetic rats with the leaf ethanol extract was caused by their biochemical and histopathological changes of pancreas, liver, and kidney. In this regard, thirty healthy adult male albino rats were divided into 5 groups for 4 weeks; the control group, the diabetic group, the diabetic extract group, the extract group, and the diabetic acarbose group. It was observed that the glucose level decreased significantly in both diabetic rats administered with the extract and acarbose. The extract improved the regeneration of pancreatic islets. It also regulated the changed liver enzymes (aspartate aminotransferase, gamma-glutamyltransferase, and alanine aminotransferase), urea, creatine kinase, total protein levels, calcium, and iron to near normal (Mohammed et al. 2021).

### Antidiarrheal

Aqueous extract of the leaf remarkably inhibited the diarrhea caused by castor oil (effective concentration producing 50% of the maximum response [$EC_{50}$] = 150 ± 6.4 mg/kg) and considerably decreased enteropooling caused by castor oil in the rats ($EC_{50}$ = 162 ± 5.9 mg/kg). The extract remarkably decreased intestinal transit of a charcoal meal and inhibited pronouncedly rat ileal smooth muscle tone as dose-dependent (EC50 = 71 ± 5.3 mg/mL). Also, the number of wet/loose feces in the rat was decreased (Qnais et al. 2012).

### Antioxidant

The antioxidant activities of different extracts of the leaves ($Et_2O$, $CHCl_3$, EtOAc, *n*-BuOH, $H_2O$) were assessed on some antioxidant systems (lipid peroxidation intensity, content of glutathione and activities of glutathione peroxidase, peroxidase, xanthine oxidase, and catalase) in the mice liver and blood-hemolysate after given the extracts, or in combination with carbon tetrachloride. The extracts displayed more protective effects on the liver than on blood-hemolysate parameters. The ethyl acetate extract displayed the strongest protective effect (Kaurinovic et al. 2010).

### Antiprotozoal

The acetonic extract of the leaves was evaluated for its in vivo chemotherapeutic effectiveness using *Babesia microti*-infected BALB/c mice. It was observed that the oral treatment of the extract prohibited *B. microti* multiplication in mice by 56.1% (Batiha et al. 2020).

### Gastroprotective

Methanolic and water extracts of the fruit healed ethanol-induced stomach ulcers in rats by 83% and 100%, respectively (Gürbüz et al. 2002).

The extracts (methanol and chloroform) obtained from the leaves showed gastroprotective activities in the rats. The gastric damage was significantly decreased by all the extracts in the rats.

Histological observations verified the results evaluated with the animal procedures. Besides, it was also stated that the antioxidant capacity of leaf extracts may lead to gastric mucosal protection. That is, a relationship between pharmacological activity and antiradical activity has been observed (Speroni et al. 2011).

### Hepatoprotective

The methanol extract of leaves (200 and 400 mg/kg) was given orally to the animals with hepatotoxicity caused by paracetamol (400 mg/kg). Paracetamol increased serum enzymes such as aminotransferase, aspartate aminotransferase, alkaline phosphatase, and bilirubin, while the group taking high dose (400 mg/kg) of the extract was observed more effective in protecting the liver against paracetamol hepatotoxicity than the low dose (200 mg/kg). This was detected with a significant decrease in the serum enzymes, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and bilirubin (Ravindran et al. 2013).

### Wound Healing

The aqueous extracts of the leaves were investigated in terms of the wound healing activity through excision and incision wound models. Wound contraction rate, the weight of granulation tissue, and hydroxyproline content were observed moderately high ($P < 0.05$) in animals treated with the extract. In the histological examination of granulation tissue of animals treated with *Laurus nobilis* leaves, more inflammatory cells and less collagen were observed compared to the group of animals treated with *Allamanda cathartica* L. leaves (Nayak et al. 2006).

### Neuroprotective

Administration of the leaves chloroform fraction at 4 mg/kg significantly reduced infarct size by 79% of vehicle control in the middle cerebral artery occlusion in vivo model conducted on the rats (Cho et al. 2010).

The *n*-hexane fraction of leaves considerably inhibited the 6-hydroxydopamin-induced tyrosine hydroxylase-positive neurons loss in the substantia nigra of a rat model of Parkinson's disease in a dose-dependent manner. The fraction also decreased dopamine-induced α-synuclein formation, one of the neuropathological hallmarks of Parkinson's disease, in SH-SY5Y cells (Ham et al. 2011).

### Other Activities

It was demonstrated that the leaves decreased the cognitive deficits induced by scopolamine in the rat brain. Behavioral effects in rats were evaluated using Y-maze, radial arm maze, and novel object recognition tests. The acetylcholinesterase activity and the oxidative stress markers in the rat hippocampus were also examined. The administration of the leaves significantly ameliorated scopolamine-induced cognitive impairment and oxidative stress (Brinza et al. 2021).

## 24.6 Clinical Studies

### Antidiabetic

Sixty-five people with type 2 diabetes were split into two groups: 50 people took capsules containing 2 g of the leaves per day for 30 days and 15 people took placebo capsules. In the plasma glucose, the treated people with the leaves were observed with significant decreases of 30% after 30 days.

Besides, total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides levels decreased with rates of 22%, 24%, 18%, and 25% after 30 days, respectively (Aljamal 2011).

### Effect on Glucose and Lipid Profile

Forty people having type 2 diabetes were separated into four groups. The three groups consumed capsules containing 1, 2, and 3 g of the ground leaves per day for 30 days by a 10 day washout period, respectively; this was also used in the placebo group. Everyone with the capsules' consumption had decreased serum glucose level between 21 and 26% after 30 days. Total cholesterol levels were reduced ranging from 20 to 24%; also there were significant decreases in low-density lipoprotein (LDL) cholesterol of 32 to 40%. High-density lipoprotein (HDL) choles-

terol levels increased 29 and 20% in the groups taking 1 and 2 g of the leaves, respectively. However, triglycerides reduced 34 and 25% in the groups taking 1 and 2 g of the leaves, respectively. There was no observed pronounced change in the placebo group (Khan et al. 2009).

The study conducted on healthy volunteers was detected to affect the plasma levels of lipid biomarkers with *L. nobilis* tea consumption. In the study, 30 Tunisian people used the infusion prepared from 5 g of dried leaves in 100 ml boiled water, once a day for 10 days. Plasma concentrations of serum LDL cholesterol, triglycerides, and HDL cholesterol were measured before and after the infusion was used. The using infusion pronouncedly increased the concentration of HDL cholesterol ([HDL cholesterol] $D_0 = 1.34 \pm 0.25$ pg/mL, $D_{11} = 1.42 \pm 0.29$, $p = 0.01$). However, a slight decrease was observed in LDL cholesterol and triglyceride levels, which was not statistically significant ($p < 0.05$) (Chbili et al. 2020).

## 24.7 Toxicological Studies

The herb and its essential oil appear to have no significant toxicity. Some reports have indicated that the herb and its essential oil may cause allergic contact dermatitis, may be induced by one or more sesquiterpene lactones (Cheminat et al. 1984; Adişen and Önder 2007).

## 24.8 Available Commercial Formulations/Products, Uses, Administration Methods and Pharmacokinetic Studies

Its essential oil is sold as commercially under various brands (Puressentiel, Olfae, PHYTOSUN arôms, Bangota, etc.) in the market. Its use is suggested as in form of drop the respiratory diseases, gastrointestinal system disease, skin problems, wounds, the neuralgias, general fatigue and low morale. Also, İts fruit oil is sold as commercially (under brands of Sva Naturals, Olive tree, Blooming Alley, etc.). It is recommended for skin and hair problems, and as muscle relaxant.

## 24.9 Gap Between Ethnomedicinal and Scientific/ Clinical Evidences

It is used especially for gastrointestinal complaints and respiratory system diseases in traditional medicine. There is no high gap between its ethnomedicinal and scientific or clinical evidences. Scientific studies conducted in line with its traditional use have approved its use. The plant contains many chemical compounds such as essential oil, fixed oil, sesquiterpenoids, tocopherols, phenolics, and isoprenoids which may be responsible for its effects. More studies are needed for scientific confirmation of their traditional use.

## 24.10 Challenges and Future Recommendations as Potential Drug Candidate

Much research conducted on the chemical composition and biological activities of Laurus nobilis until now. Biological activity studies conducted on Laurus nobilis as in vitro and in vivo have shown that it is generally safe to use for the treatment of different ailments and diseases. However, it has been observed that external applications may cause allergic contact dermatitis due to the sesquiterpene lactones in its structure. There is no record of its use during pregnancy and breastfeeding. Considering the use of ethnomedicinal, clinical studies on its extracts and isolated compounds will increase in the future and can be used as drug candidate molecules.

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# *Liquidambar orientalis* Miller

# 25

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**Abstract**

*Liquidambar orientalis* Miller (Anatolian Sweetgum Tree; Hamamelidaceae), also called Anatolian sığla (sweetgum), is ecologically and economically important relict endemic species which primarily is utilized for its balsam which is used mainly in the cosmetics and pharmaceutical industries. The wood of that tree is used for secondary purposes rather than oil. The oils of sweetgum are also known as storax that is produced from pathological wound channels. The resin of *L. orientalis* is used as a topical parasiticide, expectorant, antiseptic, and for stomach ache, asthma bronchitis, skin diseases, etc.. Many pharmacological activity studies of sweetgum oil for these uses have been identified in the literature. Also, the chemical content of oil was elaborated by different chromatographic methods.

**Keywords**

Storax · *Liquidambar orientalis* · Sweetgum Tree · Relict endemic · Medicinal and therapeutic values · Ethno medicine

## 25.1 Introduction

*Liquidambar* L. is the unique genus in the family of Hamamelidaceae. The genus has four species which are known as *Liquidambar orientalis* Mill., *Liquidambar formosana* H., *Liquidambar altingia*, and *Liquidambar styraciflua* L. *L. orientalis* is one of the most important relict-endemic species and native to south west part of Turkey (Fig. 25.1) and its native range is East Aegean Islands (Rodos) to W. & SW. Turkey (Figs. 25.2 and 25.3). It has a local distribution in Köyceğiz, Fethiye, Marmaris, and Milas of Turkey (Davis 1982). *Liquidambar orientalis* Mill. is known as "Sığlaağacı," "Amberağacı," or "Günlükağacı" in Turkey (Baytop 1999). It is also known by other names such as "Sweet Gum, Liquid Amber, Balsam Styracis, Copalm, Opossum/Gum Tree, Red and White Gum" (PDR 2000). Storax is recognized as the balsam is formed by secretory formations of secondary source formed internally in the young stem, as a result of the injury caused in *L. orientalis*. The balsam flowing from the wood stem when the stem was injured piles up between the bark and the internal part of the stem and is

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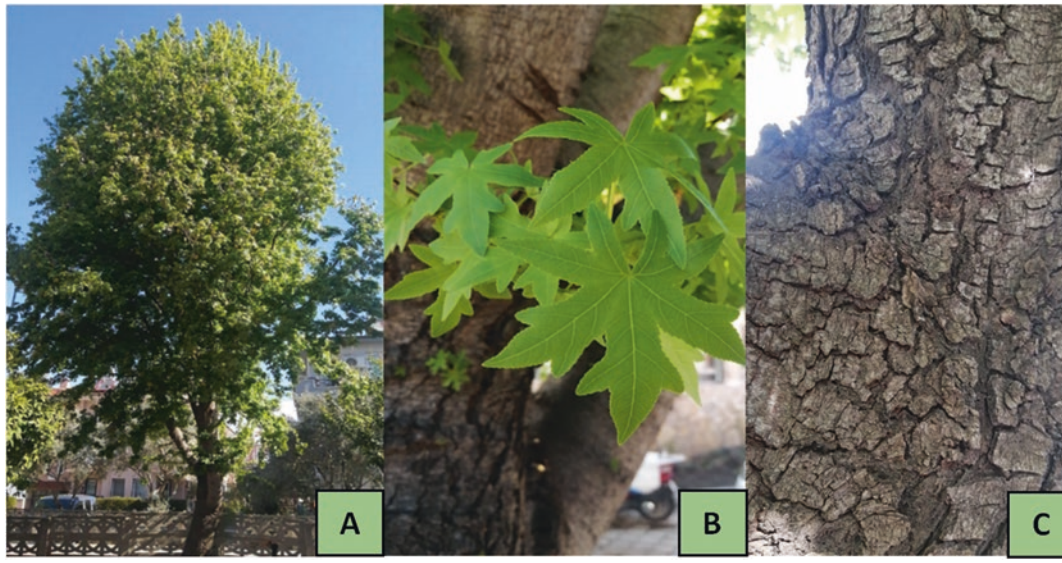


**Fig. 25.1** Natural habitat of *L. orientalis* (Location: Fethiye district of Antalya) (**a**) General appearance of tree; (**b**) Leaves of *L. orientalis*; (**c**) Stem of *L. orientalis*

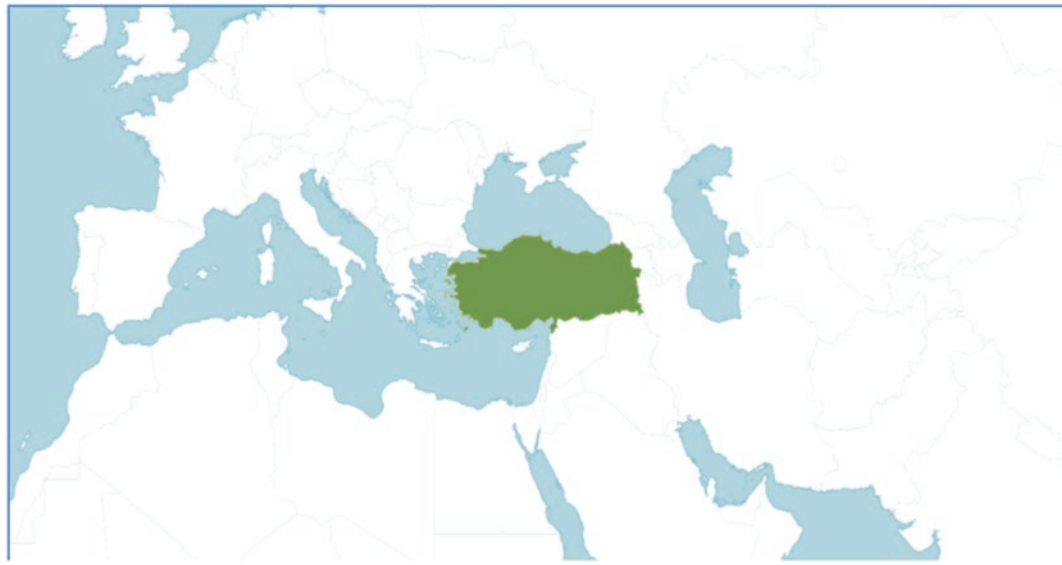

**Fig. 25.2** Native distribution of *L. orientalis* (Web-1)

removed by peeling the external part of the bark. This material is put in boiling water, extracted, and the fluid removed, in order to separate the Liquid Storaque. It is also gathered by the extraction of the bark with benzene, after forming the incision. (Costa 1994; Baytop 1999; Ozturk et al. 2008; Custódio and Veiga-Junior 2012). *L. orientalis* is an important tree for tertiary relict endemic in terms of biodiversity and has economic value due to the balsam (Bayraktar et al. 2015).

The aim of this section is to compile data on its spread in the world and in Turkey, botanical properties, traditional usage, chemical content, biological and pharmacological activities, toxicological effects of *L. orientalis*, and an endemic relict plant.

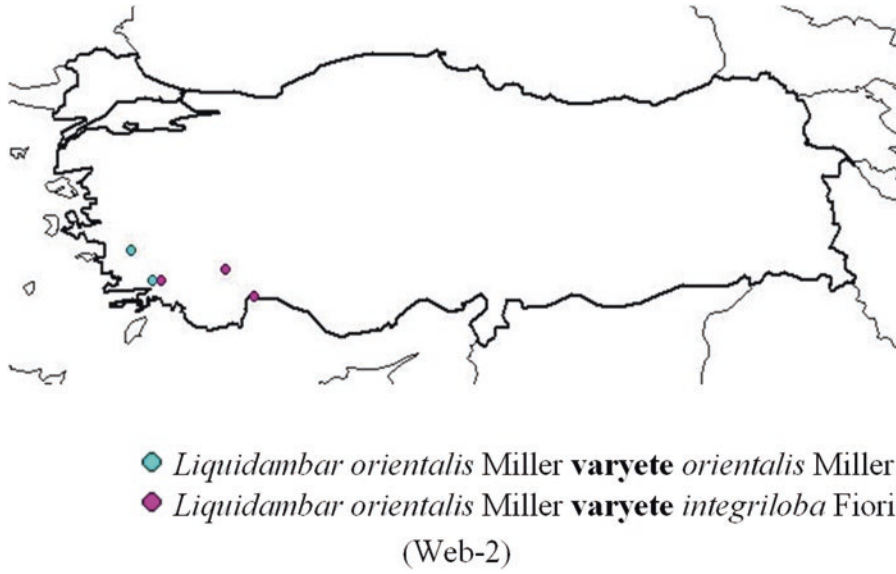


**Fig. 25.3** Distrubution of *Liquidambar orientalis* Miller **varyete** *orientalis* Miller and *Liquidambar orientalis* Miller **varyete** *integriloba* Fiori (Web-2)

## 25.2 Origin and Distribution

*L. orientalis* is spread to native range East Aegean Islands (Rodos) to West & Southwest Turkey.

## 25.3 Botanical Properties

The yellow flowers of *L. orientalis* are unisexual, monoecious, and halved in small, roundsingle capitula. In male, flowers do not have a calyx or corolla, but there are tiny scaly sepals of the female flowers, and the floret rubs are fused and there are many stamens, also the ovary is semi-inferior. The fruit is in the shape of a rigid spherical schizocarp and the deciduous tree is about 12 m tall with many branches and thick reddish-gray bark. It has alternate, usually 5-lobed leaves. The leaf blades are usually rudely toothed. Storax is a gray-brown mass, thick, viscous, sticky, aromatic, and has a slightly bitter taste (Davis 1982; PDR 2000).

## 25.4 Uses

*L. orientalis* is a herbaceous plant with medicinal and cosmetic properties (Sagdıc et al. 2005). In the Mediterranean region, it is commonly used in traditional medicine to treat health problems. The plant material has been used due to its antiulcerigenic effect in Turkish folk medicine (Honda et al. 1996; Gurbuz et al. 2013), stomach ache, wounds (Sağıroğlu et al. 2013), mouth diseases, burn (Gürdal and Kültür 2013; Nalbantsoy et al. 2016), enuresis nocturna (Everest and Ozturk 2005; Gürdal and Kültür 2013), dysentery, coughs, wounds, and infections (Lingbeck et al. 2015; Altıparmak et al. 2019), cuts, cholecystitis (Everest and Ozturk 2005), antiseptic, asthma bronchitis, antifungal, lung and skin diseases, gonorrhea, stammer, psoriasis, hemorrhoid, expectorant, psychotonic, sedative (Gulec et al. 2009; Gürdal and Kültür 2013; Nalbantsoy et al. 2016), stomach ache, mouth diseases, and also utilized as sedative (Fakir et al. 2009) for centu-

ries. Charehsaz et al. (2016) mentioned that in Turkish folk medicine, styrax has been used for treatment of various diseases such as skin problems, nocturnal enuresis, peptic ulcers, parasitic infections, antiseptic, or as expectorant. In Chinese Medicine, Storax is used to treat syncope, epilepsy and lactose intolerance in young children. Also, in Indian Medicine, it is used for fever, itching, chronic coughs, leprosy, and suppurating wounds (PDR 2000). It is a good antiseptic and is also used to treat some skin diseases, as a topical antiparasitic, and expectorant (Duru et al. 2002).

## 25.5 Chemistry

### 25.5.1 Compounds

Gum resin (storax) included some aromatic alcohols (benzyl alcohol, phenylpropyl-, cinnamic), cinnamic acid (up to 30%), styrene, triterpenes, vanillin (up to 2%), and volatile oil (changeable according to source, 1 to 20%) (PDR 2000). Courel et al. (2019) investigated content in some resins and aerial parts with GC-MS (Gas Chromatography-Mass Chromatography). Cinnamyl cinnamate and 3-phenylpropanyl and oleanonic acid (major) with 3-epi-oleanolic acid were some components in the Styrax. Resin of *L. orientalis* was analyzed by GC-TOF (time-of-flight analysis). In this content, cinnamyl cinnamate and 3-phenylpropanyl cinnamate and oleanonic acid (major), and 3-epi-oleanolic acid (minor) were found (Courel et al. 2019). Composition of the leaves and volatile oils of *L. orientalis* Mill.var. *orientalis* and *L. orientalis* var. *integriloba* from Turkey were analyzed by GC and GC–MS and monoterpenes were the dominant group of components in the essential oil. The steam distillation and extraction of oils also have similar composition. α-Terpineol was the main component in the steam distillation oils and extraction oils of var. *orientalis* and var. *integriloba*, followed by terpinen-4-ol, sabinene, and germacrene D (Duru et al. 2002). Altop et al. (2018) studied essential oil of *L. orientalis* leaf and 33 compounds were identified by GC-MS. The major constituents include terpinen-4-ol (31.86%), γ-terpinen (14.38%), α-terpinen (8.69%), sabinen (8.61%), and germacrene (5.80%). In another study, Asian styrax (*L. orientalis* oil) was analyzed by GC-MS that styrene is the major compound (70.4%), followed by α-Pinene (19.0%), β-Pinene (4.3%), Limonene (1.2%), and some minor constituents in oils (Fernandez et al. 2005). Lee et al. (2009) identified 11 major compounds [trans-cinnamyl alcohol (45.07%); hydrocinnamyl alcohol (41.13%); β-caryophyllene (3.6); styrene (1.56%); benzyl alcohol (1.22%); α-pinene (1.02%); benzaldehyde (0.47%); trans-cinnamyl aldehyde (0.24%); acetophenone (0.19); 1-phenyl-1-ethanol (0.17%); β-pinene (0.15%)] from *L. orientalis* (Oriental sweet gum) by GC–MS analysis. In another study, six compounds were identified as a result of the analysis of oriental sweetgum oil by GC (Gas Chromatography). The main components of oil were from less to more α-pinene (1.02%), benzyl alcohol (1.22%), styrene (1.56%), β-caryophyllene (3.6%), hydrocinnamyl alcohol (41.13%), and trans-cinnamyl alcohol (45.07%) (Park 2014). Koutsaviti et al. (2018) investigated that the essential oil of cultivated *L. orientalis* fresh leaves was exceptionally rich in monoterpenes (91.5%), with sabinene (38.6%) dominating in the sample.

In addition, the crude protein, condensed tannin contents, neutral detergent, and acid detergent fiber of *L. orientalis* leaves ranged from 9.11 to 12.8 (Ulger et al. 2017).

### 25.5.2 Phenolic Components

Saraç and Şen (2014) investigated that total phenolic content of leaf extract of *L. orientalis* var. *orientalis* was found as 333.14 ± 7.96 mg gallic acid equivalent/g extract. In addition, protocatechuic acid (12.232 ± 0.118 mg/g extract), (−)-epicatechin (7.954 ± 0.493 mg/g extract), and gallic acid (3.258 ± 0.035 mg/g extract) as main components were detected by High pressure Liquid Chromatography (HPLC). In another study, major phenolic acids in balsam were determined as *p*-coumaric acid (2.95 mg/g). Also, ethanol

extract of balsam was found to have both *p*-coumaric acid (11.46 mg/g) and gallic acid (1.60 mg/g) by HPLC analysis. (Charehsaz et al. 2016).

## 25.6 Pharmacological Uses

### 25.6.1 Antimicrobial Effects

In a study investigating the antimicrobial activity of free and immobilized AgNPs on cotton and cotton/polyester fabrics prepared using the leaf extract of *L. orientalis* Mill, it was stated that the fabrics exhibited in vitro bactericidal activity against *Staphylococcus aureus*, *Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae* (Bilgili et al. 2016). Sweetgum storax was dissolved in absolute ethanol and diluted to 10.0%, 1.0%, 0.4%, and 0.2% concentrations to test against some Gram-negative and Gram-positive bacteria by using agar diffusion method. It has been stated that the antibacterial effect of the storax varies among the 20 microorganisms tested. While the concentration of 10% has the highest activity, it has been determined that the 0.1% concentration has no effect on the tested microorganisms. The highest antibacterial effect of the storax was detected in Gram-positive bacteria. The highest effect observed against *B. cereus* with 16 mm inhibition zone. Then, equal zone of inhibition was observed against *M. luteus* and *S. aureus* with 14 mm. Finally, the inhibition zone of *E. faecalis* was 13 mm. Among the Gram-negative bacteria, it was determined that it has the highest effect on *P. vulgaris* and *P. aeruginosa* (12 mm) (Sagdıc et al. 2005). Oskay and Sarı (2007) investigated antimicrobial activity of Turkey-specific 19 plants. According to the results, ethanol extract of *L.orientalis* leaves has shown highest activity against methicillin-resistant *Staphylococcus aureus* (MRSA) at 8 mg/ml minimum inhibitory concentration(MIC) level. Commercial herbal essential oils from 40 plant species, one of which is *L.orientalis*, had been investigated for their antifungal capacity against *Phytophthora cactorum*, *Cryphonectria parasitica,* and *Fusarium circinatum* by Lee et al. (2009). It has been stated that the essential oil obtained from *L. orientalis* sweet gum provides effective antifungal activity against *Phytophthora cactorum* at a concentration of $28 \times 10^{-3}$ mg / mL in air. A significant morphological change was found in three phytopathogenic fungi after oil or compound application. Onaran and Bayan (2016) examined that antifungal activity of *L. orientalis* (leaf and resin) against some plant pathogenic fungi (*Fusarium oxysporum f. sp. lycopersici* (FOL) (Sacc.) W.C. Snyder and H. N. Hans, *Alternaria solani* (Ell. and G. Martin), *Botrytis cinerea pers.:*Fr, *Rhizoctonia solani* Kühn, and *Sclerotinia sclerotiorum* Lib De Bary) and hopeful results were obtained from the use of plant extracts controls. Ayrilmis et al. (2021) produced biocomposite from polylactic acid (PLA) by using *L. oriantalis* fresh leaf extract as a reducing agent in nanoparticle preparation. They examined the antimicrobial thermal and technological properties of these biocomposites. The highest inhibition zone had been observed 2.6 mm at 10% biocomposite films against *E. coli*. The porous structure loaded with L. orientalis extract was successfully prepared which can be a potential functional biomaterial with antimicrobial properties by Bayraktar and Ozyıldız (2019). The acetone, ethanol and methanol extracts of *L. orientalis* leaf showed maximum inhibition zone of 12 mm against different food pathogenes (*Yersinia enterocolitica, Listeria monocytogenes and Staphylococcus aureus*) by disc diffusion assay and calculated to MIC levels (Okmen et al. 2014).

### 25.6.2 Antioxidant Capacity

Hafizoglu (1982), one of the oldest publications, in a short note published in 1982 that when the balsam was examined, the major components were styracine (21%), phenylpropyl cinnamate (7.5%), cinnamic acid (4.0%), cinnamyl alcohol (2.0%), styrene (0.5%), phenyl-propyl alcohol (0.5%), and some unidentified compounds (60%). It has been reported that the total phenolic content of the leaves ethanolic extract of *L.orientalis var orientalis* was 333.14 ± 7.96 mg

GAE/g. The major phenolic compounds were protocatechuic acid (12.232 ± 0.118 mg/g extract), (−)-epicatechin (7.954 ± 0.493 mg/g extract), and gallic acid (3.258 ± 0.035 mg/g extract) by RP-HPLC method. The IC50 value was 3.11 ± 0.024 mg/ml by DPPH (Saraç and Şen 2014). Antioxidant activity was defined by DCF production in HL-60 cells. The hexane, dichloromethane, and methanol extracts showed a potential antioxidant efficacy with $IC_{50}$ values between 19.01 and 39.77 μg/ml (Nalbantsoy et al. 2016). The essential oils obtained from nine Turkish plants, one of which is *L. orientalis*, had been investigated by supercritical carbon dioxide ($SCCO_2$) extraction and steam distillation. Then their analysis was studied by GC-MS. In the DPPH test, it was determined that essential oils achieved by $SCCO_2$ extraction represented higher antioxidant activity than steam distillation extracts with radical scavenging activities ranging from 87.190.23% to 92.090.34% compared to butylated hydroxytoluene-positive control (91.490.21%). Topal et al. (2008) identified the major components in the supercritical fluid extraction of *L. orientalis* Mill. balsamic resin extract to be menthol (31.59%), 6a, 17b-dihydroxy-5b-androstan-3one (22.92%), octyl alcohol acetate (12.42%), N-nordextromethorphan (7.19%), and rimuene (5.82%). In steam distillation of extract, menthol (23.14%), octyl alcohol acetate (20.12%), N-nordextromethorphan (14.38%), 6a, 17b-dihydroxy-5b-androstane-3one (12.87%), phenanthrene (8.75%), and neocembrene (4.66%) were determined as main components. Its high antioxidant capacity has been connected to high concentrations of oxygenated monoterpenes and ketone groups of monoterpenes. Fernandez et al. (2005) analyzed essential oil composition of *L.orientalis* Mill. and *L. styraciflua* by GC and GC-MS. The chemical composition of the two oils was similar according to their research, but significant differences had been observed in the relative amounts of the main ingredients between them. Styrene had been found as the main compound in both oils. The β-caryophyllene was more present in *L. styraciflua* (20.2%) than in *L. orientalis* (0.2%). These results show that we can identify *L. orientalis* from *L. styraciflua* with a larger amount of styrene and a smaller amount of β-caryophyllene. Gurbuz et al. (2013) had analyzed volatiles of balsam and sub-extracts that were obtained with microdistilation technique using GC and GC-MS. In GC-MS result of the resin, 31 compounds represented 99.8% of the total oil. The main components were determined as styrene (81.9%), cinnamylalcohol (6.9%), and α-pinene (3.5%).

### 25.6.3 Cytotoxicity, Genotoxicity, and Mutagenicity

The Ames test was applied on *Salmonella* TA98 and TA100 strains with and without metabolic activation (10–30,000 μg/plate) to show in vitro mutagenicity and antimutagenicity of styrax and its ethanolic extract. The Balb C mice were used to determine genotoxicity by chromosomal aberrations assay with varied concentrations (500–2000 mg/kg body weight) in vivo. The MTT [3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazolium bromid] assay using L929 cell line has been used to determine cytotoxicity. Genotoxicological studies of styrax or its ethanolic extract demonstrated that none of the tested concentrations induced a significant increase to specify no mutagenicity to the tested strains. Moreover, test results showed that up to 2000 mg/kg body weight, styrax is not genotoxic in mammalian bone marrow chromosome aberration test in vivo. The IC50 values of styrax and its ethanolic extract were analyzed in cytotoxicity study as 50.22 ± 1.80 and 59.69 ± 11.77 μg/mL, respectively (Charehsaz et al. 2016). The leaves of *L.orientalis* ethanolic extract had shown antimutagenic efficiency at 2.5, 0.25, and 0.025 mg/plate and had a desirable antimutagenic effect (37.7–85.67%) on the TA98 strain by dose depending (Saraç and Şen 2014). According to the results of this study in which cytotoxicity and INOS inhibition of *L. orientalis* resin, hexane, dichloromethane, methanol, and water extracts were examined, the $IC_{50}$ values calculated 48 hours after the treatment of cell lines with different doses of extracts vary in the range of 6.68–48.90 μg/ml. iNOS inhibition was achieved by inducing RAW 264.7 cells with lipopolysaccha-

ride. Nalbantsoy et al. (2016) determined that nitric oxide production in activated macrophage cells was inhibited by extracts other than water extract. The NO production inhibition $IC_{50}$ values of hexane, dichloromethane, and methanol extracts were found as in order of 22, 22, and 21 μg/ml. The cytotoxic and inhibitory effects of the extract of storax balsam on cell proliferation were evaluated using the lactate dehydrogenase (LDH) test and cell proliferation (WST-1) assay. The sister chromatid exchange system frequency was found to increase when cells were treated with the extract of storax balsam at concentrations of 1.6 and 4.0 mg/mL ($p < 0.05$). Moreover, it was stated that the treatment cells at the same concentration significantly decreased the number of cells at 24 and 48 hours and increased LDH levels ($p < 0.05$) at 48 hours. It was stated by the authors that these results show that the extract of storax balsam can be used as an alternative antibacterial and antipathogenic agent due to its cytotoxic and genotoxic effects (Karadeniz et al. 2013).

### 25.6.4 In Vivo Experiments

*Liquidambar orientalis*, *Hypericum perforatum,* and propolis are all known for their positive effects on wound healing and positive synergy has been demonstrated on Fifty Spraque-Dawley rats between the compounds when used in mixture 1:1:1 ratio (Altıparmak et al. 2019). *L. orientalis* deposits neutrophils, macrophages, and fibroblasts into the healing burn wound, effectively accelerating the inflammatory process, resulting in early epithelization in an experimental rat model (Yanik et al. 2016). Guo et al. (2011) reported that after oral usage (25, 50, 100 mg/kg), styrax sodium pentobarbital-induced prolongation of sleep time and intranasal administration (12.5, 25, 50 mg/kg) extended sleep time at a lower dose than oral use. In addition, they stated styrax (100 and 200 mg/kg) provides significant preservation against pentylenetetrazol-induced attack and mortality in 30 minutes after oral usage, whereas styrax in 5 minutes after intranasal administration provides low dosages (25 and 50 mg/kg) that provided important protection. These data indicate that, intranasally, usage of styrax has a faster start of effect (5–30 min) and preferable anticonvulsant effectiveness (25, 50,100, 200 mg/kg) compared to the intragastric route. Also, Styrax has been shown to reduce spontaneous locomotor actions at 100 mg/kg at intervals of 5–60 minutes afterward oral usage. Ocsel et al. (2012) formed an experimental sixteen square excisional wounds group, 3x3 cm per animal, on 6 young Yorkshire pigs to evaluate the influences of storax on partial and full thickness wounds compared to conventional wound dressings in a pig model. One of four treatment methods was applied to the wounds: storax, hydrocolloid dressing, silver sulfadiazine, and control group. All wounds had been investigated histologically for re-epithelization and granulation tissue formation. They found that a greater depth of granulation tissue was formed in the storax group at fourth and eighth days than other groups ($p < 0.0125$). Full thickness wounds ($p < 0.0125$) were found to have a faster re-epithelization at day 21 compared to both the hydrocolloid dressing and control groups. Gurbuz et al. (2013) studied anti-ulcerogenic effects of *L. orientalis* balms and their fractions provided by sequential solvent extraction with chloroform and n-butanol. Also, their effects on peptic ulcer model induced by ethanol in rats were investigated. They reported that the chloroform extract showed a statistically significant protective effect on gastric mucosa. The oral doses of 150 and 300 mg/kg balsam to rats showed significant stomach protection.

### 25.6.5 Anti-Methanogenic Potential

Ulger et al. (2017) have demonstrated that leaves of *L. orientalis* are more efficient in reducing methane in ruminant animals than *Laurus nobilis* and *Eucalyptus globules* by the in vitro gas production technique. The methane production, gas production, metabolizable energy, and organic matter digestibility ranged from 2.62 to 4.41 mL, 21.72 to 31.54 mL, 6.62 to 9.24 MJ kg-1 dry matter, and 41.23 to 54.84%, respectively.

### 25.6.6 Molecular Studies

Albayrak and African (2009) studied similarity among *L. orientalis* populations using RAPD markers. These 84 oligonucleotide primers were used in PCR. The statistical analysis was interpreted by using 782 RAPD markers. Generated Nei-Li's coefficient showed that the highest similarity was 83.1% between samples from Koycegiz and Cine populations, while the lowest was 68.3% between samples from Gunluklu and Karacaoren populations. In another study, importance of genetic variation in seedling traits of *L. orientalis* populations was evaluated. The oriental sweet gum for conservation and use of genetic resources are prepared by European Forest Genetic Resource Programme (EUFORGEN) as a technical guideline. The population variances were showed more than family variances for the all quantitative traits, reflecting oriental sweet gum populations differentiated significantly according to results of common garden test (Alan and Ezen 2018). The genetic parameters of 9 oriental sweetgum populations were shown by using common garden test. In conclusion, this study displayed important variability in all traits evaluated. Variation among populations was three times higher than that of families in variance components. In the meantime, breast height diameter and crown diameter were more heritable for marginal populations; height was more heritable for optimal populations Alan and Ezen (2018). The genetic diversity and evolutionary divergence in *Liquidambar* species and *L. orientalis* varieties (66 genotypes from 18 different populations) were compared with respect to the matK gene. As a result, the highest evolutionary divergence was found between *L. styraciflua* and eastern Asian *Liquidambar* species (0.0102). The maximum-parsimony phylogenetic tree demonstrated that *L. styraciflua* and *L. orientalis* formed a closer clade, while East Asian species were in a separate clade (Ozdilek et al. 2012).

## 25.7 Toxicity Studies

### 25.7.1 Contact Toxicity

*L.orientalis* is one of 22 plant essential oils (EOs) and their constituents against the adult spotted wing drosophila (SWD), *Drosophila suzukii*, Fumigant, and contact toxicities were investigated by analyses by GC, GC-MS, and NMR (Nükleer Manyetik Rezonans). In contact toxicity tests, *L. orientalis* demonstrated insecticidal activity with LD50 values (μg/fly) of 2.64 against male SWD and of 3.74 against female SWD. Major components of L. orientalis essential oil have been 3-phenyl-1- propanol and trans-cinnamyl alcohol that also exhibited insecticidal activity with LD50 values of 5.52 and 2.37 against male SWD and of 7.04 and 3.99 against female SWD, respectively (Kim et al. 2016).

### 25.7.2 Fumigant Toxicity

Park (2014) investigated fumigant toxicity of Oriental sweetgum (L. orientalis) and their components against Japanese termites (Reticulitermes speratus). As a result, hydrocinnamyl alcohol and trans-cinnamyl alcohol were found to be the major contributors to the fumigant antitermitic toxicity of oriental sweetgum oil.

### 25.7.3 Hepatotoxicity

Suzek et al. (2016) examined the hepatoprotective effect and the antioxidant role of Sweetgum oil(SO) against carbon tetrachloride ($CCl_4$) toxicity. Hepatoprotection of SO is further confirmed by the nearly normal histologic findings in the $CCl_4$ + SO group against degenerative changes in the $CCl_4$ group. As a result, SO has a hepatoprotective effect and antioxidant capacity against $CCl_4$ toxicity.

## 25.8 Precautions and Adverse Reactions

No health hazards are known in connection with the proper administration of the established therapeutic dosages. Internal administration of the drug sometimes causes diarrhea. Also contact allergies can be triggered by storax (PDR 2000).

### 25.8.1 Overdosage

External application over large areas can cause absorbent poisonings that are defined by kidney damage (albuminuria, hemorrhagic nephritis) (PDR 2000).

### 25.8.2 Dosages

Mode of Administration: Storax is used as an inhalation in combination preparations for bronchitis and coughs, externally for wounds and ulcers (PDR 2000).

## 25.9 Challenges and Future Recommendation as Potential Drug Candidate

*L. orientalis* is economically important endemic species which primarily is utilized for its balsam which is used mainly in the cosmetics and pharmaceutical industries. Andrikopoulos et al. (2003) noted that among various commercially purchased natural resins, storax gum can be used in pharmaceutical preparations and protect human low-density lipoproteins from oxidation when taken orally. For the continuity of such a valuable product, new management and production plans for *L. orientalis* forests and balsam production can be implemented. As stated in many sources, balms have traditional uses for many years. Some of these uses have been supported by experimental studies. On the other hand, standardization studies of balsam, which has the potential to be a new drug candidate, should be accelerated and empirical studies should be given priority.

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# *Matricaria chamomilla* L.

26

Hafize Yuca and Songül Karakaya


## Abstract

*Matricaria chamomilla* is an annual plant and its stem is glabrous, branched, erect, and smooth and it is a well-known medical plant extensively utilized in phytotherapy and is usually mentioned as the "star amongst medicinal species." *M. chamomilla* grows naturally in Southern and Eastern Europe, Western Asia, North America, and Australia. *M. chamomilla* has been utilized since ancient times in ancient Greece, Rome, and Egypt as herbal remedies for its anti-inflammatory, wound healing, antiseptic, and antispasmodic effects. It is a multitherapeutic, cosmetic, and nutritional plant that is investigated by researches. The drug of *M. chamomilla* is found in the pharmacopeia of 26 countries. Objective of this chapter is to review the medicinal and pharmacological properties along with botanical properties and chemical composition of *M. chamomilla*. Major constituents of *M. chamomilla* essential oil are chamazulene, α-bisabolol oxide-A, α-bisabolone oxide-A, cis-trans-β-farnesene, α-bisabolol, cis-trans-farnesol, β-bisabolene, guaiazulene, α-pinene, sabinene, limonene, and caryophyllene oxide identified using GC/MS. *M. chamomilla* contain phenolic acids (caffeic, chlorogenic, ellagic acids, ferulic, rosmarinic), flavonoids (luteolin, quercetin, kaempferol, apigenin, rutin, naringenin, isorhamnetin, luteolin-7-O-glucoside, luteolin-4′-glucoside, apigenin-7-glucoside), and coumarins (herniarin, umbelliferone). It has been reported that *M. chamomilla* has anti-inflammatory, antimicrobial, antioxidant, antispasmodic, chemopreventive, antiplatelet, antiparasidic, neuroprotective, antiulcer, antipruritic, sedative, antidiarrheal, wound healing, immunomodulating, and anxiolytic activities. Chamomilla oil has been accepted to GRAS status through FEMA and is confirmed through the FDA for usage in food and cosmetics.



## Keywords

Asteraceae · Chamomile · Coumarin · Essential oil · Flavonoid · *Matricaria chamomilla*



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## 26.1 Introduction

### 26.1.1 Description of *Matricaria chamomilla* L.

*Matricaria chamomilla* is an annual plant and its stem is glabrous, branched, erect, and smooth, 10–80 cm. Long and narrow leaves have two and three-pinnate and lower leaves are 5–7 cm, glabrous, rectangular outlines, primary segments are 10–12 pairs. The flower heads (capitula) are placed apart, they are generally solitary, occasionally sub-corymbose, and have a diameter of 10–30 mm. The disc florets with 5 teeth are yellow and 1.25–2.5 mm long, whereas the 11–27 ray flowers are white, 4–11 mm long, and furnished with a ligule. The hollow receptacle is swollen and without paleae, and cone-shaped; this is being a very significant typical characteristic of the plant. The involucre is initially 5–6 mm wide, after is up to 8 mm. The phyllaries are 2.5–3.5 mm and acute, obtuse, or oblanceolate. The type of fruit is an achene; the achene is yellowish-brown and has 5 whitish ribs on the rearward surface (Fig. 26.1) (Grierson 1975; Singh et al. 2011; Imad et al. 2018).

### 26.1.2 Taxonomical Aspect with Photograph

### 26.1.3 Synonyms

*Matricaria recutita* L.
*Matricaria obliqua* Dulac.
*Anthemis vulgaris* L. ex Steud.
*Matricaria littoralis* Rouy.
*Chamaemelum chamomilla* (L.) E.H.L.Krause.
*Matricaria bayeri* Kanitz.
*Chamaemelum vulgare* Bubani.
*Matricaria chamomilla* f. *suaveolens* Fiori.
*Pyrethrum hispanicum Salzm.* ex Boiss.
*Camomilla deflexa* Gilib.
*Matricaria chamomilla* var. *pappulosa* Margot & Reut.
*Matricaria exigua* Tuntas.
*Leucanthemum chamaemelum* Lam.
*Matricaria pyrethroides* DC.
*Matricaria recutita* var. *coronata* (Boiss.) Fertig.
*Matricaria recutita* f. *kochiana* (Sch.Bip.) Fiori.
*Matricaria salina* Schur.
*Matricaria chamomilla* var. *recutita* (L.) Fiori.
*Camomilla patens* Gilib.
*Matricaria recutita* var. *kochiana* (Sch.Bip.) Greuter.
*Chamomilla courrantiana* (DC.) C.Koch.
*Matricaria chamaemilla* Hill.
*Chamaemelum suaveolens* E.H.L.Krause.
*Matricaria chamomilla* var. *coronata* Boiss.
*Chamomilla chamomilla* (L.) Rydb.
*Matricaria recutita* var. *pappulosa* (Margot & Reut.) Feinbrun.
*Matricaria patens* Gilib.
*Chamomilla recutita* (L.) Rauschert.
*Matricaria coronata* (J.Gay ex Boiss.) W.D.J.Koch *Matricaria courrantiana* DC.
*Matricaria deflexa* Gilib.
*Chamomilla meridionalis* K.Koch.
*Matricaria kochiana* Sch.Bip.
*Courrantia chamomilloides* Sch.Bip.
*Matricaria chamomilla* var. *courrantiana* (DC.) G.Nicholson.
*Chamomilla officinalis* K.Koch.
*Matricaria chamomilla* f. *kochiana* (Sch.Bip.) Fiori.
*Chamomilla vulgaris* Gray.
*Matricaria chamomilla* f. *courrantiana* (DC.) Fiori.
*Chamomilla recutita* var. *bayeri* (Kanitz) Dostál.
*Matricaria chamomilla* var. *pusilla* (Willd.) Fiori.
*Matricaria suaveolens* L.
*Chamomilla unilateralis* K.Koch.
*Matricaria tenuifolia* Salisb.
*Chrysanthemum chamomilla* (L.) Bernh.
*Matricaria pusilla* Willd.
*Chrysanthemum suaveolens* Cav.
*Matricaria chamomilla* subsp. *pusilla* (Willd.) Holmboe.

**Fig. 26.1** Taxonomical aspect with photograph of *Matricaria chamomilla*. (Photos of by Mehmet Koyuncu)

*Matricaria capitellata* Batt. & Pit.
*Matricaria suaveolens* f. *macrocephala* Probst & Thell. (http://powo.science.kew.org/taxon/154715-2#synonyms).

### 26.1.4 Local Names

Gvirila (Georgian), Camomille, Matricaire (French), Romashkaaptetsnaja (Russian), Papatya, Mayıs papatyası (Turkish), tsobaja jacteigei (Azeri), Echte kamille, Deutsche kamille (German), Chamomilla, Chamomile (English), and Erizyk (Armenian) (Bussmann et al. 2019; Özdemir 2019).

### 26.1.5 Occurrence/Habitat

*Matricaria chamomilla* usually grows along roadsides, steppe areas, railways, waste, cultivated ground, saline meadows, in gardens, kitchen gardens, around landfills, and as a weed in crops (Grierson 1975; Imad et al. 2018; Bussmann et al. 2019).

### 26.1.6 Importance

*Matricaria chamomilla* (Asteraceae) is a well-known medical herb extensively utilized in phytotherapy and it is usually mentioned as the "star

amongst medicinal species." *M. chamomilla* is one of the favorite plants in traditional medication. It is a multitherapeutic, cosmetic, and nutritional plant that is investigated by researches. The drug of *M. chamomilla* is found in the pharmacopeia of 26 countries (Singh et al. 2011; Özdemir 2019).

### 26.1.7 Objective of This Chapter

Objective of this chapter is to review the medicinal and pharmacological properties (internal and external uses, method of administration, adverse effects, contraindication, etc.) along with botanical properties and chemical composition of *Matricaria chamomilla* plant.

## 26.2 Distribution and Status of Species

*Matricaria chamomilla* grows naturally in Southern and Eastern Europe, Western Asia, North America, and Australia. It is grown commercially in Egypt, Germany, Cuba, Hungary, Brazil, Turkey, Afghanistan, USA, New Zealand, Pakistan, North India, Japan, Russia, Ethiopia, and Argentina (Sharifi-Rad et al. 2018; Özdemir 2019).

## 26.3 Comparison of Traditional/Ethnomedicinal/Local Uses in Turkey and Throughout the World (Asia and Europe)

*Matricaria chamomilla* has been utilized since ancient times in ancient Greece, Rome, and Egypt as herbal remedies for its anti-inflammatory, wound healing, antiseptic, and antispasmodic effects. It is believed by Anglo-Saxons that *M. chamomilla* is one of nine sacred plants given by the lord. It is used in hysteria, flatulence, intermittent fever, and colic, (Singh et al. 2011; Rezaeih et al. 2015). It is reported that *M. chamomilla* oil has some therapeutic effects in the most famous Traditional Persian Medicine textbooks. For instance, Ibn-e-Sina or Avicenna showed that chamomile oil was tonic for the nervous system in The Canon of Medicine (Shoara et al. 2015). The therapeutic properties of *M. chamomilla* are known for a long time, and it has been named as "Flower of the Sun God" by Egyptians. *M. chamomilla* has usually been used as infusions (a herbal tea) or tinctures (alcoholic extracts) for a long while in traditional medicine. The essential oil of *M. chamomilla* is used for the treatment of insect bites, cuts, burns, skin inflammations, rashes, and acne (Kolodziejczyk-Czepas et al. 2015). The infusion and powder forms of *M. chamomilla* are conventionally utilized for diuresis, cough, sedation, dermatological diseases, haemorrhoids, and stomach ache in Turkey (Cemek et al. 2010). It has diuretic, appetizing, sedative, carminative, and cholagogue effects. Externally, the infusion of the plant is used as a mouthwash against inflammation of the throat and is used as a medical dressing against inflamed wounds (such as hemorrhoids). Also, it is used as a pain reliever and wound healing (Baytop 1999).

## 26.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques (Classification and Structures of Few Representatives)

Flowers of *Matricaria chamomilla* contain phenolic acids (caffeic, chlorogenic, ellagic acids, ferulic, rosmarinic), flavonoids (luteolin, quercetin, kaempferol, apigenin, rutin, naringenin, isorhamnetin, luteolin-7-*O*-glucoside, luteolin-4′-glucoside, apigenin-7-glucoside), and coumarins (herniarin, umbelliferone), quantificated by using HPLC-PDA, UHPLC-MS/MS, and capillary electrochromatography, and it also contains essential oil (Baczek et al. 2019; Fonseca et al. 2007; Novakova et al. 2010; Qureshi et al. 2019). Major constituents of *M. chamomilla* essential oil are chamazulene, $\alpha$-bisabolol oxide-A, $\alpha$-bisabolone oxide-A, *cis-trans*-$\beta$-farnesene, $\alpha$-bisabolol, *cis-trans*-farnesol, $\beta$-bisabolene, guaiazulene, $\alpha$-pinene, sabinene, limonene,

caryophyllene oxide, $\alpha$-bisabolol oxide-B, $\beta$-pinene, 1,8-cineole, spathulenol, citronellol, aromadendrone, *p*-cymene-8-ol, azulene, *p*-cymene, $\beta$-elemene, borneol, $\gamma$-cadinene, $\gamma$-eudesmol, germacrene D and sesquiterpene lactones of guaianolide type (matricarin, achillin, acetoxyachillin, leucodin, 2a-hydroxyarborescin), eudesmanolide type (matricolone), and germacranolide type (dihydroridentin) identified using GC-FID and GC/MS (Alireza 2012; Baczek et al. 2019; Hosseinzadeh et al. 2018; Mavandi et al. 2019; Siadat and Direkvand-Moghadam 2017; Tschiggerl and Bucar 2012; Zaiter et al. 2007). Flowers also contain vitamin C extracted by conventional and ultrasound-assisted extraction methods (Zlabur et al. 2020), triterpenoids, and sterols (taraxerol, $\alpha$-amyrin, $\beta$-amyrin, lupeol, $\psi$-taraxasterol, taraxasterol, sitosterol, stigmasterol, campesterol, sitostanol, cholesterol) identified by GC/MS (Ganeva et al. 2003). Leaves contain phenolic acids (syringic, vanillic, caffeic, 1,5-dicaffeoylquinic acids), flavonoids (quercetin, luteolin), and coumarins (daphnetin, daphnin, herniarin, umbelliferone, skimmin) determined by HPLC-DAD-MS (Petruova-Poracka et al. 2013; Petrulova et al. 2020).

## 26.5 Scientific Evidences: Pharmacological Activities (All Major Therapeutic Activities with In Vitro and In Vivo Studies, Mechanism of Action)

### 26.5.1 In Vitro Studies

#### Anti-inflammatory Activity

Different polarity extracts prepared from *Matricaria recutita* flowers were investigated for cyclooxygenase-2 (COX-2) inhibitory and anti-inflammatory activities at 300 and 500 µg/mL concentrations. The anti-inflammatory effect was evaluated using human red blood cell membrane stabilization in comparison to standard medication diclofenac sodium, while COX-2 inhibition was investigated using enzyme immunoassay. Aqueous extract of the plant showed highest membrane stabilization (82.43%) and COX-2 inhibition (68.62%) at 500 µg/mL (Begum et al. 2017).

#### Antimicrobial Activity

Cold and boiling water extracts prepared from *Matricaria chamomilla* flower were investigated for the ability to inhibit growth of pathogenic bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Enterobacter aerogenes*, *Citrobacter freundii*, *Proteus mirabilis*, *Staphylococcus saprophyticus*) isolated from pregnant women who have infection in urinary tract using disc diffusion assay for the antibacterial activity at different concentrations (50, 100 and 150 mg/mL). Imipenem was used as standard drug at 10 µg. Aqueous extract displayed potent antibacterial effect against all species at 150 mg/mL. The diameters of inhibition zone were 29.3 ± 0.2 for *E. coli*, 26.3 ± 0.4 for *K. pneumoniae*, 26.3 ± 0.2 for *A. baumannii*, 28.3 ± 0.3 for *E. aerogenes*, 29.3 ± 0.1 for *C. freundii*, 29.3 ± 0.5 for *P. Mirabilis,* and 28.3 ± 0.2 for *S. saprophyticus* ($P > 0.05$) (Aljanaby 2018).

Essential oil of *M. chamomilla* flowers was evaluated for antimicrobial activity using the disc diffusion assay. Essential oil showed potent antibacterial activity and the diameters of inhibition zone were determined to be 13.33 mm for *Listeria monocytogenes* and 40.00 mm for *Staphylococcus aureus* (Stanojevic et al. 2016).

#### Antioxidant Activity

*Matricaria chamomilla* flower essential oil was evaluated for antioxidant activity using DPPH method. Essential oil displayed potent antioxidant properties and its $EC_{50}$ value was determined as 2.07 mg/mL (Stanojevic et al. 2016).

#### Antispasmodic Activity

Infusions prepared from *Matricaria recutita* flowers and capitulums were evaluated for spasmolytic effect using human cAMP- and cGMP-phosphodiesterases (PDE) and recombinant PDE5A1 inhibitory assay. Infusions displayed cAMP-PDE inhibitory activity ($IC_{50}$ values = 17.9–40.5 µg/mL) (Maschi et al. 2008).

### Chemopreventive Activity

*Matricaria chamomilla* flowers aqueous and methanol extracts were investigated for anticancer properties against different human prostate cancer cell lines (LNCaP, PC-3, and DU145). Aqueous extract showed to reduce cell viability which has a range of 9.8–37.2% for LNCaP cells, 8.6–33.4% for PC-3 cells, and 6.7–35.2% for DU145 cells at 1000–4000 μg/mL concentrations for 24 h treatment. Methanol extract showed reduced cell viability that ranged from 25.4 to 61.9% in LNCaP cells, from 14.7 to 47.5% in DU145 cells, and from 16.3 to 55.6% in PC-3 cells at 100 to 400 μg/mL (Srivastava and Gupta 2007).

### Enzyme İnhibitory Activity

*Matricaria chamomilla* water and *n*-butanol extracts were evaluated for inhibitory activity on purity angiotensin-converting enzyme (ACE) compared to lisinopril as a standard inhibitor. The water extract ($IC_{50}$ value = 1.292 mg/mL) and butanol extract ($IC_{50}$ value = 0.353 mg/mL) displayed significant inhibitory activity, while $IC_{50}$ value of lisinopril was determined as 0.781 nM (Bas et al. 2021).

*M. recutita* flowers essential oil and its major components were investigated for inhibitory activity on human cytochrome P 450 enzymes. Essential oil showed inhibitory activity on all enzymes, especially on CYP1A2. The components, chamazulene, *cis*-spiroether, and *trans*-spiroether displayed potent inhibitor activity with 4.41, 2.01, and 0.47 μM $IC_{50}$ values, respectively, on CYP1A2 (Ganzera et al. 2006).

### Antiparasidic Activity

*Matricaria chamomilla* essential oil was investigated against *Anisakis* larvae. The essential oil (125 μg/ml) caused the death of all nematodes, which indicated cuticle changes and intestinal wall rupture. In the in vivo tests, only 2.2% ± 1.8 of infected rats treated with essential oil revealed gastric wall lesions compared to 93.3% ± 3.9 of control. It showed changes of cuticle and rupture of intestinal wall at 125 μg/mL (del Carmen et al. 2012).

## 26.5.2 In Vivo Studies

### Anti-inflammatory Activity

Essential oil obtained from *Matricaria chamomilla* by hydrodistillation from flowers was investigated for anti-inflammatory effect in edema induced by carrageenan and experimental trauma in rats hind paw at 100 and 200 mg/kg doses compared with standard drug indomethacin and with control group. The essential oil displayed significant anti-inflammatory effect ($P < 0.001$) with 92.65% and 94.94% inhibition of inflammation induced by carrageenan at 100 and 200 mg/kg, respectively, while indomethacin showed 63.59% inhibition. In experimental trauma-induced hind paw edema assay, the essential oil displayed 91.21% and 75.16% at 100 and 200 mg/kg, respectively, while indomethacin showed 75.16% inhibition (Hajjaj et al. 2016).

### Chemopreventive Activity

Aqueous extract of *Matricaria chamomilla* flowers was investigated for anti-carcinogenic effect against colorectal cancer induced by 1,2-dimethylhydrazin in male Balb/c mice at 150 mg/kg body. The extract regulated Wnt pathway in tissues of colon. Also, it significantly reduced levels of COX-2 and activities of iNOS (El Joumaa et al. 2020).

### Neuroprotective Activity

*Matricaria chamomilla* tea was evaluated for neuroprotective activity against Parkinson's disease-like symptoms in rats (2.14 mL/ kg P.O.). Tea minimized catalepsy as standard drugs levodopa/carbidopa ($P < 0.005$). It was shown that presence of proliferative blood vessels increased cellularity with reactive glial cells as compared to chlorpromazine group in rats' midbrain sections with treated *M. chamomilla* tea. Also, this brain region showed few CD68 cells and no polymorphs neutrophils after CD21 staining (Khan et al. 2020).

### Antiulcer Activity

Extracts prepared from *Matricaria chamomilla* flower were evaluated on ulcer models induced by indomethacin in rats. Ethyl acetate and chlo-

roform extracts displayed antiulcer effect by 84% and 80%, respectively. Furthermore, petroleum ether and aqua-ethanol extracts showed 57% and 50% antiulcer effect, respectively (El Souda et al. 2015).

### Antipruritic Activity

Ethyl acetate extracts of *Matricaria recutita* flowers were evaluated for antipruritic effects in mice. The extract (1.2 wt./wt.%) was given to mice for 11 days. It potently put down scratching induced by compound 48/80otently p with oxatomide (10 mg/kg) (Kobayashi et al. 2003).

### Sedative Activity

Methanol extract of *Matricaria chamomilla* L. flower was evaluated for sedative effect using pentobarbital sodium-induced loss of righting reflex as sleep disturbed model. The extract (300 mg/kg, i.p.) displayed significantly restful and hypnotic effect as regards both latency to sleep (31.9%, $P < 0.001$) and duration time (53.3%, $P < 0.01$) (Taher et al. 2016).

### Nephroprotective Activity

Ethanol (95%) extracts of *Matricaria chamomilla* leaves and flowers were investigated for protective effect in cisplatin nephrotoxicity rat model. *M. chamomilla* (50 mg/kg, i.p.) potently caused to rise body weight, to normalize kidney functions, to improve apoptotic markers, to reduce oxidative stress markers, and to correct the hypocalcemia (Salama 2012).

### Antidiarrheal and Antioxidant Activity

*Matricaria recutita* decoction was investigated for antidiarrheal effect against diarrhea induced by castor oil and antioxidant activity against oxidative stress in rats. Decoction displayed dose-dependent antidiarrheal activity and intestinal fluid accumulation. Furthermore, it cancelled all biochemical changes. It increased malondialdehyde level, depleted of antioxidant enzyme effects as catalase, superoxide dismutase, and glutathione peroxidase, and enhanced gastric and intestinal mucosa-free iron and hydrogen peroxide levels (Sebai et al. 2014).

### Wound Healing Activity

The flowers extract in olive oil of *Matricaria chamomilla* applied topically was evaluated for wound healing effect on linear incisional wound model in rats. *M. chamomilla* displayed significant wound healing activity ($p < 0.05$) (Jarrahi et al. 2010).

### Immunomodulating Activity

*Matricaria chamomilla* heteropolysaccharides administrated intragastric and parenteral were investigated for immunomodulating effect in Wistar rats and hybrid mice F1(CBAxC57Bl) upon air cooling and immersion cooling. The heteropolysaccharides displayed immunomodulating activity by induction of effect of erythrocytes, immunoregulatory cells activation of the peripheral blood, and increased effector cells sensitivity to helper signals (Uteshev et al. 1999).

## 26.5.3 Ex Vivo Studies

### Antispasmodic Activity

Flavonoids-rich fraction prepared from *Matricaria chamomilla* flowers aqueous-alcoholic extract was evaluated for spasmolytic effects on rat-isolated uterus. The fraction diminished uterus contractile activities against contractions induced by KCl ($IC_{50}$ value = 85 ± 12 μg/mL), by acetylcholine ($IC_{50}$ value = 119 ± 11.4 μg/mL), by electrical field stimulation ($IC_{50}$ value = 74 ± 12.2 μg/mL), and by oxytocin ($IC_{50}$ value = 105 ± 14.6 μg/mL), while $IC_{50}$ values of standard drug nifedipine were 22 ± 9.5 nM, 160 ± 42 nM, 90 ± 27 nM, and 2.15 ± 0.35 μM, respectively (Sadraei et al. 2019).

## 26.6 Clinical Studies (Ongoing, Proposed, and Completed Studies)

### 26.6.1 Anxiolytic Effect

The people who have a principle diagnosis of moderate-to-severe Generalized Anxiety Disorder (GAD) were treated with *Matricaria*

*chamomilla* pharmaceutical-grade extract 1500 mg (500-mg capsule 3 times daily) for 12 weeks along phase 1. The therapy responders were randomized to either 26 weeks of pursuance *M. chamomilla* treatment or placebo in a double-blinded, placebo-substitution design along with phase 2. The mean time to recrudesce was 6.3 ± 3.9 weeks for placebo and 11.4 ± 8.4 weeks for *M. chamomilla*. The risk of recrudesce was non-considerably lower for *M. chamomilla* (risk ratio, 0.52; 95% CI, 0.20–1.33; $P = 0.16$). Long-term *M. chamomilla* was safe and considerably decreased moderate-to-severe GAD symptoms, however did not considerably decrease the ratio of recrudesce (Mao et al. 2016).

The people who have moderate to severe GAD were treated with open-label therapy with pharmaceutical-grade *M. chamomilla* extract 1500 mg/day for 8 weeks. Important progress over time was also seen on the GAD-7 rating ($\beta = -8.4$ [95% CI = −9.1 to −7.7]). *M. chamomilla* extract showed a clinically significant decrease in GAD symptoms compared to traditional anxiolytic medicine treatment (Keefe et al. 2016).

### 26.6.2 The Effect on Carpal Tunnel Syndrome

The standardized topical oil of *Matricaria chamomilla* was tested on 26 patients with severe carpal tunnel syndrome and they were cured with a night splint plus topical *M. chamomilla* oil or placebo for four weeks. Important healing of symptomatic and functional conditions of patients in the oil group was detected (p ¼ 0.019 and 0.016, in order of) in comparison with those in the placebo group. The oil healed the symptomatic and functional conditions of patients (Hashempur et al. 2015).

### 26.6.3 The Platelets Activity

The activity of polysaccharide–polyphenolic conjugates obtained from *Matricaria chamomilla* was tested on blood platelet aggregation of patients who took combined anti-platelet treatment complex with clopidogrel and acetylsalicylic acid at 10, 25, 50, and 100 g/mL concentrations. The therapy of platelet-rich plasma (PRP) gained from healthy donors with compounds isolated from *M. chamomilla* eventuated with a dose-dependent reduction of platelet aggregation induced by ADP, arachidonic acid, and collagen agonists (Bijak et al. 2013).

### 26.6.4 Effect on Knee Osteoarthritis

The topical *Matricaria chamomilla* oil was tested on patients (randomized and cured with oil, diclofenac, or placebo for three weeks) with knee osteoarthritis. The oil considerably decreased the patients' necessity for acetaminophen ($P = 0.001$) in comparison with diclofenac and placebo and patients declared no side effects about oil (Shoara et al. 2015).

### 26.6.5 Effect on Migraine

A *Matricaria chamomilla* oil preparation was formulated and standardized (chamazulene and apigenin). Hundred patients were treated with the formulation or placebo. The data indicated that pain, phonophobia, nausea, photophobia, and vomiting considerably ($p < 0.001$) reduced by utilizing chamomile oleogel on the patients after 30 min. The data approved the effect of *M. chamomilla* oleogel as an analgesic in migraine without aura (Zargaran et al. 2018).

### 26.6.6 Effect on Breast Pain (Mastalgia)

*Matricaria chamomilla* was tested on pain check of cyclic mastalgia and 60 patients with mastalgia were divided into two groups: *M. chamomilla* ($n = 30$) and placebo ($n = 30$). The important decrease was detected in both the groups (*M. chamomilla* and placebo) after two months ($p < 0.0001$ and $p = 0.048$, in turn of) in compari-

son with baseline and between two groups ($p = 0.007$). *M. chamomilla* was found as a well-tolerated, safe and efficient medication for healing women with mild to moderate mastalgia (Saghafi et al. 2017).

### 26.6.7 Effect on Minor Aphthous Stomatitis

The extract of chamomile and triamcinolone in Orabase was compared on oral mucosal minor aphthous stomatitis. Forty-five patients were divided into 3 groups and cured with placebo, triamcinolone in Orabase, and extract in Orabase. Triamcinolone and extract in Orabase decreased ulceration size by day 3 and pain by days 3 and 6 similarly with an important differentiation from the placebo group. *M. chamomilla* extract reduced the pain of the ulcerations and produced pleasure for the patients (Tadbir et al. 2015).

## 26.7 Toxicological Studies (Dose and Safety Profile, Acute, Chronic, and Mutagenicity Studies to Demonstrate Broad Spectrum Safety, GARS Status)

### 26.7.1 Dose and Safety Profile

#### Internal Usage

**Adults:** As a tea infusion: 3 g of the medication to 150 ml of hot water, 3 to 4 times daily.

**Liquid extract** (1:2; 50% ethanol as chosen extraction solver): 3–6 ml daily.

**Dried extract:** 50–300 mg 3 times daily.

**Aged:** Dose like for adults.

**Children:** The ratio of adult dose accordingly age or bodyweight (ESCOP Monographs 2003).

#### External Usage

For compressors, rinses, garglings, or poultices: 3–10% m/V infusion or 1% V/V liquid extract or 5% V/V tincture, 3–10 percentile infusions.

For baths: 5 g of the medication, or 0.8 g of alcoholic extract, per liter of water, 50 g-10 liters of water.

For solid and semi-solid preparations: hydroalcoholic extracts equaled to 3–10% m/m of the medication.

For vapor inhalation: 10–20 ml of alcoholic extract per liter of hot water (ESCOP Monographs 2003; Blumenthal 1999).

#### Method of Administration

Fluid and solid preparations for external and internal administration (Blumenthal 1999).

#### Contraindications

Sensitivity to *Matricaria* genus or other members of the Asteraceae family (ESCOP Monographs 2003).

#### Interactions with Other Medications

It has been reported that *Matricaria chamomilla* increased international normalized ratio (INR) and prothrombin time and ecchymosis (Segal and Pilote 2006). *M. chamomilla* may increase the effectiveness of the drug when used with anticoagulant drugs (Warfarin) due to the hydroxycoumarins it carries. The plant has weak anxiolytic properties at the benzodiazepine receptor site. For this reason, it should not be used with alcohol or benzodiazepine group drugs (Yılmaz 2017).

#### Pregnancy and Lactation

There have been no reports on harmful effects.

#### Works Required Attention

None reported.

#### Overdose

None reported.

#### Duration of Use

Although there is no record, it is not appropriate to use it for more than 2 months (Yılmaz 2017).

### 26.7.2 Acute, Chronic, and Mutagenicity Studies to Demonstrate Broad Spectrum Safety

#### Acute Toxicity

The acute toxicity towards *Vibrio fischeri* of aqueous extract of *Matricaria chamomilla* was evaluated at the three temperatures. *M. chamomilla* indicated a strong effect to inhibit bioluminescence of *V. fischeri* with EC50 value lower than 0.2 mg/ml at incubation at 15 min. Especially, extracts at 80 ° C and 100 ° C demonstrated strong toxicity, while the extract at 25 ° C had lower toxicity (Nefeli et al. 2020). Chamomilla essential oil is generally considered safe by the FDA. Sensitized individuals may develop an allergic reaction, observed as contact dermatitis. Since daphnetine (coumarin) and its glycoside, which are found in the flowers and leaves of the plant, may cause allergic reactions, the presence of these compounds in commercial preparations should be investigated (Yılmaz 2017).

#### Chronic Toxicity

No toxic effects were observed in long-term oral administration of Chamomilla extract to rats and dogs. In addition, no teratogenic effect was observed in long-term applications on rats and puppies and there was no change in the prenatal development of the puppies. Chamomilla extract was administered by cutaneous to rabbits and by inhalation to guinea pigs for 3 weeks and no toxic effects were observed (Yılmaz 2017).

#### Mutagenicity and Teratogenicity

Aqueous extract of Chamomilla flowers prepared with boiled water produced a relatively high level of mutagenicity in the Ames test. Polysaccharides polyphenolic conjugates obtained from Chamomilla flowers have not shown any cytotoxic effects on human blood platelets, mouse fibroblast culture L-929, and human lung cells A-549 (Yılmaz 2017).

### 26.7.3 GRAS Status

Chamomilla oil has been accepted to GRAS status through FEMA and is confirmed through the FDA for usage in food and cosmetics (ESCOP Monographs 2003).

## 26.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies (with Special Focus on Bioavailability and Metabolism of Active Constituents)

### 26.8.1 Commercial Formulations/ Products

- **Helago-Care Oil (Combined).**
- **Ingredients:** Sage (*Salvia officinalis* L.), Chamomile (*Matricaria chamomilla*).
- **Uses:** Mouth inflammation, pressure points (e.g., due to dental prostheses), wound nose (in case of cold), sunburn burns, skin abrasions, scratches, rhagades (skin cracks), insect bites.
- **Administration method:** Apply several drops of oil undiluted several times daily to the sensitive or irritated areas of the skin or oral mucosa.
- **Kamillosan Mouth Spray 30 ml spray (Combined).**
- **Ingredients:** Water (aqua)/alcohol (25%), extracts of chamomile (*Matricaria chamomilla*), oils of chamomile (*M. chamomilla*),

peppermint (*Mentha piperita*), anise (*Pimpinella anisum*).
- **Uses:** Spray provides healing relief for mouth sores.
- **Administration method:** Spray into the mouth or throat three times a day after meals.
- **Supherb Climex Tablets (Combined).**
- **Ingredients:** Dong quai, *Matricaria recutita* L.
- **Uses:** It is used to relieve premenopausal and menopausal symptoms in women. It relieves symptoms such as irritability, hot flashes, weakness, and insomnia.
- **Administration method:** 2 tablets 2–3 times in a day between meals.
- **Alvityl Peaceful Night (Combined).**
- **Ingredients:** Lemon balm (*Melissa officinalis* L.), chamomile (*Matricaria chamomilla*), linden (*Tilia cordata* Mill.), magnesium.
- **Uses:** It soothes, relaxes, and fosters a restorative sleep, naturally and smoothly contribute to the good functioning of the nervous system day and night and participates in bone growth.
- **Administration method:** From 3 years old, teenager, adult: 10 mL once a day, preferably in the evening after dinner.
- **Day and Night Syrup 200 mL (Combined).**
- **Ingredients:** Phosphor, magnesium, manganese, vitamin C, chamomile (*Matricaria chamomilla*), lemon balm (*Melissa officinalis* L.), orange (*Citrus aurantium* L. var. *dulcis* L.), lavender (*Lavandula angustifolia*), marjoram (*Origanum majorana* L.), hawthorn (*Crataegus oxycantha* L.).
- **Uses:** It helps prevent night awakenings, which are very common in children.
- **Administration method:** It is recommended to consume 1 teaspoon (5 ml) preferably after meals.
- **Iberogast (Combined).**
- **Ingredients:** Bitter candytuft (*Iberis amara*), milk thistle (*Silybum marianum*), angelica (*Angelica archangelica*), chamomile (*Matricaria chamomilla*), peppermint (*Mentha* x *piperita*), caraway (*Carum carvi*), liquorice (*Glycyrrhiza glabra*), lemon balm (*Melissa officinalis*), greater celandine (*Chelidonium majus*).
- **Uses:** It is an efficacious, fast, well-tolerated treatment for multiple digestive disorders.
- **Administration method:** Dilute it in a small amount of liquid (like water, tea, or juice) and drink it before or along with meals. Adults and adolescents aged 13 years and above; children aged between 6 and 12 years; and children aged between 3 and 5 years should get 20 drops, 15 drops, and 10 drops, respectively, at a time.
- **IntimClean Vaginal Douche (Combined).**
- **Ingredients:** Horsetails (*Equisetum arvense*), chamomile (*Matricaria chamomilla*), thyme (*Thymus vulgaris*), eucalyptus (*Eucalyptus globulus*).
- **Uses:** Vaginal douching is used in accordance with the physiological pH value of the female genital system, as it creates a softening, soothing, and refreshing effect when applied to both the external genital organs and the vaginal mucosa.
- **Administration method:** At most 2–3 washes per week.

### 26.8.2 Pharmacokinetic Studies

Quercetin, luteolin, and apigenin in rat plasma afterwards oral administration of *Matricaria chamomilla* extract was determined simultaneously using HPLC-UV. The extracts included 8.51 mg/kg quercetin, 56.49 mg/kg luteolin, and 13.82 mg/kg apigenin and were prepared in 0.5% sodium carboxymethyl cellulose and then taken orally to rats. Blood specimens (0.5 mL) were gathered. The maximum plasma concentration was found as 0.29 ± 0.06 μg/mL for quercetin, 3.04 ± 0.60 μg/mL for luteolin, and 0.42 ± 0.10 μg/mL for apigenin. Times to reach maximum plasma levels were 0.79 ± 0.25, 0.42 ± 0.09, and 0.51 ± 0.13 hours, in turn (Dong et al. 2017).

MChamazulene carboxylic acid (CCA) is natural propene with anti-inflammatory activity and a degradation product of proazulenic sesquiterpene lactones, for example, matricin. Chamomile contains both CCA and proazulenes.

It showed anti-inflammatory activity in various animal models with local and systemic applications. When matricin was given orally to human volunteers, plasma levels of CCA were seen in the micromolar range. The matricin was converted to CCA in artificial gastric fluid and has been suggested to be anti-inflammatory via conversion to CCA. Matricin was converted to chamazulene carboxylic acid in fluid of artificial gastric, while it was not in fluid of artificial intestinal (Ramadan et al. 2006).

## 26.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

Chamomile is well-known plant and has been used traditionally since ancient times as anti-inflammatory, wound healing, antiseptic, antispasmodic, diuretic, appetizing, sedative, carminative, cholagogue, and more. When scientific and clinical evidences were examined, it was seen that almost all usages of chamomile were evaluated and have been verified. Nevertheless, the number of in vivo and clinical studies should be increased especially for safety reasons.

## 26.10 Challenges and Future Recommendations as Potential Drug Candidate

Chamomile is used in both medicine and cosmetics industry due to its rich content and many medicinal properties. There are many products prepared from the *Matricaria chamomilla* essential oil and extracts in the world market. Most of these products are sold with indications. On the other hand, the true *M. chamomilla* is very frequently confused with herbs similar in appearance including poisonous ones. As should be considered in the preparation of all herbal products, it is very important that the products prepared from chamomile are both prepared from the right source and standardized that have been evaluated in terms of quality. It is recommended to grow *M. chamomilla* with better quality check of target bioactive ingredients necessary for medicinal effect. This is the most important step. Furthermore, it is needed to grow required quantities to ensure sustainability, so the plant should be cultivated. If the plant is cultivated, both the sufficient amount of plants will be grown and all the quality controls on the way from the plant to the drug will be done more accurately. Clinical studies of herbal products prepared from chamomile should also be carried out, and the products should be released to the market after passing all the necessary tests. However, more work is needed to explore other aspects of chamomile that may be candidates for medicine.

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# *Melissa officinalis* L.

27

Bilge Aydin

**Abstract**

Lemon balm (*Melissa officinalis* L.; Lamiaceae) is a perennial, bushy plant, native to West Asia and the Eastern Mediterranean regions, usually growing in clusters along roadsides. The main active components of the plant can be listed as volatile compounds, triterpenes, and phenolic compounds. In traditional folk medicine, it is used for the treatment of many diseases such as nervous system, gastrointestinal system, immune system, and cardiovascular system diseases and also used in aromatherapy. Studies have shown that the extracts prepared from the plant and some compounds obtained from the plant have many effects such as antiviral, antidepressant, antiulcer, antimicrobial, antispasmodic, hypolipidemic, antidiabetic, antioxidant, and neuroprotective effect. Therefore, it can be considered that the extract prepared and the active compounds obtained from *Melissa officinalis* L. will be beneficial in the treatment and prevention of many diseases.

**Keywords**

Lamiaceae · *Melissa officinalis* · Lemon balm · Bioactive compound · Folk medicine · Pharmacological properties

## 27.1 Introduction

### 27.1.1 Description of *Melissa officinalis* L.

*Melissa officinalis* L. is a perennial, bushy plant that usually grows wild in clusters on forests and roadsides. Its height can be between 20 and 150 cm. This plant in the Lamiaceae (Labiatae) family has toothed margins on the ovate-lanceolate leaves and has hairs on both sides. Veins are prominent on the lower face of the leaves. The calyx is 6–10 mm, short, with or without glandular hairs, and without glands. Corolla can be pale yellow, white, and sometimes pale purple (Fig. 27.1). Its taste is aromatic and has a lemon scent (Davis 1982; Baytop 1999).

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**Fig. 27.1** Flowers, seeds, and leaves of M. officinalis L.

### 27.1.2 Taxonomical Aspect with Photograph

### 27.1.3 Synonyms

*Melissa (M.) romana* Mill.,
*Melissa cordifolia* Pers.,
*Melissa altissima* Sm.,
*Melissa hirsuta* Hornem.,
*Melissa graveolens* Host,
*Melissa officinalis* var. *villosa* Benth.,
*Melissa taurica* Benth.,
*Melissa occidentalis* Raf. ex Benth.,
*Melissa officinalis* var. *cordifolia* (Pers.) K.Koch,
*Melissa officinalis* var. *altissima* (Sm.) K.Koch,
*Melissa officinalis* var. *hirsuta* K.Koch,
*Melissa officinalis* subvar. *altissima* (Sm.) Nyman,
*Melissa officinalis* var. *graveolens* (Host) Nyman,
*Melissa officinalis* var. *foliosa* Briq.,

*Melissa officinalis* subsp. *altissima* (Sm.) Arcang.,
*Melissa bicornis* Klokov,
*Faucibarba officinalis* (L.) Dulac,
*Melissa corsica* Benth.,
*Melissa foliosa* Opiz ex Rchb.,
*Mutelia officinalis* (L.) Gren. ex Mutel,
*Thymus melissa* E.H.L.Krause,
(http://www.theplantlist.org/tpl1.1/record/kew-124103)

### 27.1.4 Local Names

Lemon balm, bee balm, sweet balm, blue balm, balm mint, english balm, common balm, citronmelisse, citra, citronellae, sweet mary, cure-all, dropsy plant (English), limon otu (Turkish), melissenblatt, melissengeist (German), toronjil, toronjina, cedron, cidronella, melisa, limonera (Spanish), valverde boutons de fievre crème (French), badrangboya, taragarbha (Persian), mufarrehal qgalb, utrajul raihath (Arabic), and billi lotan (Hindi) (Basar and Zaman 2013; powo.science.kew.org; Ulbricht et al. 2005).

### 27.1.5 Occurrence/Habitat

*Melissa officinalis* usually grows along scrub, macchie, rocky slopes and crevices, streamsides, forest clearings, waste places, and roadsides (Davis 1982).

### 27.1.6 Registered Pharmacopoeias and Monographs

Pharmacopoeia of American, German, European, French, English, Spanish, Austria, Belgium, Switzerland, Hungary, Romania. Martindale, ESCOP monographs, Commission E monographs, PDR for herbal medicine, WHO monographs, and FFD monographs.

### 27.1.7 Importance

*Melissa officinalis* is traditionally preferred for the treatment of many diseases, especially nervous and digestive system diseases, for more than 2000 years (Shakeri et al. 2016). French priests and nuns and Swiss doctor and chemist Paracelsus (1493–1541) made use of this plant when preparing the tonic, which he described as the "life elixir" (Moradkhani et al. 2010).

Thanks to the effective compounds it contains, it has been shown by research that it provides success in the treatment of many diseases.

It is also used in cosmetics and food. *Melissa officinalis* is registered in the pharmacopeia books of many countries (Shakeri et al. 2016).

### 27.1.8 Objective of This Chapter

Objective of this chapter reviews the medicinal and pharmacological properties (internal and external uses, method of administration, adverse effects, contraindication, etc.) along with botanical properties and chemical composition of *Melissa officinalis* plant.

## 27.2 Distribution and Status of Species

*Melissa officinalis* L., known as Turkish "Oğulotu," English "Lemon Balm," is distributed in Southern Europe, Western Asia, Eastern Mediterranean, Caucasus, Northern Iran, Northern Iraq, and Southern Alps. In Turkey, it grows naturally in coastal areas of Anatolia and the Mediterranean region (Baytop 1999; Shakeri et al. 2016). Native to West Asia and the Eastern Mediterranean region, this plant is cultivated almost everywhere in Europe and the USA (Bisset 1994).

## 27.3 Comparison of Traditional/Ethnomedicinal/Local Uses in Turkey and Throughout the World (Asia and Europe)

*Melissa officinalis* is used for sore throat and cough treatment in Croatia. It is known that Spanish physicians use this plant as a refreshing, emeneog, and analgesic. It is used as tranquillizer, heart tonic, and antispasmodic in Traditional Moroccan Medicine (Shakeri et al. 2016). In Argentina, Patagonia, and Brazil, the leaves of the plant are consumed as a sedative (Bieski et al. 2015; de Albuquerque et al. 2007; Estomba et al. 2006; Hilgert 2001). Likewise, in different regions of Italy, infusions and decoctions prepared from the aerial parts of the plant are used as a sedative (Ballero et al. 2001; Cornara et al. 2009; Fortini et al. 2016). It is also consumed in different parts of Spain as a sedative and used for abdominal pain, as well as as a digestive, antidiarrheal, and carminative (Benítez et al. 2010; Bonet et al. 1999; Carrió and Vallès 2012; Cavero et al. 2011). In the North-West Ligurian Alps, it has been reported that the decoction prepared from the leaf and aerial parts of the plant is used as a wound cleanser against dyspepsia (Cornara et al. 2014). In Danish folk medicine, *Melissa officinalis* is used to treat insomnia caused by sadness and depression (Jäger et al. 2006). In Austrian folk medicine, it is used internally as a tea and also its essential oil is used externally for diseases of the gastrointestinal system, nervous system, liver, and bile (Vogl et al. 2013). It is recorded among the people of Lebanon that the leaves of the plant are used to treat migraine and stomach problems, memory, and strengthen heart functions (Salah and Jäger 2005). In Iranian folk medicine, the leaves of the plant are effective in the treatment of functional gastrointestinal disorders and are used as tonic, diuretic, sedative, and analgesic (Miraj et al. 2017).

There are three subspecies of *Melissa officinalis* in Turkey: M. *officinalis* L. subsp. *officinalis*, M. *officinalis* subsp. *inodora* (Bornm.), and M. *officinalis* subsp. *altissima* (Sm.) Arcangeli; however, only *Melissa officinalis* subsp. *officinalis* is used in the form of infusion for sedative, digestive, carminative, diaphoretic, and antiseptic effects. The most well-known form of this drug as sedative is "Mürekkep Melisa Alkolası." This compound, which is successfully used as a sedative and for mild stomach ailments, is prepared as follows:

| | |
|---|---|
| Lemon balm leaves (fresh if possible) | 120 g |
| Fresh lemon peel | 30 g |
| Nutmeg | 30 g |
| Coriander | 30 g |
| Clove | 15 g |
| Cinnamon | 15 g |
| Alcohol | 2000 g |

The above drugs are broken down and kept in alcohol for 8 days. At the end of this period, it is filtered and filled into bottles. 5–20 g is taken a day (Baytop 1999). It is recorded that the aerial parts of the plant are used in the treatment of migraine in the Sakarya region and in the treatment of heart diseases, diabetes, asthma, and upper respiratory tract infections in the Kırklareli region (Kültür 2007; Şaşkara et al. 2010; Uzun et al. 2004). In Balıkesir, İzmir, Denizli, and Uşak provinces, it is used in the treatment of various diseases such as asthma, liver and stomach disease, psychological disorders, diabetes, pharyngitis, head, tooth, ear pain, and tinnitus. In addition, it is used as stimulating, soporific, calming the nervous system, relaxing heart vessels, and blood cleanser (Sarı et al. 2010).

## 27.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques (Classification and Structures of Few Representatives)

The major active ingredients of *Melissa officinalis* are volatile compounds, triterpenes, and phenolic compounds (Argyropoulos and Müller 2014). The medicinal effect of the plant is mostly due to its phenolic compounds and essential oil (Schnitzler et al. 2008). Its essential oil is impor-

tant in aromatherapy in terms of the digestive system, immune system, psychology, and skin health (Basta et al. 2005).

### 27.4.1 Volatile Compounds

The rate of essential oil in the plant varies between 0.02% and 0.30%. The essential oil ratio of *Melissa officinalis* is lower compared to other members of the Labiatae family, and therefore its market price is high (Meftahizade et al. 2010). *Melissa officinalis* essential oil has a characteristic lemon scent and light yellow color. It is obtained from the fresh or dry drug by hydrodistillation or chemical extraction methods. The main component of the essential oil contains 39% citronellal, 33% citral (linalool, citronellol) and 2% geraniol, β-pinene, α-pinene, and β-caryophyllene. These components comprise 96% of the essential oil content. Besides, it contains triterpenes, phenolic acids such as rosmarinic, and flavon glycoside acids in a low ratio (Moradkhani et al. 2010).

It has been recorded by studies that the essential oil obtained from the leaves of the plant contains alpha-humulene, beta-caryophyllene, beta-ocimene Z, beta-ocimene E, carvacrol, caryophyllene oxide, citronellyl formate, citronellal, geraniol, geranial, geranyl acetate, germacrene D, globulol, humulene epoxide, neral, thymol, and 5-cedranone (Moradkhani et al. 2010).

The essential oil obtained by hydrodistillation of dry leaves is rich in geranial and neral components in the first year of the plant, while in the second year of plant, it is rich in carvacrol, caryophyllene oxide, citronellal, E-caryophyllene, geraniol, geranyl acetate, germakren D, and isogeranial components (Nurzyńska-Wierdak et al. 2014).

It has been determined that the major component of the essential oil acquired by hydrodistillation of the flowers of the plant is *trans*-carveol and also contains citronellol, δ-3-carene, citronellal, geraniol, 1-octene-3-ol, and spathulenol compounds (Adinee et al. 2008).

Internal and external factors, including soil, climate conditions, plant growth periods, age of the plant, dry or fresh of the plant, collection and storage conditions, may change the components of the essential oil. It has been found that the most suitable harvest time to obtain high content essential oil and quality drug is the development period just before flowering. (Kızıl 2009; Toth et al. 2003).

### 27.4.2 Triterpenes

The main extract prepared by treating the aerial parts of the plant (1:1) with EtOH: $H_2O$ was fractionated using n-butanol; Triterpenes such as ursolic and oleanolic acid were isolated from this fraction (Mencherini et al. 2007).

### 27.4.3 Phenolic Compounds

#### Phenolic Acids

The main component of the aerial parts of the plant is hydroxycinnamic acid derivatives present at 4–7%. Among these derivatives, there is the highest amount of rosmarinic acid and smaller amounts of catechin, p-coumaric acid, gallic acid, caffeic acid, chlorogenic acid, ferulic acid, and syringic acid (Arceusz and Wesolowski 2013; Shakeri et al. 2016). In addition, it has been determined that the aerial parts of the plant contain benzoic acid derivatives including elagic acid, gentic acid, p-hydroxybenzoic acid, protocatechic acid, epicatechin, and vanillic acid (ESCOP Monographs 2003; Shakeri et al. 2016; WHO Monographs 1999).

It was determined that the extract prepared by decoction of the leaves contained the highest amount of rosmarinic acid and lithospermic acid A, respectively (Carocho et al. 2015).

Betulinic acid, betulin, and 2-hydroxytriterpenic acid were obtained from the roots of the plant (Brieskorn and Krause 1974).

#### Flavonoids

The aerial parts of the plant contain flavonoids such as apigenin, luteolin, quercetin, chemferol, rutin, naringin, hesperidin, naringenin, and luteolin-3′g-lucuronite (ESCOP Monographs 2003; Shakeri et al. 2016; WHO Monographs 1999).

Flavonoids are isolated from the leaves of the plant: apigenin-7-*O*-beta-D-glucopyranoside, luteolin, luteolin 3′-*O*-beta-D-glucuronopyranoside, luteolin 7-*O*-beta-D-glucopyranoside, luteolin 7-*O*-beta-D-glucuronopyranoside, and luteolin 7-*O*-beta-D-glucopyranoside-3′-*O*-beta-D-glucuronopyranoside (Patora and Klimek 2002).

### 27.4.4 Other Compounds

The petroleum ether fraction prepared from the aerial parts of *Melissa officinalis* L. was determined by GC-MS method and it was determined that the major component was palmitic acid. In addition, fatty acids such as arachidic acid, myristic acid, linolenic acid, and linoleic acid were observed in this fraction (Abdel-Naime et al. 2019a).

It was determined that the extract prepared by decoction of the leaves contains fructose, glucose, and γ-tocopherol (Carocho et al. 2015).

*Melissa officinalis* L. also contains holocellulose, lignin, and hemicellulose molecules composed of glucose and xylose (Shakeri et al. 2016).

## 27.5 Scientific Evidences: Pharmacological Activities (All Major Therapeutic Activity with In Vitro and In Vivo Studies, Mechanism of Action)

### 27.5.1 Antiviral Effect

#### In Vitro Experiments

In a study comparing the antiviral activity of the aqueous extract prepared from *Melissa officinalis* leaves and the rosmarinic acid, caffeic acid, and *p*-coumaric acid compounds acquired from this plant, the aqueous extract of *Melissa officinalis* stopped replication of *Herpes simplex* type-1 virus (HSV-1) at 15 μg/ml concentration, and this effect showed an antiviral effect 10 times below the maximum noncytotoxic dose. On the other hand, rosmarinic acid was found to be not as selective as the *Melissa officinalis* aqueous extract, although it was the major compound showing antiviral effect depending on the dose (Astani et al. 2012).

The effects of the aqueous extract obtained from *Melissa officinalis* leaves and the caffeic, rosmarinic, and p-coumaric acids obtained from this extract on acyclovir-resistant, acyclovir-sensitive strains of H. simplex type-1 virus (HSV-1) were investigated on RC-37 (African green monkey kidney cell) cell lines. The aqueous extract has inhibited the penetration of the acyclovir-resistant and acyclovir-sensitive strains into cells by 96% and 80%, respectively; IC50 values of the extract were found at the level of 0.4 μg/ml (for both strains). Although rosmarinic acid was the compound with the highest antiviral effect among the isolated compounds, it was found that its effect was lower than the aqueous extract (Astani et al. 2014).

Seventy percent ethanolic extract prepared from the dried leaves of *Melissa officinalis* has shown strong anti-adenovirus effect by disrupting protein synthesis after adenovirus entered the host cell. (SI = 19.66) (Moradi et al. 2016).

*Melissa officinalis* essential oil has been observed to exhibit antiviral activity by stopping the replication of the virus at doses of 0.1 and 0.5 mg/ml after the infection of avian influenza A subtype H9N2 (Pourghanbari et al. 2016).

Methanolic extract prepared from dried aerial parts of *Melissa officinalis* has shown antiviral effect by inhibiting plaque formation, cytopathic effect, and viral protein synthesis in infected cells at a dose of 156 μg/ml against enterovirus 71 infection endemic to Asia-Pacific regions ($IC_{50}$ = 45.92 ± 1.05 μg/ml) (Chen et al. 2017).

It has been recorded that the hydroalcoholic extract prepared from *Melissa officinalis* showed inhibition against the human influenza virus (New H1N1) at concentrations more than 0.05 mg/ml (Jalali et al. 2016).

It has been determined that an aqueous extract of *Melissa officinalis* leaves is also effective on HIV-1 ($ED_{50}$ = 16 μg/ml) (Yamasaki 1998). Also, it has been shown that the aqueous extract inhibits the capacity of HIV-1 virions to enter into target cells in HIV-1-infected ex-vivo tonsil

histocultures, primary macrophages, and T-cell lines (Geuenich et al. 2008).

### 27.5.2 Antimicrobial Effect

#### In Vitro Experiments

It has been recorded that *Melissa officinalis* essential oil has an antibacterial effect on *Streptococcus pyogenes* at a concentration of 8 mg/ml (MIC = 0.5 mg/ml) (Behbahani and Shahidi 2019).

In one study, it has been stated that the essential oil of the plant had an antimicrobial effect on *Staphylococcus aureus* (MIC = 0.12 mg/ml), *Escherichia coli* (MIC = 2.00 mg/ml), *Salmonella typhimurium* (MIC = 1.00 mg/ml), and *Listeria monocytogene* (MIC = 1.00 mg/ml) (Ehsani et al. 2017).

It has been recorded that four compounds in ursan triterpene glycoside structure isolated from the aerial parts of the plant had an antimicrobial effect on Gram (−) bacteria such as *Pseudomonas aeruginosa, Candida albicans,* and *Klebsiella pneumonia* at a dose of 1 mg/ml (Abdel-Naime et al. 2019b).

It has been found that the essential oil obtained by distilling water from the aerial parts of the plant was effective on all Gram (+) and Gram (−) bacterial strains in different proportions and showed high antimicrobial activity, especially against *Escherichia coli* and *Shigella sonnei*. The essential oil has also been shown to have an antifungal effect against *Trichophyton tonsurans* (15 µl/ml) (Mimica-Dukic et al. 2004).

It has been stated that rosmarinic acid has a bactericide effect against *Staphylococcus aureus* and *S. epidermidis* strains. The antibacterial activity of petroleum ether and aqueous extracts prepared from the leaves has been demonstrated against Staphylococcus aureus and Bacillus cereus (MIC = 1.25 mg/ml) (Canadanovic et al. 2008).

Disk diffusion test has been performed on hexane, acetone, and ethanol extracts prepared from the leaves of the plant to evaluate their antimicrobial activities. As a result of the experiments, it has been concluded that acetone and hexane extracts have the most antimicrobial effect on gram (+) bacteria such as *Staphylococcus aureus* (25 ± 0.6 mm) and *Pseudomonas aeruginosa* (17.50 ± 0.40 mm), while ethanolic extract has a strong antimicrobial effect on *E. coli* (18.10 ± 0.70 mm) (Mabrouki et al. 2018).

### 27.5.3 Antispazmodic Effect

#### In Vitro Experiments

The 30% alcoholic extract of aerial parts of *Melissa officinalis* has been found to have an antispasmodic effect on the rat duodenum. (Barnes et al. 2005). The antispasmodic effect of the essential oil of the leaves of the plant has been demonstrated on the isolated rat duodenum, vas deferens (semen channel), and guinea pig ileum also on aorta and jejunum of the rabbit. It has also been reported that the plant has a relaxing effect on guinea pig tracheal muscles ($EC_{50}$ = 22 mg/L) and inhibits phasic contractions in the ileal myenteric plexus longitudinal muscle preparation that is stimulated with electricity ($EC_{50}$ = 7.8 mg/L) (ESCOP Monographs 2003).

In an ex-vivo study with *Melissa officinalis* extract, it was shown that mice jejunum has spasmolytic activity (Aubert et al. 2016; Heghes et al. 2019).

#### In Vivo Experiments

It was observed that 70% ethanol extract prepared from the leaves of the plant exerted an antispasmodic effect through muscarinic receptors and calcium channels on N-Mari rat ileum at a dose of 4 mg/ml (Khalaj and Khani 2018).

It was determined that the essential oil obtained from the aerial parts of *Melissa officinalis* decreased the tonic and phasic contractions induced by KCl, Ach, and 5-HT in rat ileum in a dose-dependent manner (Sadraei et al. 2003).

### 27.5.4 Antioxidant Capacity

#### In Vitro Experiments

In a study investigating the free radical scavenging effect of 70% ethanolic extracts prepared

from the root and leaves of the *Melissa officinalis* plant against 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical, the % inhibition value of the standard substance ascorbic acid ($IC_{50}$ = 3.22 × 10.6 mg/ml) at a concentration of 0.1 mg/ml was 94.17; the % inhibition value of the leaf extract ($IC_{50}$ = 0.66 mg/ml) at a concentration of 10 mg/ml was 91.43; and also the % inhibition value of the root extract ($IC_{50}$ = 10.27 mg/ml) at a concentration of 12.5 mg/ml was 94.68 (Alina Moacă et al. 2018).

*Melissa officinalis* essential oil has been found to have a strong free radical scavenging effect due to its high amount of phenolic compounds (For DPPH free radical scavenging effect ($IC_{50}$ = 7.58 µg/ml)) (Behbahani and Shahidi 2019).

In a study investigating the scavenging effects of methanolic extract prepared from *Melissa officinalis* leaves and methylene chloride, ethyl acetate, butanol, and petroleum ether extracts obtained by fractionation of this extract with solvents of different polarity against DPPH radical, $IC_{50}$ values were found as, respectively, 125.72, 146.67, 83.95, 94.58, and 905.79 µg/ml and it was concluded that it has a strong antioxidant effect (Hassan et al. 2019).

β-Carotene/Linoleic Acid Bleaching Test, Ferric-Reducing Antioxidant Power (FRAP), Oxygen Radical Absorbance Capacity (ORAC), Hydroxyl Radical Adverting Capacity (H-ORAC), and DPPH Radical Scavenging Activity tests were performed in the hexane, acetone, and ethanol extracts prepared from the leaves of the plant. As a result of the experiments, it was found that ethanol extract has the strongest antioxidant effect (Ethanolic extract $EC_{50}$ = 18.16 µg/ml for DPPH test) (Mabrouki et al. 2018).

In a study, it has been observed that Melissa officinalis L. has a protective effect on the cell membrane by eliminating free radicals (Hemolysis inhibition value $IC_{50}$ = 2.0 ± 0.5 µg/ml$^{-1}$) (Franco et al. 2018).

It has been observed that the essential oil obtained from the aerial parts of the plant has a strong antioxidant effect ($IC_{50}$ = 7.58 µg/ml) against DPPH radicals and prevents lipid peroxidation in the Fe $^{+2}/H_2O_2$ reduction system (94.59% for 2.13 µg/ml) (Mimica-Dukic et al. 2004).

DPPH and ABTS (2,2-azinobis-(3-ethylbenzthiazoline-6-sulfonic acid)) tests have been performed to determine the free radical scavenging effects of 50% ethanolic and aqueous extract obtained from the leaves of the plant in human colon cancer cell line (HCT-116). Both extracts have been showed antioxidant effects (ethanolic extract DPPH $IC_{50}$ = 11.04 µg/ml; ABTS $IC_{50}$ = 8.60 µg/ml; aqueous extract DPPH $IC_{50}$ = 17.11 µg/ml; ABTS $IC_{50}$ = 9.22 µg/ml) (Encalada et al. 2011).

## In Vivo Experiments

The biological activity of the hydroalcoholic extract obtained from *Melissa officinalis* has been measured using *Caenorhabditis elegans* as a model. The extract is in doses of 50 and 100 µg/ml; it has been shown to reduce the oxidative stress caused by juglone, lower the intracellular ROS level, and modulate the expression of the GST-4 antioxidant enzyme (Gayoso et al. 2018).

The study investigating the antioxidant effect of the aqueous extract prepared from the aerial parts of the plant against chronically manganese-induced oxidative stress in mice brains has been carried out in two stages and randomly. TBARS production, total thiol content, superoxide dismutase, and catalase inhibition parameters have been evaluated in the study. Mn-induced TBARS level and oxidative damage have been decreased in cortex and cerebellum in mice treated with the extract (cortex and cerebellum levels, respectively, TBARS = 295.60 ± 56.02 ve 323.78 ± 51.74; total thiol seviyesi = 2.39 ± 0.31 ve 2.47 ± 0.23) (Martins et al. 2012).

The antioxidant effect of essential oil obtained from *Melissa officinalis* leaves has been tested on mice using DPPH radical. It has been observed that essential oil has a scavenging effect on free radicals, depending on the dose (Chung et al. 2010).

Albino BALB/c mice have been used in the study investigating the effects of 70% ethanolic extract prepared from aerial parts of *Melissa officinalis* on anxiety and depression by preventing central oxidative stress. The extract has been administered for 14 days at doses of 50, 75 and 150 mg/kg. And then, experimental animals have been taken to behavioral tests (open field, forced swimming, elevated plus maze, tail suspension). After the behavioral tests, experimental animals have been anesthetized and intracardiac blood samples were taken. Brain tissue has been removed before being sacrificed. Malondialdehyde concentration, superoxide dismutase and glutathione peroxidase activities, and total antioxidant capacity level have been measured in homogenized brain tissues. The CORT level in blood samples decreased in the 75 and 150 mg/kg doses of extract groups compared to the control group. It was concluded that the extracts applied in doses of 75 and 150 mg/kg had an antioxidant activity (Ghazizadeh et al. 2020).

### 27.5.5 Cytotoxic and Antiproliferative Effect

#### In Vitro Experiments

It was determined by MTT test that *Melissa officinalis* essential oil has antiproliferative effects on three different human tumor cell lines: MCF-7, MOLT-4, and NCI-H460 ($GI_{50}$ values 6 ± 2; 31 ± 17; ˂5 µg/ml, respectively) (Nikšić et al. 2019).

MTT tests were performed to determine the cytotoxicity of a dose range of 0–1000 µg/ml of the hydroalcoholic extract prepared from the plant of *Melissa officinalis* on SKOV3 (ovarian cancer cells), PC-3 (prostate adenocarcinoma), A549 (lung nonsmall cell cancer cells), and MCF-7 (breast adenocarcinoma). In all cancer cells, the extract has been found to reduce cell viability below 33%, even at the lowest doses. $IC_{50}$ values were below 5 µg/ml in all cell lines; mean growth inhibition was 77.8%, 79.9%, 73.1%, and 86.7% in A549, PC-3, SKOV3 and MCF-7 cells, respectively (Jahanban-Esfahlan et al. 2015).

It was determined that the dichloromethane extract prepared from the leaves of *Melissa officinalis* had the highest cytotoxic effect on the breast MCF7 cell line in a dose-dependent manner. Besides, ethanolic extract and dichloromethane extract were compared in terms of cytotoxic effects on MCF7, LNCAP, and PC3 cell lines in the study. Accordingly, the $IC_{50}$ values of the dichloromethane extract were 30.90, 71.21, and 173.93 µg/ml, respectively, and the $IC_{50}$ values of the ethanol extract were 35.52, 136.40, and 237.82 µg/ml, respectively (Khallouki et al. 2020).

In a study conducted to determine the antiproliferative and proapoptotic effects of *Melissa officinalis* ethanolic extract on HT-29 and T84 cell lines, it was observed that it inhibited proliferation of cancer cells 3–4 days after the administration of the extract (HT-29 $IC_{50}$ = 346; T84 $IC_{50}$ = 120 µg/ml) (Weidner et al. 2015).

#### In Vivo Experiments

In a study investigating the antitumor effect of *Melissa officinalis* aqueous extract on DMBA-induced breast cancer model in rats, 21 female rats were used. The experimental animals were divided into three groups. Groups 1 and 2 were given a single dose subcutaneous injection of DMBA into the right pectoral area. Four weeks after DMBA injection, *Melissa officinalis* aqueous extract was applied to animals in group 2 and group 3, and as a result of the experiment, it was observed that TUNEL positive cells and the expression of Caspase-7 protein were increased; Ki-67 expression was decreased in the rats treated with *Melissa officinalis*. Also, the tumor volume inhibition rate was found to be 40% in the treated group compared to the nontreated group (Saraydin et al. 2012).

### 27.5.6 Enzyme Inhibition Effect

#### In Vitro Experiment

*Melissa officinalis* essential oil has been shown to inhibit the *acetylcholine esterase* (AChE) enzyme by 65.3% at a concentration of 1 mg/ml (Ferrira et al. 2006).

The aqueous extract prepared from the leaves has been shown to affect neurotransmission and brain GABA level by highly inhibiting the GABA transaminase (GABA-T) enzyme ($IC_{50}$ = 35 mg/ml) (Awad et al. 2007).

The activity of 45% water-ethanol extract prepared from the leaves of *Melissa officinalis* on the AChE inhibitor for 10 min was estimated to be equivalent to the activity of 1.72 ± 0.16 μg physostigmine (Dastmalchi et al. 2009).

In order to investigate the effect of drying the ethanol extract prepared from the leaves of *Melissa officinalis* with hot and cold air on COX-2, COX-2 expression levels were examined on KB cells by TPA-induced inflammation and it was observed that both extracts reduce COX-2 expression in a concentration-dependent manner. It was concluded that the cold air-dried extract was more effective at the same concentration (Lin et al. 2012).

In the study conducted for the inhibition effect of *Melissa officinalis* ethyl acetate extract and the polyphenol compounds isolated from the plant on AChE, it was reported that the inhibition effect of the extract was due to the synergistic effect of these compounds (Pereira et al. 2014).

### 27.5.7 Genotoxic Effect

#### In Vitro Experiments

In a study on human peripheral leukocyte cells, the extract prepared from *Melissa officinalis* leaves with 70% ethanol was given in the dose range of 10–50–100 and 150 μg/ml and no genotoxic effect was observed (Kamdem et al. 2013).

#### In Vivo Experiments

In the study evaluating the antigenotoxic and antimutagenic effects of methanol and water extracts prepared from *Melissa officinalis* on CF-1 male mice, no mutagenic or genotoxic effects were observed in bone and blood marrow samples after treated with ethanolic (250 and 500 mg/kg) and water (100 mg/kg) extract (Cassettari de Carvalho et al. 2011).

### 27.5.8 Sedative Effect

#### In Vivo Experiments

Thirty percent *Melissa officinalis* leaf extract in lyophilized form was administered intraperitoneally to mice at different doses, and sedation-inducing effects of the extract were tried to be understood by conducting behavioral tests (two-compartment test, locomotor activity test, staircase test), sleep induction test, and sleep potentization test. In the staircase test, it was observed that the extract caused significant sedation at a dose of 25 mg/kg. It was found that sleep was induced in rats given an infra-hypnotic dose of phenobarbital at doses of 3 and 6 mg/kg of the extract and it was concluded that sleeping time was increased at doses of >6 and 50 mg/kg (Soulimani et al. 1991).

*Melissa officinalis* essential oil showed sedative and narcotic effects when administered orally to mice at a dose of 3.16 mg/kg (ESCOP Monographs, 2003).

It has been determined that *Melissa officinalis* dry extract exerts anti-aggressive activity on Wistar strain rats and laboratory mice by affecting the central nervous system (Ulbricht et al. 2005).

*Melissa officinalis* ethanolic extract has been shown to have a sedative effect at the GABA (A) -benzodiazepine region in mice (Salah et al. 2005; Ulbricht et al. 2005).

### 27.5.9 Antidepressant Effect

#### In Vivo Experiments

Aqueous extract and the essential oil obtained from *Melissa officinalis* leaves were intraperitoneally injected in albino male mice at different

doses and forced swimming test (FST) was performed (positive control: imipramine). During the test, the swimming behaviors, climbing, and immobility of the animals were evaluated. As a result, it has been stated that both the essential oil and the aqueous extract of the plant have an antidepressant effect (in spontaneous motor activity test, aqueous extract: 100 counts/5 min at 300 mg/kg, essential oil: ~500 counts at 10 mg/kg; aqueous extract in climbing test: ~30 counts/5 min at 25 mg/kg, essential oil: ~35 counts/5 min at 300 mg/kg; aqueous extract in swimming test: ~7 counts/5 min at 150 mg/kg, essential oil: 5 counts/5 min at 300 mg/kg; in immobility test, aqueous extract: ~27 counts/5 min at 75 mg/kg, essential oil: 17 counts/5 min at 300 mg/kg) (Emamghoreishi and Talebianpour 2009).

In a study examining the effects of 70% ethanolic extract prepared from aerial parts of *Melissa officinalis* on anxiety and depression through prevention of central oxidative stress on albino BALB/c mice, the extract was given at doses of 50, 75, and 150 mg/kg for 14 days, and then the behavioral tests (tail suspension, elevated plus maze, forced swimming, open field) were enforced. The extract has been found to have an antidepressant effect at doses of 75 and 150 mg/kg (Ghazizadeh et al. 2020).

### 27.5.10 Anxiolytic Effect

#### In Vivo Experiments

It has been determined by the elevated plus maze and open field tests that extract prepared from the aerial parts of the plant with ethanol reduced anxiety-like behaviors on mice in a dose-dependent manner (Ibarra et al. 2010).

### 27.5.11 Antiulcer Effect

#### In Vivo Experiments

Effects of ethanol extract prepared from *Melissa officinalis* leaves have been investigated on gastric ulcer induced by indomethacin in rats. It has been observed that the extract decreases acid secretion, increases the amount of mucin, increases prostaglandin E2 release, and decreases leukotrienes at doses of 2.5–10 ml/kg. As a result of the trial, it has been determined that it has an antiulcer effect in a dose-dependent manner (Khayyal et al. 2001).

The effects of 80% methanol extract prepared from *Melissa officinalis* leaves were investigated on gastric ulcer models induced by indomethacin and WIR (water immersion restraint) in Wistar male rats. It was noted that the extract administered at a dose of 450 mg/kg significantly changed the ulcer index on WIR-induced in comparison to the control group. It was observed that the extract administered at doses of 150 and 300 mg/kg significantly reduced the mucosal lesion on the indomethacin-induced gastric ulcer (Saberi et al. 2016).

### 27.5.12 Anti-inflammatory Effect

#### In Vivo Experiments

The aqueous extract prepared from the aerial parts of *Melissa officinalis* was injected at four doses (50–100–200 and 400 mg/kg) to determine its anti-inflammatory effects on paw edema induced by histamine and carrageenan in Sprague-Dawley rats. In histamine-induced paw edema test, it was observed that the extract inhibits edema by 64.2%, −45.7%, −57.6%, −88.0%, respectively. At the same time, 76.85% inhibition was observed in the indomethacin group. In the carrageenan-induced paw edema test, it was observed that the extract inhibited the edema by 48.5%, −45.7%, −29.4%, −40.3%, respectively. At the same time, 59.3% inhibition was observed in the indomethacin group (Birdane et al. 2007).

The effect of essential oil obtained from the leaves of the plant was evaluated on carrageenan-induced and trauma-induced paw edema tests in rats. It was determined that essential oil given orally at doses of 200 mg/kg inhibits carrageenan-induced inflammation by 61.76% and inhibits trauma-induced inflammation by 91.66% (Bounihi et al. 2013).

### 27.5.13 Antinociceptive Effect

#### In Vivo Experiments

In various studies, the antinociceptive effect of the extract prepared with ethanol from the leaves of *Melissa officinalis* and the isolated active compound (rosmarinic acid) was evaluated in mice. It was determined that the extract inhibited acetic acid-induced visceral pain in the dose range of 3–1000 mg/kg in a dose-dependent manner ($ID_{50}$ = 241.9 mg/kg; 52 ± 5% inhibition at 1000 mg/kg dose). In the formalin-induced pain model, it was observed that the extract given at a dose range of 30–1000 mg/kg significantly inhibited both neurogenic pain and inflammatory pain (33 ± 7 and 48 ± 5% inhibition at 100 mg/kg dose). It was determined that the extract inhibited glutamate-induced pain in animals in the dose range of 10–1000 mg/kg in a dose-dependent manner ($ID_{50}$ = 198.5 mg/kg; 62 ± 5% inhibition at the 1000 mg/kg dose). Rosmarinic acid has been shown to have a stronger antinociceptive effect in experimental studies ($ID_{50}$ = 2.64 mg/kg). It was also found that ethanol extracts did not change the locomotor activity in mice (Guginski et al. 2009).

The antinociceptive effect of essential oil of plant on diabetic hyperalgesia was determined in streptozotocin-induced diabetic rats. The essential oil was given at doses of 0.01, 0.02, and 0.04 mg per day for 4 weeks, and pain thresholds were measured in the formalin test. Long-term use of the essential oil at a dose of 0.04 mg has been shown to have an antinociceptive effect in diabetic hyperalgesia (Hasanein and Riahi 2014).

### 27.5.14 Hypolipidemic Effect

#### In Vivo Experiments

In a study conducted to determine the effects of aqueous extract prepared from *Melissa officinalis* leaves on lipid metabolism, experimental animals (rats) were fed specifically for 42 days. Rats were showed symptoms of hyperlipidemia after 14 days. The aqueous extract was administered from the 14th day at a dose of 2 mg/kg/day for 28 days and the degenerative changes were examined morphologically and biochemically in the liver tissue. According to the results of the experiment, it was observed that the serum total lipid level decreased significantly in hyperlipidemic rats treated with the extract (14th day: 28.83 ± 10.16; 42nd day 36.70 ± 5.41 p = 0.017) (Bolkent et al. 2005).

The effects of *Melissa officinalis* essential oil were confirmed on serum lipid levels in cholesterol-fed rabbits. In this study, 20 rabbits were divided into four groups, and the control group was fed with the standard diet. The other three groups were fed a cholesterol-rich diet. Also, 1% and 3% essential oils were added to diets of the third and fourth groups, respectively. This treatment was continued for 4 weeks. As a result of the experiment, it was concluded that the essential oil has a hypolipidemic effect by significantly reducing the serum lipid level (Karimi et al. 2010).

In the study conducted to examine the hypolipidemic effects of the extract prepared with 96% alcohol from the aerial parts of *Melissa officinalis* on a cholesterol-rich diet in rats, decreased serum cholesterol, triglyceride, and LDL levels were observed (Changizi-Ashtiyani et al. 2013).

### 27.5.15 Antidiabetic Effect

#### In Vivo Experiments

In a study, *Melissa officinalis* essential oil was administered in type-2 diabetic mice for 6 weeks and serum insulin level tests, oral glucose tolerance tests, and various genetic tests were performed. In the group where essential oil was administered, the glucose level in the blood decreased to 64.6%, and glucose tolerance and serum insulin levels increased. With essential oil administration, hepatic GCK (glucokinase) activity increased; however, G6Pase (glucose-6-phosphatase) and PEPCK (phosphoenolpyruvate carboxykinase) decreased significantly. GLUT4, which is involved in glucose reabsorption in adipose and muscle tissues, and PPAR-gene expression, which has a role in hypoglycemic effect, increased due to insulin. Accordingly, *Melissa*

*officinalis* essential oil was evaluated to be antihyperglycemic (Chung et al. 2010).

In the study conducted to examine the antidiabetic effects of the extract prepared with 70% ethanol from *Melissa officinalis* leaves on alloxan-induced diabetic rats, the animals were divided into five groups. The first group consists of the healthy control group. The second group consists of alloxan-induced diabetic rats. Groups 3, 4, and 5 that consist of alloxan-induced diabetic rats were treated with 20, 100, and 500 mg/kg extract, respectively. At the end of the experiment, blood glucose levels were measured with a glucometer and it was determined that the hypoglycemic effect was at the maximum level at a dose of 100 mg/kg (Khodsooz et al. 2016).

In the study conducted to examine the antidiabetic effects of hydroalcoholic (70% ethanol) extract prepared from Melissa officinalis leaves, 150 and 300 mg/kg extract was given for 14 days on streptozotocin-induced diabetic rats. At the end of 14 days, the pancreases were removed for stereological examination, and animals were sacrificed. The total volume of islets, numerical density of beta cells, and the total number of islets increased in groups treated with the extract. A significant decrease in blood glucose levels has been detected and it has been determined that the extract has a hypoglycemic effect (Ashkani-Esfahani et al. 2021).

### 27.5.16 Effect of Cardiovascular System

Effects of aqueous extract prepared from *Melissa officinalis* leaves on cardiac rate were tested on heart tissue isolated from rats. For this, the heart tissue was isolated and the extract was administered at doses of 0.038 mg, 0.38 mg, 3.8 mg, and 38 mg after 5, 15, 60, and 300 seconds, respectively. It was observed that the *Melissa officinalis* extract reduced the cardiac rate at all doses and reached the control level in the 300th second (Gazola et al. 2004).

In the comparison of the aqueous extract prepared from the aerial parts of *Melissa officinalis* with amiodarone (antiarrhythmic drug), selected as positive control, QTc, PR, and QRS values were compared. The extract has been shown to have a mild protective activity against reperfusion-induced fatal ventricular arrhythmia in rats (Joukar et al. 2014).

### 27.5.17 Neuroprotective Effect

Both in vivo and in vitro experiments were conducted to determine the neuroprotective activity of *Melissa officinalis* essential oil on hypoxia-induced neuronal damage. Transient hippocampal ischemia was induced in rats and they were used in in vivo studies. The most effective dose of 100 mg/kg of plant material was administered to experimental animals. As a result of the experiment, it was concluded that the plant could be protective in various neurological diseases and ischemic brain injuries (Bayat et al. 2012).

## 27.6 Clinical Studies (Ongoing, Proposed, and Completed Studies)

### 27.6.1 Effect on Cognitive Performance and Attention Increase

In the study conducted to investigate the effectiveness of *Melissa officinalis* standardized leaf extract on cognitive performance and mood, the extract was applied to experimental groups at doses of 300, 600, and 900 mg for 4 days. Cognitive performance measurement on each treatment day, respectively, has been measured at the predose period 1 hour, 2.5, 4, and 6 hours using a Cognitive Drug Research computerized test battery. Calculations were made with the subjective mode Bon-Lader visual analog scale. A significant improvement in attention quality was noted 2.5 hours after 600 mg administration and 2.5 and 5 hours after 900 mg administration ($p = 0.029$; 0.0022 and 0.002) (Kennedy et al. 2002).

### 27.6.2 Effect on Alzheimer Disease

Standardized *Melissa officinalis* extract has been tested for its efficacy and safety for the therapy of mild to moderate Alzheimer's disease. In a double-blind, placebo-controlled, multicenter study, patients aged 65–80 with a history of mild and moderate Alzheimer's for 6 months were given 60 drops of extract daily for 4 months. At the end of this period, the cognitive activities of the patients who took the extract increased significantly compared to the placebo group. In comparison with the placebo group, less agitation was observed in the subjects in the groups that received the extract; in addition, no significant side effects were detected (Akhondzadeh et al. 2003).

Aromatherapy was performed with *Melissa officinalis* essential oil to alleviate the symptoms of agitation (behavioral and psychological) seen in Alzheimer's patients. Normally, antipsychotics are preferred in order to relieve such symptoms in Alzheimer's patients. However, these drugs have quite a lot of undesirable side effects. In this study, *Melissa officinalis* essential oil was compared with the anticholinesterase drug donepezil. It was concluded that essential oil does not have any superiority over donepez, but both drugs reduce agitation (Burns et al. 2011).

### 27.6.3 Sedative Effect

Double-blind, placebo-controlled, and randomized studies were conducted on 18 healthy volunteers to examine the effects of 300 and 600 mg doses of standardized plant extract prepared from *Melissa officinalis* on laboratory-induced psychological stress. The results showed that standardized extract (defined intensity stressor simulation) applied at a dose of 600 mg enhanced the negative mood effects of DISS, significantly elevated calmness parameters, and significantly decreased alertness (Kennedy et al. 2004).

### 27.6.4 Antispazmodic Effect

Capsules containing 600 mg of *Melissa officinalis* extract were administered to 100 female students (high school) twice a day. As a result of the study, it was found that it significantly reduced the symptoms of Premenstrual Syndrome (Akbarzadeh et al. 2015).

In order to determine the sedative and antispasmodic effect of *Melissa officinalis* on primary dysmenorrhea, 110 volunteers were randomly divided into 2 groups, 55 in each group. While capsules containing 330 mg of plant extract were given to the volunteers in the first group, similarly to the other group, capsules containing corn starch were given following the same procedure. In both groups, a decrease in pain intensity was observed after the application, and it was found that the intensity of pain decreased much more in the group where the plant extract was administered (Mirabi et al. 2017).

### 27.6.5 Antiviral Effect

In the study conducted with 60 healthy volunteers, *Melissa officinalis* gel and 5% acyclovir cream have been compared in terms of antiviral effect against Recurrent Herpes labialis (RHL) infection, which is common in humans. Among the participants randomly divided into two groups, Melissa gel was applied to the group A for therapeutic purposes, while 5% acyclovir cream was applied to the group B. Topically applied treatment was examined in terms of clinical parameters on days 1, 2, 4, and 7. Considering the changes in the redness around the lesion, size of the lesions, and the healing time (except day 4), there was no critical difference between group A and B. The changes in pain intensity between the two groups differed significantly on the second and fourth days. Melissa gel effectively decreased the severity of pain on the second and fourth days, but was not effective for treating RHL (Ahadian et al. 2015).

### 27.6.6 Analgesic Effect

Capsules prepared from *Melissa officinalis* were examined in terms of pain relief, since pharmaceutical analgesics have negative effects on maternal and infant health in reducing postpartum pain. For this, 110 women who just gave birth were divided into two groups. 250 mg of mefenamic acid to the first group and 395 mg of *Melissa officinalis* capsule to the second group were administered orally for 24 hours at 6-hour intervals. *Melissa officinalis* reduced postpartum pain by working much better than mefenamic acid (Dastjerdi et al. 2019).

### 27.6.7 Effect on Cardiovascular System and Diabetes

Sixty-two patients were randomly divided into two groups in a study conducted to determine the effects of the hydroalcoholic extract of *Melissa officinalis* on lipid profile, glycemic control, and inflammation on type-2 diabetic patients. While the first group received 700 mg of the extract twice a day for 12 weeks, the second group was registered as the placebo group. While significant differences were noted between the two groups in terms of serum FBS, HbA1c, $\beta$-cell activity, TG, HDL-c, hs-CRP, and systolic blood pressure levels, no significant difference was observed between the levels of total cholesterol, LDL-c, insulin, and HOMA-IR. *Melissa officinalis* was found to be effective in regulating blood lipid levels by showing the most significant change on HDL-c (Asadi et al. 2018).

In the study conducted to investigate the effects of 500 mg capsules prepared from *Melissa officinalis* on dyslipidemic diabetic patients, a decrease in serum triglyceride levels was observed in both the placebo and extract groups at the end of 2 months of administration. In patients treated with *Melissa officinalis* and with higher baseline levels, serum triglyceride levels decreased at the end of the third month (Nayebi et al. 2018).

### 27.6.8 Effect on Anxiety and Insomnia

In a study conducted on 20 people with moderate and severe anxiety and sleep disorders, standardized *Melissa officinalis* leaf extract was administered at a dose of 600 mg twice a day for 15 days. According to the results of the research, it was determined that the extract reduces insomnia by 42%, anxiety by 18%, and anxiety-related symptoms by 15% (Cases et al. 2011).

In a double-blind, placebo-controlled clinical study with 80 participants, the participants were divided into 2 groups and one of the groups was given 3 g of *Melissa officinalis* capsule daily for 8 weeks. According to the results of the DASS-21 (depression, anxiety, and stress scale) test, it has been determined that the plant significantly reduces the scores of depression, anxiety, stress, and sleep disorder (Haybar et al. 2018).

## 27.7 Toxicological Studies (Dose and Safety Profile, Acute, Chronic, and Mutagenicity Studies to Demonstrate Broad Spectrum Safety, GARS Status)

### 27.7.1 Dose and Safety Profile

#### Internal Usage

##### Adults

**Tea** As a tea infusion, it can be consumed as 1.5–4.5 g drug a few times a day.

**Liquid Extract** (1:5; 45% ethanol as chosen extraction solvent): 2–6 ml 3 times daily; liquid extract is used 60 drops once a day in Alzheimer's patients.

**Leaves** The leaves are used 8–10 g per day (Ulbricht et al. 2005).

### External Usage

#### Adults

**Cream** The extract standardized in the treatment of active viral herpes infection can be used up to 4 times a day.

**Tea** 2–3 g (2–3 teaspoons) leaves are infused in 150 ml of boiled water for 5–10 min and filtered. This tea is absorbed in cotton and used topically several times a day in herpes infections (Ulbricht et al. 2005).

### Method of Administration

Comminuted plant, plant powder, fluid, or dry extracts for teas and other galenical preparations for external and internal administration (The German Commission E Monographs 1999).

### Contraindications

Allergy, contact dermatitis, and hypersensitivity in people with sensitivity to *Melissa officinalis* (Ulbricht et al. 2005).

### Interactions with Other Medications

It is thought that taking *Melissa officinalis* together with alcohol could theoretically increases the sedative effect (Kennedy et al. 2002; Wong et al. 1998). It has also been shown in animal studies to increase the hypnotic effects of barbiturates (Hajhashemi and Safaei 2015). It can increase intraocular pressure by interacting with glaucoma drugs (Ulbricht et al. 2005). It has been determined that its extract can interact with thyroid drugs and lower serum TSH levels (Zarei et al. 2015).

### Pregnancy and Lactation

Since sufficient data are not available, it should not be used during pregnancy without consulting a doctor (WHO Monographs, 1999). Sedation may occur in the baby as a result of the active substances carried by the plant passing into the milk (Baykan and Demiröz 2017).

### Works Required Attention

None reported.

### Overdose

None reported.

### Duration of Use

Not enough records were found.

## 27.7.2 Acute, Chronic, and Mutagenicity Studies to Demonstrate Broad Spectrum Safety

### Acute Toxicity

In a study investigating the acute toxicity of essential oil prepared from aerial parts of *Melissa officinalis* on BALB/c mice, changes were detected in both behavior and biochemical parameters expressing kidney and liver functions of experimental animals. Pathological findings were found in the duodenum, kidneys, liver, and stomach of experimental animals that were administered doses higher than 1 g/kg. All these data show that the essential oil produces moderate toxicity in oral use (Stojanović et al. 2019).

Intravenous injection of 25 mg/kg dose of extract prepared with aqueous ethanol from *Melissa officinalis* leaves to healthy rats caused a decrease in TSH concentration in serum and pituitary glands (Baykan and Demiröz 2017).

### Chronic Toxicity

Thirty Sprague-Dawley rats were used to establish the toxicity of hydroalcoholic extract prepared from *Melissa officinalis* in chronic use.

The experimental animals were divided into 3 groups; group A was given 600 mg/kg, group B 1200 mg/kg, and group C saline for 30 days. At the end of the study, tissue and blood samples were taken from the experimental animals. In the blood samples of the groups treated with *Melissa officinalis*, a significant increase was observed in the levels of alanine amino transferase, creatine phosphokinase, and lactate dehydrogenase, while a decrease in total albumin and protein concentrations was observed. The highest creatine concentration was detected in group B. Histopathological studies revealed hepatocyte degeneration in the liver, tubular degeneration,

and necrosis in the kidneys (Hashemnia et al. 2017).

### Mutagenicity and Teratogenicity

In the AMES test using *Salmonella typimurium* strains (TA48, TA100) with and without metabolic activation, it was determined that 70% ethanolic extract prepared from *Melissa officinalis* leaves gave negative results and did not show mutagenic effects (Baykan and Demiröz 2017).

No record of abortifacient or teratogenicity has been found in the literature.

### 27.7.3 GRAS Status

*Melissa officinalis* has been accepted the Generally Regarded As Safe (GRAS) status by the FDA in the USA for a maximum of 0.5% use in baked goods (Ulbricht et al. 2005).

## 27.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies (with Special Focus on Bioavailability and Metabolism of Active Constituents)

### 27.8.1 Available Commercial Formulations/Products, Uses, Administration Method

Available commercial products are given in Table 27.1.

**Table 27.1** Commercial products of *M. officinalis*

| Name of the product | Content | Purpose of usage |
|---|---|---|
| | **Europe** | |
| Gastrovegetalin solution | *Melissa officinalis* L. leaf extract | Gastrointestinal disorders |
| Lomaherpan cream | *Melissa officinalis* L. leaf extract | *Herpes simplex* virus treatment |
| SED infant gastro Lösung | *Melissa officinalis* L. leaf extract | Gastrointestinal disorders |
| ME-Sabona Hartkapseln | *Melissa officinalis* L. leaf extract | Sedative, sleep disturbances, gastrointestinal disorders |
| Schoenenberger naturreiner Heilpflanzensaft Melisse | *Melissa* herb press juice | Dyspepsy and mild gastrointestinal disorders |
| Melissengeist | *Melissa officinalis* L. Extract | Sedative, sleep disturbances, gastrointestinal disorders, also externally for the treatment of mild muscle and headache |
| Cyracos | *Melissa officinalis* L. leaf extract | Stress-related symptoms, sleep disturbances |
| | **Turkey** | |
| BayBay drop | *Melissa officinalis* L. extract | Relaxing and sleeping aid for babies |

### 27.8.2 Pharmacokinetic Studies

In a single dose administration of *Melissa officinalis* extract containing rosmarinic acid, in the study designed to evaluate its pharmacokinetics, tolerability, and safety, 11 healthy individuals were randomly divided into two groups. The level of rosmarinic acid in the serum was measured colorimetrically using a HPLC electrochemical detector. The plant extract containing 500 mg rosmarinic acid was applied on an empty stomach and 1 hour after the administration, the serum concentration reached the highest value with 162.20 nmol/L. It has been found that food intake prolongs the time to reach maximum serum concentration. It has been concluded that a single dose of plant extract may be safely tolerated in healthy humans (Noguchi-Shinohara et al. 2015).

## 27.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

*Melissa officinalis* L. is used internally and externally in folk medicine in the treatment of many disorders, particularly microbial diseases, digestive system, central nervous system, and cardiovascular system disorders. Scientific and clinical studies recorded in the literature support all these beneficial effects.

## 27.10 Challenges and Future Recommendations as Potential Drug Candidate

The use of plants for therapeutic purposes is as old as human history. We can understand from the remaining inscriptions and archeological materials that ancient civilizations used plants in the treatment of diseases and distinguished between drugs and poisons. Today, these plants constitute an important source of drug active ingredients. Active compounds contained in *M. officinalis* L. are promising in the treatment and prevention of many diseases. Medicinal products prepared using this herb can help patients improve their quality of life.

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# *Momordica charantia* L.

28

Marjan Talebi

**Abstract**

*Momordica charantia* L. (MC, bitter melon) is a cultivated plant from the family Cucurbitaceae. Regarding metabolomics and phytochemical studies, it has phenolic compounds, terpenoids, saponins, peptides and proteins, and polysaccharides as main constituents with pharmacological effects. Preclinical and clinical studies exhibited numerous biological activities attributed to MC or its constituents. Antidiabetic, cardioprotective, antidyslipidemia, antiobesity hypotensive, antioxidant, anti-inflammatory, hepatoprotective, renoprotective, neuroprotective, anticancer antiviral, antibacterial, antifungal, anthelmintic, antimalarial, and wound healing are significant beneficial properties of MC and its ingredients. Although its safety and toxicity are not vastly studied in clinical trials, some adverse clinical manifestations have been reported afterward its consumption. Modification of its bioavailability by fabrication of nanotechnology-based formulations and conducting more clinical trials for investigation of its efficacy and toxicity are the future prospects.

**Keywords**

Cucurbitaceae · Phytochemicals · *Momordica charantia* · Bitter melon · Bitter gourd · Pharmacological applications · Chemical components

## Abbreviation

| | |
|---|---|
| ALT | Alanine aminotransferase |
| AMPK | Adenosine 5′-monophosphate (AMP)-activated protein kinase |
| AR | Androgen receptor |
| BM | Bitter melon |
| CAT | Catalase |
| ERK | Extracellular signal-regulated kinases |
| ER-α | Estradiol receptor-alpha |
| GST | Glutathione S-transferase |
| HDL | High-density lipoprotein cholesterol |
| HIV | Human immunodeficiency virus |
| IFN-γ | interferon-gamma |
| IL | Interleukin |
| iNOS | Inducible nitric oxide synthase |
| IR | Insulin receptor |
| JNK | c-Jun N-terminal protein kinase |
| LDL | Low-density lipoprotein cholesterol |
| LPS | Lipopolysaccharide |
| MAP30 | Momordica anti-HIV protein of 30 kDa |
| MAPK | Mitogen-activated protein kinase |

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| | |
|---|---|
| MC | M. charantia |
| MMP | Matrix metalloproteinase |
| MW | Molecular weight fraction |
| NF-κB | Nuclear factor-kappa B |
| NO | Nitric oxide |
| PARP | Poly(ADP-ribose) polymerase |
| PPAR | Peroxisome proliferator activated receptor |
| PSA | Prostate-specific antigen |
| RIPs | Ribosome-inactivating proteins |
| ROS | Reactive oxygen species |
| SAM | S-adenosine methionine |
| SOD | Superoxide dismutase |
| STZ | Streptozotocin |
| TNF | Tumor necrosis factor |
| VLDL | Very low-density lipoprotein cholesterol |

## 28.1 Introduction

World Health Organization (WHO) recommends medicinal plants as alternative medications (Robinson and Zhang 2011). Medicinal plants are an exact rich source of novel phytoconstituents with various therapeutic potentials which are related to different mechanistic pathways (Talebi et al. 2021a). According to shreds of evidence, these medicinal plants have low cost, great therapeutic index, fewer adverse effects, and possible accessibility (Roshanravan et al. 2020; Talebi et al. 2021b). To date, these edible natural products are used in the form of raw material, standardized preparations, phytopharmaceuticals, nutraceuticals, and phytochemicals with the capability to be used as drug leads (Pourbagher-Shahri et al. 2021; Yazdani et al. 2019; Talebi et al. 2020a, 2021c; Atanasov et al. 2021).

Bitter melon (BM) also recognized as balsam pear, bitter gourd, Karella, Carla, Assorossie, Ampalaya, Nigauri or Goya, Kho qua, Ko guai, Ku gua, pare, and kudret narı in Turkey, scientifically named as *Momordica charantia* L. is an herbaceous plant with bitter-tasting from the family Cucurbitaceae. *Momordica charantia* (MC) is a slender and hairy/hairless herb classified as an annual or perennial plant with 3–4 m height (Brower 2008; Villarreal-La Torre et al. 2020; Wang et al. 2017; Jandari et al. 2020; Sharifi-Rad et al. 2020).

It is well-known for its vast traditional and nutritional indications throughout the universe. *Momordica charantia* is cultivated in regions with possession of tropical and subtropical status such as Asia, Africa, the Caribbean, South America, and some regions of Amazon (Uysal et al. 2019; Grover and Yadav 2004).

Various pharmacological properties are reported by attribution to bitter melon and its active constituents. Several biological effects are observed in preclinical and clinical studies, including antidiabetic (Basch et al. 2003; Efird et al. 2014), hypotriglyceridemic, hypocholesterolemic, cardioprotective (Krawinkel et al. 2018), antiobesity (Zeng et al. 2018), hypotensive, antioxidant, anti-inflammatory (Alam et al. 2015), analgesic, hepatoprotective, nephropreotective (Bortolotti et al. 2019), neuroprotective (Saeed et al. 2018), adaptogenic (Valarmathi et al. 2020), antiulcerogenic (Sharifi-Rad et al. 2020), anticancer (Yook et al. 2020), antitumor (Nerurkar and Ray 2010), antileukemia (Fang and Ng 2011), immune-modulator (Farooqi et al. 2018), antiallergic (Scherer et al. 2011), antiviral (Bawara et al. 2010), antibacterial, antifungal, antiprotozoal (Brower 2008), anthelmintic (Puri et al. 2009), insecticidal (Poolperm and Jiraungkoorskul 2017), antimalarial (Bhalerao 2020), antipyretic (Bortolotti et al. 2019), antimutagenic (Villarreal-La Torre et al. 2020), antifertility (Abdillah et al. 2019), wound healing (Gupta et al. 2011), osteoprotective (Devaki et al. 2015), antipsoriasis (Rahman et al. 2020), and hindering of multidrug resistance properties (Dasgupta et al. 2011). Moreover, *M. charantia* extract could be used as food preservative according to its influence to inhibit the formation of amines with biogenic activity by the way of nutrition-borne pathogens and fish deterioration bacteria (Raina et al. 2016).

In this chapter, first I discussed the chemical composition of MC and afterward the biological effects of MC and its bioactive components came into focus.

## 28.2 Bioactive and Nutritional Composition of *Momordica charantia*, Existing Extraction Techniques, and Biological Applications of These Components

Active phytochemicals, for example, polysaccharides, steroids, fatty acids, proteins, amino acids, phenolic compounds, flavonoids, triterpenoids, alkaloids, glycosides, quinine essential oils, saponins, and in somehow trace components, are responsible for their medicinal uses (Kuley et al. 2019; BaldemİR et al. 2018). Moreover, *M. charantia* possesses the maximum nourishing values among cucurbits and comprises more than 30 medicinal produces, containing fibers, carbohydrates, proteins, vitamins (A, B1, B2, B3, B9, C, and E), and mineral compounds (calcium, magnesium, zinc, iron, potassium, and phosphorous) (Zhang et al. 2018; Sur and Ray 2020; Joseph and Jini 2013).

### 28.2.1 Phenolic Compounds and Flavonoids

Flavonoids and phenolic compounds are significant constituents which are existing in *M. charantia*. Various compounds are categorized in this class including (+)-catechin, (−)-epicatechin, ferulic, benzoic, gallic, caffeic, sinapinic, protocatechuic, o-coumaric, p-coumaric, vanillic chlorogenic, gentistic, syringic, t-ferulic, and t-cinnamic -acids. The most plentiful available flavonoids isolated from MC were quinic acid and catechin which have been determined by UPLC-MS (Mahwish et al. 2018). Total phenolic BM leaf extract (TPE) successfully inhibited *Propionibacterium acnes*-stimulated inflammatory reactions in mice skin through attenuation of ear swelling along with microabscess. TPE treatment reduced neutrophils' migration and populations of IL-1β+ in vivo. It was perceived that in *P. acnes*-motivated THP-1 cells of monocytes, TPE repressed IL-8, IL-1β, and TNF-α at mRNA levels. Moreover, TPE inhibited *P. acnes*-persuaded MMP-9. Furthermore, by considering recent literature, it was found that TPE obstructed the activation of NF-κB and MAPK (Jia et al. 2017). Total anthocyanins of MC might interestingly be used for incorporation in pharmaceutical formulations, and likewise, it could be utilized as food additives owing to its radical scavenging features (Huang et al. 2015).

### 28.2.2 Saponins and Terpenoids

Saponins are present in the stems, roots, fruits, and leaves of MC. Recent published studies have revealed that tetracyclic triterpenoids and their glycosides are the main phytochemical constituents of MC. A large proportions of these compounds are mentioned as cucurbitanes and are celebrated for their toxicity and bitter-tasting. MC cucurbitane glycosides, comprising momordicine I, momordicine II, momordicoside K, and momordicoside L, are responsible for their bitterness and are nontoxic (Guder 2016; Zhou et al. 2019).

Numerous pharmacological researches specified that cucurbitanes isolated from BM are accountable for their antidiabetic potential and cytotoxic accomplishments (Jiang et al. 2016). Some cucurbitane-type triterpenoids are involved in mechanisms representing partial agonist/antagonist activity intended for estrogen receptors (Hsu et al. 2011). Kuguacin J is a triterpenoid which is available in MC leaf from exerted anticancer effects against LNCaP human prostate cancer cells. It was found that kuguacin J inhibited growth of cancer cell through G1 arrest and apoptotic cell death initiation. Attenuation of Cdk2, Cdk4, cyclin-D1, and cyclin-E and augmentation of p21 and p27 were attributed to the activities of kuguacin J. Its ability for induction of programmed fate of cells was in consort with a rise in cleavage of caspase-3 and PARP, responsible for decrease of survivin levels and expansion of Bax/Bcl-2 and Bad/Bcl-xL. Kuguacin J also alleviated the PSA expression and AR through induction of P53 protein (Pitchakarn et al. 2011).

Weng et al. found that 5β,19-epoxy-19-methoxycucurbita-6,23-dien-3β,25-diol induced

G1 arrest which might have responsibility for the management of p53, CDK6, and cyclin D1 phosphorylation and expression and downregulation of histone deacetylase-1 expression which led to increase in acetylation of histone H3. Altogether, these outcomes advised that the aforesaid terpenoid compound of MC might have therapeutic uses in MCF-7 cells treatment through activation of PPARγ (Weng et al. 2017).

Lee and colleagues isolated eight novel cucurbitane-type triterpenoidal saponins, yeojoosides A−H, two of which showed selective suppressive effects against PTPN2 as a protein tyrosine phosphatase associated with insulin resistance (Lee et al. 2021). Wang et al. reported that the hypoglycemic action of BM saponins might be imputed to the modulation of the AMPK/NF-κB signaling conduit and bodily energy metabolism (Wang et al. 2019a). Cucurbitane-type triterpenoids might have the main function for emerging anti-inflammatory potential of BM in rat primary hepatocytes (Dwijayanti et al. 2019). Antihepatic fibrosis and antihepatoma potential of a cucurbitane triterpenoid known as karaviloside III were detected in vitro (Yue et al. 2019).

### 28.2.3 Proteins and Peptides

Proteins and peptides are likewise the crucial purposeful constituents in the seeds and fruits of MC. A number of categories of peptides and proteins have been isolated from diverse parts of MC, for instance RIPs, MCL, MAP30, α-momorcharin (α-MMC), β-MMC, γ-MMC, δ-MMC, and ε-MMC, which own antioxidant, immunosuppressive, antimicrobial, antitumor, anticancer, antilipidemic, antidiabetes, RNA N-glycosidase, DNase-like, PAG, SOD, and phospholipase -activities (Poovitha and Parani 2020).

Short half-life and compelling immunogenicity are limiting factors to use α-MMC for clinical application (Sun et al. 2018). Sun and coworkers found that chemosynthesis of site-specific N-terminally PEGylated α-MMC could help in overcoming trypsin resistance and immunogenicity of α-MMC, as well as moderate antitumor efficacy in vitro *(*Sun et al. 2018*)*.

MCL and α-MMC could considerably impede nasopharyngeal cancer in vitro (Fang et al. 2012). Fan and coworkers elucidated seven crystal complex configurations of α-MMC with diverse substrate analogs including adenine, ADP, AMP, cAMP, dAMP, GMP, and xanthosine which can help in developing new inhibitors to combat α-MMC poisoning (Fan et al. 2020).

MAP30 is a single chain RIP, entitled for its MW of 30 kD. MAP30 demonstrated robust antitumor potential the same as MCL. MAP30 inhibited cellular multiplying and induced apoptosis in a section of malignant cells including hepatocellular, lung, breast, bladder, prostate, and brain glioblastoma (Jia et al. 2017; Tan et al. 2017; Wong et al. 2020; Yang et al. 2016).

Regarding the bioinformatics analysis, MAP30 and its derivative peptides could be utilized as food preservatives, and consequently, these analyses might offer worthwhile perceptions into designing clinically appropriate antibiotic agents (Moghadam et al. 2016). MAP30 exerted antiviral activities mostly about its potential to inhibit HIV viral integrase and to irreversibly lead to the relaxation of supercoiled viral nucleic acids. These aforementioned alterations rendered viruses incapable to integrate themselves into host cell genomes. Moreover, MAP30 attenuated degrees of T-lymphocyte infection with HIV type 1 and abridged rates of viral replication in infected cells in vitro (Basch et al. 2003). One of the proteins isolated from MC showed antiviral effects against a number of new emerging subtypes of influenza A in vitro (Pongthanapisith et al. 2013).

Zhang and Shi showed that encountering human bladder cancer cells with MAP30 repressed the progression of cancerous cells, particularly cell migration and invasion by means of Akt cascade suppression, downregulation of NF-kB, JNK, and MMP2, upregulation of caspase-3, and augmentation of ROS (Zhang et al. 2020a; Shi et al. 2020). Chan and coworkers found that MAP30 led to activation of AMPK signaling via CaMKKβ and prompted S-phase arrest. MAP30 suppressed GLUT-1/-3-mediated

adipogenesis, glucose uptake, and formation of lipid droplets in gates connected to progression and growth of tumor. MAP30 induced augmentation in intracellular concentration of $Ca^{2+}$ ion, which is associated with ROS-facilitated cancer cell death through ferroptosis and apoptosis (Chan et al. 2020). Jiang and coworkers concluded that MAP30 showed apoptotic effects on U87 and U251 glioma cell lines through repression of Wnt/β-catenin and LGR5 the signaling pathway, and augmenting Smac expression (Jiang et al. 2018). MAP30 induced apoptosis in PCa and PIN prostatic cancer cell lines and blocked PC-3 growth in vivo. Mechanistically, MAP30 inhibited HDAC-1 activity and promoted histone-3 and -4 protein acetylation. Moreover, induction of PTEN expression in PCa and PIN cell lines caused hindering of Akt phosphorylation. Additionally, MAP30 impeded Wnt signaling cascade via the mitigation of β-catenin nuclear accumulation and deterioration in c-Myc and Cyclin-D1 levels (Xiong et al. 2009).

Coadministration of MAP30 with chloramphenicol or erythromycin might reduce the adverse effects of these antibiotics and lowered the required concentrations of antibiotics (Chang et al. 2017).

Yuan-Biao et al. indicated that MAP30 phosphorylated derivatives had antifungal effects against *Candida albicans* resistant to ketoconazole (Yuan-Biao et al. 2020). Deng et al. found that α-MMC exhibited its immunosuppressive effects via attenuation of monocytes and intensification of eosinophils and basophils percentages. Hampering of cytokine expression in peripheral blood mononuclear cells and elevation of cytokine expression in spleen T cells were gained following α-MMC treatment in rats. Besides, pretreatment of mononuclear cell line THP-1 cells with α-MMC caused apoptosis in high doses and regulation of cytokine expression for fending in low doses which could all in all be helpful for tumor suppression (Deng et al. 2019a). Regulation of inhibitory cytokine expression by α-MMC was attributed to deterring the expression of IL-2, IL-9, IL-1β, IL-8, IL-12, MCP-1, TNF-α, and MIP-1α/β and expression and augmenting expression of IL-1ra and RANTES. On the whole, immunosuppression by α-MMC in monocyte THP-1 cells was interceded by silencing the LRP1 receptor, probable via the MAPK signaling pathway (Deng et al. 2019b). PEGylation of α-MMC prolonged its half-life, lessened its nonspecific toxicity, and improved its antitumor efficacy (Deng et al. 2016).

BM peptide insulin receptor (IR)-binding protein (mcIRBP)-19 demonstrated antidiabetic effects by regulation of blood sugar levels in diabetic patients (Hsu et al. 2020). Lo et al. discovered that administration of mcIRBP-9 orally could ameliorate the HbA1c levels and glucose tolerance in diabetic mice via directing the transduction IR signaling pathway (Lo et al. 2017).

MCLO-12, an oligopeptide of MC, induced apoptosis in NSCLC A549 cells, upregulated ROS and caspase-3, -9, and PARP activities, intimidated the Trx system, and consequently led to activation of Trx-dependent pathways responsible for apoptosis, comprising the ASK1, MAPK-p38, and JNK pathways (Dong et al. 2019).

BG-4 as a novel peptide extracted from BM showed anticancer effects in HT-29 and HCT-116 human colon cancer cells. BG-4 attenuated Bcl-2 expression and elevated Bax expression which resulted in overexpression of caspase-3 and modulation of p21 and CDK2 expression which were attributable to apoptosis (Dia and Krishnan 2016).

### 28.2.4 Polysaccharides

Polysaccharides are one of the imperative classes of active constituents of MC. It was revealed that polysaccharides isolated from fruits of BM have numerous biological activities, such as antidiabetic, antioxidant, neuroprotective, antitumor, improving immunity, clearing away heat, detoxification, and antimicrobial effects (Yan et al. 2021; Chen et al. 2021; Huang et al. 2020).

Extraction methods such as traditional techniques based on hot-water, alkali, and acid extractions, three-phase partitioning at room temperature, ultrasonic-, microwave-, and enzyme-assisted extractions, and next solvent

precipitation were used for separating BM crude polysaccharides (Yan et al. 2021; Yang et al. 2020).

Specifically, MC polysaccharides improved oxidative damage, dyslipidemia, inflammatory responses, and apoptosis in the course of myocardial infarction by impeding the NF-κB and regulating Bax, caspase-3, and Bcl-2 (Raish 2017).

MC polysaccharides also could develop production of total volatile FAs, modify the rumen fermentation gate, and affect the cellulolytic bacteria proportion count (Jia et al. 2017; Zhang et al. 2016).

Zhu et al. found that water- and alkali-soluble polysaccharides from *M. charantia* exerted great feature according to reduction of fat in HepG2 cells and *Caenorhabditis elegans* through stimulation of GLUT4 and PEPCK (Zhu et al. 2021). Synthesized selenylated polysaccharides from bitter melon exhibited hypoglycemic properties in vivo (Ru et al. 2020). Transcriptional factors hsd11β1, fads2, msmo1, pdk4, pkl, and rbp4 showed a great role in the modulation of T2D by MC polysaccharides (Bai et al. 2018a). Raish et al. found that MC polysaccharides could alleviate the advancement of STZ-induced diabetic nephropathy in rats by overpowering oxidative damage and improvement of the HO-1/Nrf2 pathway (Raish et al. 2016).

Wang et al. mentioned that polysaccharides of bitter melon suggestively had the ability to promote the antioxidant capability by elevation of SOD and alleviation of MDA and mitigated the mice pancreatic β cells impaired by STZ (Wang et al. 2019a). Perveen and coworkers indicated that CCPS treatment lessened the toxicity of NaAsO2-induced womanly reproductive disorders cum infertility in rats by controlling the SAM pool components, B12, folate, and homocysteine. It also regulated the ER-α and downregulated NF-κB, TNF-α, and IL-6. Additionally, this pectic polysaccharide of bitter melon led to upregulation of caspase-3, PARP, PCNA, Bax, and p-p53, and subsequently downregulated Bcl-2 and Akt cascade in the company of regeneration of uterine tissue in As3+ encountered rats (Perveen et al. 2019). Chemically, modifications of MC polysaccharides through phosphorylation, sulfating, and carboxymethylat made various compounds with a diverse spectrum of antioxidant, antilipid peroxidation, and radical scavenging activities (Chen et al. 2019; Chen and Huang 2019). MC polysaccharides showed administered prophylactically to reduce EtOH-induced gastric damage in rats via inhibition of IL-6, MPO, TNF-α, and prohibited gastric lipid peroxides (e.g., GSH and CAT) activity, downregulated NF-κB and upregulated IκBα, suppressed Bax and caspase-3 activity, and improved Bcl-2 (Raish et al. 2018). Qin et al. observed that the fabrication of MC polysaccharides nanoparticles improved their antimicrobial efficacy and unveiled long-acting antibacterial action (Qin et al. 2018). Tan and coworkers elucidated that a MC bioactive polysaccharide with a pectin-like structure showed free radical scavenging activity, angiotensin-converting, and enzyme inhibition α-amylase inhibition which might have antioxidant, hypotensive, and antidiabetic effects, respectively (Tan and Gan 2016).

### 28.2.5 Other Components

In addition to the aforesaid bioactive ingredients above, alkaloids, unsaturated FAs, amino acids, vitamins, and minerals are likewise existent in MC (Jia et al. 2017; Kwatra et al. 2016; Li et al. 2020). The alkaloid momordicine, steroidal glycosides, and alkaloid are furthermore imperative active substances in ripe fruit of *M. charantia* (Desai et al. 2020). According to biochemical analyses of some genotypes of Turkish BM seeds, they possessed palmitic, eleostearic, oleic, linoleic, and stearic -acids as main FAs. α-Eleostearic acid positively affected lipid metabolism in liver by elevation of cellular NAD+/NADH ratio and activation of AMPK, PPARα, and SIRT1 pathway (Chen et al. 2016; Chang et al. 2016). Supercritical fluid extraction was utilized for the isolation of β-carotene from ripe *M. charantia* pericarp (Patel et al. 2019). Phytosterols isolated from *M. charantia* skin, for instance, charantin and momordicine, are well-known for their antidiabetic properties (Mishra et al. 2022).

## 28.3 Preclinical Pharmacological Activities of *Momordica charantia*

### 28.3.1 Antidiabetes Effects of Bitter Melon

White and coworkers discovered that administration of *M. charantia* in the combination of a chromium propionate complex led to alleviation of insulin resistance in diabetic rats which were fed with high-fat diet and STZ. This nutritional values were attributed to the connecting of Cr by the polyphenol substances existent BM (White et al. 2021). Jiang et al. represented that BM extract had antidiabetes effects in the STZ animal model through modulating oxidative stress, decreasing p-IRS-1 (S307) expression, and increasing p-Akt (S473) and p-IRS-1 (Y612) expressions in the hepatic and pancreatic tissues of rats (Jiang et al. 2020).

Soliman and colleagues found that *M. charantia* extracts protected diabetes-linked spermatogenic dysfunction in male rats. The involved mechanisms were elevation of levels of serum insulin, reduction in FBS, and HbA1c, TST, FSH, and LH. It increased SOD, CAT, GPx, GSH, and attenuated MDA levels in the testicular homogenate of the studied population. Administration of BM reversed histopathological alterations of the testes and reduced Sertoli cell and spermatogenic apoptotic death. Besides, it excellently repressed testicular apoptosis, via downregulation of Bax and caspase-3, upregulation of Bcl-2, and mitigation of the mRNA expression of Bax/Bcl-2 (Soliman et al. 2020). Rajesh et al. indicated that bitter melon seed extract possessed comparable effectiveness to pioglitazone in the anticipation of dexamethasone-brought hyperglycemia, dyslipidemia, and hepatomegaly (Rajesh et al. 2020). According to the research conducted by Malekshahi et al., *M. charantia* increased size and number of pancreatic islets and elevated insulin and Pdx1 genes expression; however, it deprecated GLUT-2 expression in STZ-diabetic rats (Malekshahi et al. 2019). *Lactobacillus plantarum*-fermentation boosted the antidiabetic possessions of BM juice through regulation of gut microbiota and mitigation of the formation of acetic, butyric, propionic -acids, and total SCFAs in the colon of STZ-diabetic rats (Gao et al. 2019). BM lyophilized superfine grinding powder (BLSP) meaningfully mitigated the ratio of *Firmicutes* to *Bacteroidetes* in rats which had diabetes, whereas the relative ampleness of *Bacteroides, Ruminococcus*, and *Ruminococcaceae* were pointedly reduced. As well, BLSP meaningfully repressed the activation of MAPK (JNK and p38). The outcomes indicated that BLSP could considerably amend the populations of specific gut microbiota in rats that suffered from diabetes deprived of troubling the normal proportion miscellany (Zhu et al. 2016). MC extracts exerted unswerving pro-angiogenic signaling intervened via RAGE to overwhelm the antiangiogenic properties of high bovine serum albumin-derived AGEs, emphasizing the biphasic RAGE-dependent working convoluted in animals suffering from diabetes-impaired wound-healing (Aljohi et al. 2018).

### 28.3.2 Antiobesity Effects of Bitter Melon

Obesity is a universal pandemic disorder that is closely associated with cardiovascular diseases, diabetes mellitus, abnormality of lipids profile, and hypertension (Farkhondeh et al. 2020). Regarding preclinical studies, supplementation with *M. charantia* led to the anticipation of the body weight expansion, visceral fat mass, peritoneal fat deposition, attenuation of white adipose tissue, adipose leptin, mRNA content of resistin, augmentation of acyl-CoA dehydrogenase and mitochondrial CPT-1 in liver and muscles, the elevation of UCP1 in brown adipose tissue and UCP3 in red gastrocnemius muscle, increase in transcription of coactivator PGC-1α expression, rise in lipolysis, upregulation of pAMPK and tAMPK, and reduction in mRNA expression of PPARγ, SREBP, and perilipin, normalization of fasting plasma glucose, insulin resistance, and lipids profile in animal models fed with high-fat diet (Alam et al. 2015; Fan et al. 2019). Wen and

coworkers discovered that fermentation of *M. charantia* enhanced its antiobesity effects (Wen et al. 2019). Metabolomics data elucidated that excess generation of energy and metabolism of nutrient in obese animals were reinstated by MC usage. The anti-inflammatory and inhibitory properties of MC against insulin resistance in obesity were demonstrated with the reinstatement of FFAs and eicosanoids (Gong et al. 2017). BM improved insulin sensitivity and inflammation in obese rats through a relative regulation of specific gut microbiota. Cell extents of adipose tissues in epididymis, IL-6, TNF-α, IL-10, JNK/p38 MAPKs, and NF-κB were ameliorated following BM administration. The number of the endotoxin-generating opportunistic pathogens decreased and butyrate makers increased (Bai et al. 2016). BM supplementation could modify important colon roles by changing transcriptomic profile including *PRKCβ* and *Pla2g2a* in obese rats (Bai et al. 2018b).

### 28.3.3 Antidyslipidemia Effects of Bitter Melon

Zhang and coworkers realized that the fruit of *M. charantia* might display hypolipidemic effect in mice fed with high-fat diet by modulating the gut microbiota and augmentation of SFCAs creation. In accumulation, bitter melon improved the richness of SCFAs-producing *genera Faecalibacterium*, *Lachnospiraceae* UCG-006, *Lachnoclostridium*, and *Roseburia,* and reduced *Ruminococcaceae* UCG-014 and opportunistic pathogens-comprising *genera Escherichia-Shigella* and *Defluviitaleaceae* UCG-011 (Zhang et al. 2020b). Zeng et al. observed that BM abridged the serum triglycerides, weight gain, atherosclerotic plaque zone, collagen fibers levels in atherosclerotic plaques, P-selectin levels, and the serum-soluble VCAM-1 along with the expressions of IL-6 and MCP-1 in aortas of HFD-fed ApoE−/− knocked-out mice (Zeng et al. 2018). Inhibition of apoB secretion and TG synthesis which might be entailed in lowering plasma lipid and VLDL were feasible mechanisms for the treatment of dyslipidemia in animal studies (Nerurkar et al. 2005).

### 28.3.4 Anticancer Effects of Bitter Melon

Cancer is the second reason for mortality occurred throughout the world (Talebi et al. 2021d). It is appraised that by 2020, in each year around 16 million new cases of patients with cancer will be detected (Farkhondeh et al. 2021).

#### Breast Cancer

Treatment of MCF-7 cells with bitter melon extract showed great uptake of Technetium-99m radiolabeled paclitaxel which is supposed to come about owing to ER-dependent dealings of *M. charantia* extract (Kilcar et al. 2020). Basaran and coworkers comprehended that seed and aryl extracts of bitter melon repressed MCF-7 and MDA MB-231 cells growth and induced apoptotic death via upregulation of mRNA levels of caspases-3 and -9. Moreover, the extracts repressed EGF, phosphorylation/activation of PI3K/Akt, and MAPK pathways, and induced EGFR phosphorylation/activation (Basaran et al. 2020). BM extract inhibited the growth of TNBC cells via hampering of ACAT-1 expression (Shim et al. 2018). Muhammad et al. found that BM extract repressed breast cancer growth in cells and xenograft mouse models. Treatment with BM induced autophagosome-LC3-B and accumulated p62 in breast cancer cells. Furthermore, BM treatment increased p-AMPK expression and inhibited the mTOR/Akt cascade in breast cancer cells (Muhammad et al. 2017).

#### Ovarian Cancer

Cotreatment with BM extract and cisplatin significantly diminished tumor growth in human HOSEs cells and nude mice. BM extract motivated AMPK and suppressed the AKT/ERK/FOXM1 (Forkhead Box M1) and/or the mTOR/p70S6K cascade (Yung et al. 2016).

#### Prostate Cancer

MC leaf extract suppressed the progression of rat prostate cancer through antimetastatic mechanisms in vitro and in vivo. These belongings were observed by inhibiting the excretion of MMP-9, MMP-2, and uPA from PLS10 cell and significantly augmented the TIMP-2 mRNA level,

recognized for inhibitory properties on MMP-2 activity (Pitchakarn et al. 2010).

### Liver Cancer

Methanolic extract of MC might show a prophylactic potential through alleviation of COX-2, HDAC, MMP-2, MMP-9, and VEGF, and elevation of caspase-3,-8 as compared to diethylnitrosamine-treated rats, which confirmed that the antineoplasm outcome of MC might come from activation of apoptosis and inhibition of proliferation, angiogenesis, and metastasis (Ali et al. 2018).

### Pancreatic Cancer

BM juice modified pancreatic cancer metabolomics phenotype and modulated primarily efflux of lactate and metabolism of glucose, unambiguously GLUT1 and MCT4 transporters in a PANC1 xenograft model (Dhar et al. 2019). Administration of BM in vitro and in vivo exhibited potent impacts in attenuation of Akt and ERK1/2 phosphorylation and practicality of gemcitabine-resistant pancreatic cancer cells (Somasagara et al. 2015).

### Gastric Cancer

Lin and colleagues found that MC extract showed powerful apoptotic and autophagic possessions in AGS and SC-M1 gastric cancer (GC) cells. The MCE-induced inhibited p38 MAPK and activated 5′-AMPK which led to the pro-autophagic function in GC cells. BM extract induced autophagy through modulation of autophagy-associated proteins expression, such as p62 and LC3-II. Moreover, downregulation of SIRT1 was observed following pretreatment of GC cells with MC extract (Lin et al. 2018).

### Head and Neck Carcinoma (Oral Cancer)

Head and neck squamous cell carcinoma characterizes various sicknesses, and oral cavity squamous cell carcinomas comprising tongue cancers have more often happened. Following gene ontology and pathway evaluations, BM alleviated expression of s100a9, IL23a, IL1β, MMP9, and PDCD1/PD1, during 4-nitroquinoline 1-oxide induced oral cancer in mice (Sur et al. 2018). Sur et al. found that treatment of Cal27 and JHU022 cells oral cancer cell lines with bitter melon extract significantly abridged GLUT-1, LDHA, PDK3, PFKP, and PKM at mRNA/protein levels. Administration of the extract led to reduction in levels of lactate and pyruvate and the rate of glycolysis in oral cancer cells. Moreover, lipogenesis-associated genes entailed in the biogenesis of fatty acids including ACC1, ACLY, and FASN were abolished. Attenuation of phosphatidylethanolamine, phosphatidylcholine, and plasmenylethanolamine, and iPLA2 activity was other finding following treatment of oral cancer cells with the bitter melon extract. Hindering of lipid raft marker flotillin expression and alteration of its subcellular localization were attributed to MC. ERS-linked CHOP expression and mitochondrial ROS production which facilitated apoptosis were also reached (Sur et al. 2019). Also, BM reduced this malignancy by aiming c-Met signaling (Rajamoorthi et al. 2013).

### Lung Cancer

Crude water extract of Indian MC induced apoptosis in A549 human lung cancer cells and zebrafish embryos (Thiagarajan et al. 2020).

### Leukemia

Following pretreatment cancerous cells with *M. charantia*, inhibition in leukemia cell proliferation and induction of apoptosis were observed. Additionally, hindering of tumor creation in mice and augmentation of survival rate and immune role were found (Grover and Yadav 2004).

## 28.3.5 Anti-inflammatory Effects of Bitter Melon

### Colitis

Bitter melon elucidated its anti-inflammatory effects on 2,4,6-trinitrobenzene sulfonic acid-induced colitis model in rats through regulation of the levels of TNF-α, IL-17, IL-1β, IL-6, IL-10, IFN-γ, myeloperoxidase, and modulation of vitamin D metabolism (Ünal et al. 2020; Semiz et al. 2020).

#### Inflammatory Bowel Disease

BM extract effect on ameliorating tunicamycin-induced ERS was assessed by utilizing human colonic adenocarcinoma LS174T cells. Pretreatment of LS174T cells with BM extract showed a noteworthy decline in ATF6, GRP78, CHOP, PERK, and XBP1 mRNA expression and CHOP and GRP78 protein expression (Kunde et al. 2017).

#### Macrophages Inflammation

Lee and Yang studied the anti-inflammatory potential of BM in LPS-stimulated reactions associated with inflammation in RAW264.7 murine macrophages in two separate studies. Findings of the aforesaid researches overall presented that MC inhibited NF-κB (p65) nuclear translocation and AP-1 (c-Fos) by way of down-regulating ERKs and Akt which were responsible for the mitigation of TAK1 and alleviated expression of IL1β, iNOS, TNF-α, COX2, IL6, and IL10 in LPS-preserved macrophages. Additionally, *M. charantia* decreased the expression of HK2 and GLUT1 and lactate production leading to glycolysis hindering (Lee et al. 2020; Yang et al. 2018). Nerurkar et al. found that freeze-dried bitter melon juice could induce discomfit in the recruitment of macrophages into adipose tissue. Moreover, it alleviated SPK1 mRNA, IL-1β secretion, and NLRP3 inflammasome in HFD-fed mice (Nerurkar et al. 2019).

#### Pulmonary Epithelial Cells Inflammation

Sung et al. demonstrated that BM pointedly lowered the TNF-α-stimulated adhesion molecule ICAM-1 expression in A549 cells and miR-221/-222 knocked-out mice via the inhibition of Akt, PI3K, NF-κB, IκB phosphorylation, and attenuation of leukocyte adhesion (Sung et al. 2018).

#### Sepsis

MC improved inflammation in LPS-induced sepsis in mice through lowering blood lipids levels including TG, cholesterol, and NEFA, recovering blood glucose concentrations, attenuating concentrations of GPT, GOT, C-RP, and NO, mitigating levels of IL-1, IL-6, TNF-α, and elevating IL-10, and inhibiting iNOS, COX-2, and NF-κB (Chao et al. 2014).

### 28.3.6 Antimicrobial Effects of Bitter Melon

Various techniques are used for the assessment of antibacterial properties, including the agar cup well technique, disc diffusion method, and micro-dilution (Villarreal-La Torre et al. 2020). The methanolic extracts from the stem and leaf of BM showed an amazing antibacterial action against *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Klebsiella pneumonia, Escherichia coli*, and *Staphylococcus aureas* (Villarreal-La Torre et al. 2020). Green-synthesized copper oxide nanomaterial derived from *M. charantia* showed inhibitory effects contrary to a great number of the resistant human pathogenic strains containing both gram-positive and gram-negative bacteria, and *Streptococcus viridians, Corynebacterium xerosis*, and R2B strain of Newcastle disease (Qamar et al. 2020). Synthesized AgNPs of *M. charantia* revealed outstanding antibacterial action to combat *Staphylococcus aureus* and *Escherichia coli (*Galatage and Parpolkar 2020*)*. BM fruits showed antimicrobial activity combat *Aspergillus niger*; oil and seeds of BM exhibited antimicrobial activity against *A. niger* and *E. coli* (Yaldız et al. 2015). Ethanolic extracts of MC fruits showed potential to combat microbes and acted counter to species of standard and multiresistant bacteria including *E. coli*, *Salmonella paratyphi, Shigella dysenterae*, *Helicobacter pylori, S. aureus, P. euruginosa, Providencia rettgeri, Proteus mirabilis,* and combat *Candida* species accountable for important limited and general infections in human beings (Lucena Filho et al. 2015).

### 28.3.7 Antimalarial Effects of Bitter Melon

MC-synthesized TiO2 NPs were able to alleviate populations of malaria vectors even at low doses.

In *Plasmodium falciparum* strains which were resisted to efficacy of chloroquine, MC extracts and biosynthesized TiO2 had the feasibility to be employed as an alternative source of drugs (Gandhi et al. 2018).

### 28.3.8 Neuroprotective Effects of Bitter Melon

Neurodegenerative diseases are chronic progressive neurological disorders.

Alzheimer's disease (AD) is the most commonly happened disorder by aging accompanying by neuronal degeneration (Talebi et al. 2021e, f, g).

#### Alzheimer's Disease and Memory Deficits

Ethanolic extract which was obtained by using the fruits of BM led to the alleviation of memory loss and ameliorated learning and memory in AD mice through impeding of lipid peroxidation and hindering of acetylcholinesterase activation. Moreover, administration of *M. charantia* exerted neuroprotective features in scopolamine-induced AD rats and mice. Cotreatment of fruit powder of *M. charantia* attenuated side effects of pharmacotherapy with lithium chloride in 3 × Tg-AD mice and streptozotocin-induced AD mice. All together, anti-AD effects of *M. charatia* were attributed to its potential of reducing gliosis, oligomeric Aβ formation, hyperphosphorylated tau protein level, and neuronal loss (Valarmathi et al. 2020). Cotherapy with MC and LiCl attenuated neuronal loss, gliosis, tau hyperphosphorylation, and oligomeric Aβ level and augmented the synaptic-linked protein and pS9-GSK3β at expressed levels in the STZ ovariectomized 3 × Tg-AD mice (Huang et al. 2018). Sepehri and coworkers found that administration of *M. charantia* in high-fat-fed rats improved the spatial-memory performance (Sepehri et al. 2019).

#### Neuroinflammation

In a mouse model of chronic social defeat stress, administration of *M. charantia* downregulated expression of IL-6, TNF-α, and IL-1β, reduced hippocampal expression of P-110β, c-Jun, JNK3, and augmented PI3K and AKT. *Momordica charantia* mitigated neuroinflammation following high-fat diet-fed in mice, through normalization of the levels of IL-16, IL-17R, IL-22, and NF-κB. Iba1, CD11b, GFAP, and S100β (Valarmathi et al. 2020).

#### Anxiety and Depression

Methanolic extract of bitter melon revealed antidepressant effects which were attributed to activation of receptors for noradrenergic, serotonergic, muscarinic cholinergic, and dopaminergic. Its anxiolytic properties were ascribed to the motivation of receptors for GABAAergic neurons (Valarmathi et al. 2020).

#### Cerebral Ischemia

*Momordica charantia* demonstrated neuroprotective properties combat cerebral ischemia-reperfusion via scavenging of ROS and NOS and blockage of JNK3/c-Jun/Fas-L and JNK3/cytochrome C/caspases-3 signaling pathways in animal models (Valarmathi et al. 2020).

### 28.3.9 Hepatoprotective Effects of Bitter Melon

Fatty liver disease, also known as steatosis, is one of the most usually occurring problems of the liver (Talebi et al. 2020b). Administration of methanolic extract of MC leaf in alloxan-persuaded hepatopathy in rats led to hepatoprotective activities. These protective effects were caused through a fall in blood glucose level, MDA, and H2O2, upsurge in levels, and accomplishments of protein and nonprotein -thiols, GPx, GST, GSH, and SOD representing its antioxidant feasibility. Besides, caspase-9 and IL-1β expressions were mitigated (Ofuegbe et al. 2020). Moharir et al. observed that the capacity of BM in reduction of liver enzymes in CCl4-induced hepatotoxicity was comparable to Liv-52 as a standard Ayurveda hepatoprotective supplement (Moharir et al. 2019). Lee et al. discovered that BME exhibited hepatoprotective effects through

hindering of markers associated with endoplasmic reticulum stress comprising phospho-eIF2α, CHOP, and phospho-JNK in palmitate-induced apoptotic death of HepG2 cells. Also, BM extract alleviated the cleaved caspase-3 activation and DNA fragmentation in HepG2 cells. High-fat/high-fructose-diet-stimulated NAFLD in mice has ameliorated afterward the reduction in ALT and TG levels by BM extract medication therapy (Lee et al. 2018).

### 28.3.10 Renoprotective Effects of Bitter Melon

Offor and coworkers found renoprotective properties of MC extract in rats subsequently taking highly active antiretroviral therapy (HAART) regimen triplavar. Administration of MC extract led to modulation of oxidative stress enzyme levels comprising CAT, SOD, and GSH. Besides, the levels of TBARS were abridged. BM-treated rats indicated a reduction in blood glucose levels, normal renal histology, restored renal function, and alleviation in body weight loss following HAART (Offor et al. 2018).

### 28.3.11 Reproductive Health Effects of Bitter Melon

Pulp and peel of MC showed antioxidant activities and prevented testicular damage in valproic acid-induced reproductive toxicity in male rats. The mechanisms answerable for these special effects were prevention of the decrease of steroidogenic acute regulatory (StAR) proteins and phosphorylated testicular tyrosine-protein expression in rats' testis (Maneenin et al. 2018). MC exhibited regulated uterine estrogen response and possibly assisted as a novel phytoestrogen agent for the handling of postmenopausal symptoms in ovariectomized rats. Regulation of ROS, ESRα, ESRβ, NF-kB, caspases-3 and -9, TNF-α, IL-6, IL-10, and Bcl-2 expression was reported as involved mechanisms (Cevik et al. 2015).

### 28.3.12 Antiulcer Effects of Bitter Melon

Turkish folklore medicine recommended BM for overcoming peptic ulcers. Ethanolic extract of MC fruits showed momentous potential to combat HCl–EtOH-brought ulcerogenesis phenomenon in indomethacin-administered rats and diethyldithiocarbamate-brought ulcer representations. However, some studies contradicted this activity (Gürbüz et al. 2000).

### 28.3.13 Wound-Healing Effects of Bitter Melon

In the assessment of the rapidity of wound contraction, collagen content, the weight of the granulation tissue, and skin breaking strength, it was comprehended that BM had wound healing activity in rats (Singh et al. 2018). Hashmi et al. found that electrospun *M. charantia*-incorporated polyvinyl alcohol nanofibers had antibacterial properties against both gram-positive and gram-negative bacteria stains, and due to the modified delivery system, it was anticipated that organized composite nanofibers could have impending uses as sustainable antibacterial wound coverings for the charming and quick recapture of open wounds (Hashmi et al. 2020). Olive oil macerate of MC presented noteworthy wound healing action in incision and excision wound representations in rat mucosa and validated anti-inflammatory action (İlhan et al. 2015). MC extract cream increased the number of fibroblasts and helped in rabbits' skin wound healing (Pişkin et al. 2014).

### 28.3.14 Miscellaneous Effects of Bitter Melon

Wang and coworkers observed that supplementation of orchidectomized mice with bitter melon powder might improve castration-induced weakening of grip power, exercise presentation, and muscle mass and upregulated Pgc1α, Ucp2, and

biogenic genes of mitochondria in certain muscles, but did not raise the prostate mass (Wang et al. 2019b). Chan and colleagues understood that BM seed oil enhanced endurance dimensions through inspiration of mitochondrial biogenesis and utility which led to activation of PPARδ ligand-binding domain, possibly prompting muscle metabolism and fiber-form arrangement in sedentary mice (Chan et al. 2018).

Kuruoglu and coworkers found that MC had feasibility to endorse new bone formation and angiogenesis subsequent lumbar laminectomy in rats (Kuruoglu et al. 2017).

## 28.4 Clinical Studies

A systematic review and meta-analysis, a literature review, and a prospective study demonstrated that formulated/non-formulated products of bitter melon and its active constituents reduced fasting plasma glucose, 2-h glucose, HbA1c, postprandial serum glucose, glucose tolerance, fructosamine level, significant decrease requiring to oral hypoglycemic medications, and rise in insulin secretion in clinical studies (Efird et al. 2014; Pahlavani et al. 2019; Peter et al. 2019; Cortez-Navarrete et al. 2018). BM has appreciated possessions on diabetic patients to manage glucose levels; nonetheless, it could not recover diabetic foot ulcers (Rosyid et al. 2018).

As stated by findings of RCT conducted by Kumari and coworkers, consumption of 1.5 g/day of MC was operational in glycaemic control, enhancing insulin resistance, decreasing total cholesterol, and improving HDL-C in patients with T2D (Kumari et al. 2018). Kinoshita et al. realized the feasible potential of BM extract in lower LDL-C levels in a Japanese RCT (Kinoshita and Ogata 2018).

A recently published meta-analysis revealed that consumption of *M. charantia* preparations was not correlated to a noteworthy decline in systolic and diastolic blood pressure. On the other hand, a significant hypotensive effect of bitter melon was perceived in younger individuals and during the short-term interventions (Jandari et al. 2020).

Kwak and colleagues indicated that intake of bitter melon extract (100 mL MCE/dose, 6 times a day) for 4 weeks in high-intensity proficient athletes at high-temperature could significantly reduce fatigues. In the study, central (prolactin, serotonin, and dopamine) and peripheral (ammonia and uric acid) fatigue factors were assessed (Kwak et al. 2020).

A three-month single-blinded randomized controlled clinical study displayed that BM supplementation (three capsules 500 mg of BM in each thrice daily) not only reduced pain and improved symptoms in patients with primary knee osteoarthritis, but also alleviated the necessity for consumption of analgesic medications (Soo May et al. 2018).

## 28.5 Safety, Toxicity, and Drug Interactions of *Momordica charantia*

Regardless of the wide biological impacts of bitter melon especially for T2DM, concise documents describe its safety and toxicity in human beings. *Momordica charantia* and its deriving products should not be consumed in persons with a reported allergy to plants of the Cucurbitaceae and subjects with G6PD deficiency. People with the purpose of impregnation should be cautious because of antifertility effects witnessed in preclinical researches. Besides, prodigious caution should be considered for usage of *M. charantia* during pregnancy, due to the abortive effects of its proteins in vivo. Khan et al. discovered that a toxicological study in zebrafish embryos led to teratogenicity due to consumption of seeds extract (LD50 = 50 μg/ml) and cardiac toxicity following usage of the fruits' extract (safer than seeds, no lethality was observed even to 200 μg/ml), which gave warnings to avoid these supplementations in pregnancy (Khan et al. 2019).

According to animal studies, caution is needed in patients suffering from liver diseases. Convulsions and subsequently hypoglycemic coma was observed in two children afterward consumption of bitter melon product on an empty stomach. A case report of acute interstitial nephri-

tis was documented in a 60-years man with T2D and high blood pressure that consumed an Ayurveda preparation comprising *M. charantia.* The nephrotoxicity was previously stated in mice treated with bitter melon 4 g/kg for a duration of further than a week (Bortolotti et al. 2019). Scoliosis of zebrafish larvae was comprehended in 125–1000 μg/ml concentrations of *M. charantia* extract (Thiagarajan et al. 2019). Measurement of the blood glucose, blood pressure, liver, and kidney function, after the intake of 500 mL of MC juice concentrate, caused an acute gastric ulcer and intestinal bleeding which might be attributed to alkaloids, lectins, or charantin existing in *M. charantia (*Fan et al. 2019*)*. Nonallergic type I hypersensitivity was reported following evaluation of the expression of CD203c and CD63 on peripheral blood basophils (in vitro) encountered with fruit extract of MC at 1/100 and 1/1000 dilutions (Sagkan 2013).

In a study, GI side effects such as abdominal discomfort and diarrhea were reported (Leung et al. 2009). *Momordica charantia* did not display any hallmark related to hepatotoxicity and renal failure due to the findings of histopathological and biochemical assessments afterward consumption of therapeutic doses in vivo (Offor et al. 2019, 2020). No-Observed-Effect Level (NOEL) for McB-E60 (a *Momordica* sp. extract) was reported for more than 1000 mg/kg bw/day in rats (Deshmukh 2016).

## 28.6 Available Commercial Formulations/Products and Pharmacokinetics Studies

Right now, wild bitter gourd is utilized in the case of folk medicine in the consumption form of fruit, juice, and decoction. In the United States, a commercial supplement of *M. charantia* extract is available which is named Glycostat, and has protective properties in cardiometabolic conditions (Ngo et al. 2019). Commercial BM products include powder, capsule, and paste in olive oil in Turkey (AkyÜz et al. 2020). Preparation of *M. charantia* extracts loaded-phytosomes (%W/W extract and phosphatidylcholine 1: 3) could help in the development of its transdermal delivery (Sasongko et al. 2019). Production of nanoliposomal encapsulation of bitter melon fruit extract assisted in its possibility to be added as a health enhancer in food and drink formulations (Rezaei Erami et al. 2019). Preparation of spheroids which is a patented novel drug delivery for herbal extracts protected the constituents of herbal preparations from gastric degradation and gut bacteria, and also enhanced their stability and bioavailability, and the antidiabetes effects of a polyherbal formulation containing bitter melon, cucumber, and tomato (Virk et al. 2020). Encapsulation of BM juice by spray drying method and adding of alginate–gelatin beads to MC helped in masking its bitter taste (Goyal et al. 2020; Sutriyo and Fauzi 2018). The mixture of HPMC and PEG 400 20% as a plasticizer helped in improving the appearance and masking the bitter taste of MC (Iswandana et al. 2018). BM seed priming is a deliberate pre-sowing semi-bioengineering method for enhancement of biological efficacy, e.g., antidiabetes activity (Farah et al. 2018).

Production of encapsulated spherical beads using electrospraying helped in the enhancement of MC extracts stability, antioxidant activity, and phenolic content appraisal to conventional methods like spray drying (Torkamani et al. 2018).

Phytochemicals available in *M. charantia* may cause interference in the pharmacokinetics of drugs by inducing alteration in absorption, distribution, metabolism, and excretion (ADME) of therapeutic drugs. *Momordica charantia* could augment the toxicity or diminish the therapeutic efficacy of a different drug by induction/inhibition of numerous metabolism-linked enzymes including p-glycoprotein and Cytochrome-P450 enzymes and drug transporters comprising of BCRP, MRP-2, and Pregnane X receptor (Raina et al. 2016; Limtrakul et al. 2004). A case report of warfarin-BM interaction was reported in a Brazilian anticoagulation clinic (Leite et al. 2018).

## 28.7 Conclusion and Future Direction

As yet, there was too much interest on research the bioactive components of *M. charantia* and their related broad spectrum biological applications. The isolation and identification of bioactive constituents from BM have fascinated extraordinary consideration, and still preserve an upward trend. Clinical studies of the plant, its components, and toxicological studies should be concerned more in the future.

**Conflicts of Interest** There are no conflicts of interest.

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# *Nigella sativa* L.

29

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**Abstract**

*Nigella sativa* (also known as black seed) has recently become popular for its many effects and is among the most demanded herbs. *Nigella sativa* seeds, which are among the herbs used for medicinal purposes, are used in traditional medicine in Asia, Far East, and Middle East countries for purposes such as headache, abdominal pain, diarrhoea, asthma, cough, and rheumatism. The anti-inflammatory, analgesic, anticancer, antitumoural, antibacterial, antifungal, antioxidant, immunological, antidiabetic, antihistaminic, antisestodal, and hepatoprotective effects of the plant's seed have been determined through in vitro and in vivo biological activity studies conducted for about 30 years. Various pharmacological effects of the plant, which is generally used as a spice to decorate and flavour donuts in our country, have also been discovered in recent years, supported by experimental data. In this section, studies on the botanical characteristics, chemical content, and biological activity of *N. sativa* have been compiled.

**Keywords**

*Nigella sativa* · Anti-inflammatory · Antibacterial · Antitumoural · Antibacterial · Antioxidant

## 29.1 Introduction

Plant extracts and phytotherapeutics prepared from plants have been preferred in the treatment of many diseases for centuries, due to their effects on human health and their easy accessibility (Ahmad et al. 2021). According to the data of the World Health Organization, more than 20,000 plant species are used for various purposes (Palhares et al. 2015). It is seen that herbs/herbal products have no harm and side effects among the people, and they are preferred more than medicines, as they are thought to be completely natural, and even the first referenced source (Ünal et al. 2021). This section contains general information and chemical and biological activity studies of *Nigella sativa* L. plant belonging to the Ranunculaceae family.

## 29.2 Systematic Position

The Nigella genus is an annual herbaceous plant with very finely divided leaves. The leaves are 1–3 pinnates, the upper parts are sometimes

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fragmented or complete. The flowers are actinomorphs, greenish-light blue, and surrounded by an involucrum made of finely divided leaves underneath. The flower cover is perigon-shaped, calyx light blue and oval five pieces, corolla in white, pink, yellow, pale blue or pale purple, 510 pieces with lobes, and nectariums in the inner circle. Ginekeum has five pieces. The stylus is long, curved outward, and permanent at the fruit crest. The fruit is in the form of a capsule formed by the partial or complete combination of five multiseeded follicles. Seeds are the most important part of the plant, numerous, black, and angular (Davis 1965, 1988). Twenty species of Nigella genus have been identified in the Mediterranean countries. It has been found that 17 species belong to the genus Nigella in Turkey (Dadandi et al. 2009). These are *N. sativa*, *N. arvensis*, *N. damascena*, *N. orientalis*, *N. fumariifolia*, *N. latisecta*, *N. elata*, *N. oxypetala*, *N. segetalis*, *N. stellaris*, *N. nigellastrum*, N. *unguicularis*, *N. assyriaca*, *N. glandulifera*, and *N. turcica*. Among these, *N. arvensis*, *N. icarica*, *N. turcica,* and *N. lancifolia* are endemic species. Besides, N. *sativa*, *N. damascena,* and *N. arvensis* are the three most consumed species among Nigella genera. However, *N. sativa* is the most widely consumed and therapeutic species on which the most research has been done (Evans 2002; Dönmez and Mutlu 2004; Dadandi et al. 2009). The place of *N. sativa* in plant systematic is as follows (Davis 1965, 1988);

Kingdom: Plantae
Subkingdom: Tracheobionta
Superdivision: Spermatophyta
Division: Magnoliophyta
Class: Dicotyledons
Subclass: Dialypetals
Order: Ranunculales
Family: Ranunculaceae
Gender: Nigella
Species: *N. sativa*

**Synonyms** *N. cretica* Mill., *N. indica* Roxb., *N. truncata* Viv.

## 29.3 Common Names (English)

Black caraway, black cumin, black seed, nigella, fennel flower, and black caraway.

## 29.4 Local Names

The names of black seed in other languages are as follows; **Chinese:** Hak Jung Chou, **Farsian:** Siah Daneh, **French:** Cheveux De Vénus, Cumin Noir, Nigelle, Nigelle Cultivée, Nigelle De Crète, Poivrette, Toute Épice, **German:** Echter Schwarzkümmel, Nigella, Römischer Kümmel, Schwarzer Coriander, Schwarzkümmel, Zwiebelsame, **Greek:** Melanthion, **Indian:** Kalojeera, Kalonji, Kalanji, Kolanji, **Arabic:** Habah Al-Brekah, Habbah Al-Baraka, Habbah Sauda, Habbeh As-Sudah, Habbeh Al-Suda, Habba Sawda, **Italian:** Cuminella, Cumino Romano, Erba Spezie, Gittaione, Grano Nero, **Kurdish:** Reşreşik, Polish: Czarnuszka Siewna, **Russian:** Černuška Posevnaja, Chernushka, **Spanish:** Ajenuz, Neguilla, **Turkish:** Çörekotu.

## 29.5 Etymology

The genus Nigella L. was named after the characteristic black seeds found in most species of Nigella. The Latin term "nigellus" is the diminutive of "niger," which means black. In Greek, *N. sativa* is called "melanthion" which is derived from the words "melas" meaning black and "anthos" meaning flower. The name "çörek out," which literally means "bread grass," refers to its traditional use in Turkey. In Kurdish, "reşreşik" refers to the black colour of the seed, just like "black seed" in English, "schwarzkümmel" in German, and "habba sawda" in Arabic.

## 29.6 Botanical Description of *N. sativa* L.

*Nigella sativa* is an herbaceous, annual plant with an erect, ribbed, angular, and branched stem, about 60 cm in height, bearing bi- or tripennate

leaves, oblong oval, composed of oblong lanceolate segments, with pubescent petiole. There are no leaves united in involucre immediately around the flower, unlike *N. damascena* L. The flowers are solitary, axillary and terminal, bisexual, radial, very rich in nectar. The calyx has five petaloid sepals, whitish to pale blue in colour, quite abruptly narrowed at their base. The corolla is made up of five petals smaller than the sepals and each having the shape of a bilabie horn, the upper lip of which is divided into two. The petals have two small rounded greenish-yellow swellings at their top. Each flower has eight nectar-bearing cones, a bi-lobed lower lip with lobes ending in a blunt protuberance, and a punched upper lip. The androecium is made up of numerous stamens attached to the receptacle by long threads. The gynoecium consists of five fused follicles, each with an indehiscent long style and composed of five carpels fused together to the base of the persistent styles. The plant is an autonomously reproducing hermaphrodite. Corresponding to all fused follicles, the fruit forms the capsule containing several whitish triangular seeds that turn black when the capsule comes into contact with the air when the capsule ripens. The seeds are ovoid and measure 2–3.5 mm; they have 3 or 4 angles with a finely granular and reticulated upper face (Evans 2002; Davis 1965, 1988).

## 29.7 Distribution and Status of *N. sativa* L.

*Nigella sativa* is native to the Mediterranean regions and Western Asia, and its culture has spread from Asia to Africa and America. It is widely responded to in India, Iraq, and some Mediterranean countries, notably Syria, Turkey, and the countries of North Africa (Davis 1965, 1988). Although the producer countries mostly consume black seed as a spice, its use as a food supplement and remedy is increasing day by day. The production of aromatic and medicinal plants has only increased over the years. Some countries, at the base exclusively producer-consumers, have become exporters. One can cite as an example Turkey which produced only for its population until 2001 and then started to export, but especially to import black cumin from India in particular. On average, it exports 125 tons, against 430 tons imported (Akbulut and Bayramoglu 2013).

The plant is very undemanding and grows on clay or sandy soils, in warm places with little humidity. The seeds are usually sown in the spring; they begin to germinate within three to four weeks. After about six months of vegetative growth, flowering occurs and continues to mature until the seeds find a suitable environment. From the yellowing of the leaves, the browning of the follicles, harvest can be done in the fall for drying in the shade. In warm regions, with a mild winter, such as India, the seeds are sown in the fall-winter for a spring-summer harvest (Davis 1965, 1988).

## 29.8 Comparison of Traditional Uses of *N. sativa* L. in Turkey and Throughout the World

*Nigella sativa*, a member of the Ranunculaceae family, has a very old historical and religious history. It has been widely used in many countries for a long time as an ornamental element in bakery foods such as bread, donuts, and some types of cheese, as well as to give flavour, aroma, and aroma. First, black cumin seeds were found in the tomb of the ancient Egyptian king Tutankhamen. The private doctors of the pharaohs ensured that they always keep the seeds of black seed ready with them, to ease digestion after food feasts, to use as a medicine for colds, inflammations, headaches, and toothaches. The ancient Egyptian queen Cleopatra, famous for her beauty, used black seed oil for health and beauty purposes (Hussain and Hussain 2016).

*N. sativa* is recorded as a medicinal herb in the Bible. Dioscorides, Hippocrates, and Plinus mentioned the effects of black seed for diuretic, stomachic, milk enhancer, antispasmodic, appetizing, menstrual purposes, and as a spice (Botnick et al. 2012). This plant has a special and important place in Islamic culture. In a hadith, Prophet Mohammed Mustafa said, “Give a

special value to black seed, because it is a cure for every problem other than death" (Ali et al. 2018). It has been found that the seeds were used by the Assyrians as flavouring to bread and the oil used as an antibacterial. It gained great importance in European countries in the Middle Ages. German kings Karl and Ludwing der Fromme encouraged the cultivation of black cumin in their countries (Botnick et al. 2012).

It was used due to its appearance, taste, and pleasant smell in many dishes such as ashura, bread, pita, donut, pastry, and yoghurt in the Seljuks and Ottomans. The ground seed can be mixed with honey and sprinkled on salads. It is also used to remove bad breath. In addition, it is put in the shroud and washing water of the dead in Anatolia and this tradition still continues in many regions. Famous Turkish medical scholar and philosopher, İbn-i Sina (Avicenna), described the therapeutic and versatile properties of black seed in his works (Salem 2005). Until the eighteenth century, black seed has been used by the people as a stimulant, diaphoretic, emmenagogue, galactagogue, anti-helminthic, anti-inflammatory, antitumoural, and in the treatment of rabies and snake bites. It is known that seed oil and sap are used against scorpion and spider bites, cat and dog bites, insects, viruses, and bacteria in Central Asia. The use of this plant has increased towards the end of the twentieth century and has become interesting all over the world with its long-standing use. In Egypt and the Middle East, black seed oil is used in respiratory system diseases, chronic cough, pharyngitis, influenza, and bronchial asthma. The seeds were used as an expectorant and were thought to stimulate body energy and help relieve fatigue (Botnick et al. 2012).

The seeds of the plant have been widely used as a spice for centuries in Southeast Asian, Middle Eastern, and Mediterranean cuisines. In addition, it has been used in the treatment of autoimmune disorders in order to maintain health and fight diseases in traditional treatment. It is used by ancient Egyptian and Greek physicians to treat nasal congestion, headache, toothache, milk enhancer, menstrual cycle, and intestinal worms. It is traditionally used in the Middle East and Far East in the treatment of a wide range of diseases, including asthma, bronchitis, headache, back pain, various infections, dysentery, hypertension, and gastrointestinal problems. While it is cooked in the Near East, it is also used as an ornament on bread and buns and also for making brine. It is widely used as incense against the evil eye, and its seeds are used as incense to repel insects, reptiles, and pests from the environment. It is used by applying oil against hair loss and dandruff, eczema, and skin diseases (Botnick et al. 2012).

In Turkey, the black seed oil is used orally for its carminative, bronchodilator, expectorant, antihypertensive, diuretic, diaphoretic, digestive, anti-helminthic, liver strengthening, and stomachic activities. It is recommended to be used topically against muscle spasms, sciatica, and rheumatism in folk culture. Black cumin seeds and oil, taken alone or in addition to other medicines, are effective against alopecia, vitiligo, and other skin conditions. It facilitates bowel movements and evacuation and is used in the treatment of abdominal pain and many diseases. Around Akşehir (Konya, Turkey), adults are given powdered seeds for abdominal pain, and a few drops of fixed oil to children. Seeds are used as abortive in Central Anatolia and also tea is prepared from seeds. After the boiled seeds cool a little, they are wrapped on the breast and used for colds. When crushed and mixed with water, it is good for hand and foot swelling. In addition, it is still consumed by women who are breastfeeding because it increases milk secretion. It has been used by dropping it into the ear for ear pains around Ermenek (Karaman, Turkey). In Muğla region (Turkey), it is used in patients with kidney stones (Tennekoon et al. 1991).

In Ayurvedic medicine, *N. sativa* seeds are used for indigestion, menstrual pain, bronchial inflammation, and as an anthelmintic. In Unani medicine, black seed is considered an abortifacient and diuretic; it is used for ascites, cough, eye pain, jaundice, paralysis, haemorrhoids, and third fever. In Indonesia, the seeds are added to astringent drugs to combat intestinal disorders. In Malaysia, seed poultices are used for headaches, abscesses, nasal ulcers, orchitis, and rheumatism.

Arab women use the seed of *N. sativa* as a galactogen. In Egypt, it is used against asthma. Externally as an ointment, the seeds are used in the treatment of abscesses, haemorrhoids, testicular inflammation, and pediculosis. In Saudi Arabia, the oil is used externally for stiffness and pain in the joints, as well as asthma and eczema (Tennekoon et al. 1991).

## 29.9 Bioactive and Nutritional Composition and Available Extraction Techniques of *N. sativa L.*

The seeds of the *N. sativa* and the oil obtained from the seed are mostly used for medicinal purposes. For this reason, most of the scientific studies are on extracts obtained from seeds, fixed, and essential oils. *Nigella sativa* seeds contain more than 100 chemical components. Various seed extracts are rich in phenolic compounds, steroids, proteins, and alkaloids. In addition, raw fibre, minerals (Fe, Na, Cu, Zn, P, K, Mg, Se, and Ca), vitamins A, B and C, thiamine, niacin, pyridoxine, and folic acid have also been found. Also, *N. sativa* seeds contain fixed oil (35.6–41.6%), essential oil (0.5–1.6%), protein (22.7%), amino acids (e.g. lysine, leucine, isoleucine, valine, glycine, alanine, phenylalanine, cystine, glutamic acid, aspartic acid, proline, serine, treonine, tryptophan, and tyrosine), essential fatty acids (lineloic acid, oleic acid), palmitic acid, reducing sugars, mucilage, alkaloids, organic acids, tannin, resin, toxic glucoside, bitter principles, metarbin, melanthin, melanthigenin, phytosterols, glycolipids, and phospholipids. In seed oil, the presence of free sterols, sterile esters, sterile glucosides, triterpene, tannins, flavonoids, cardiotonic heterosides, and anthraquinones has been demonstrated (Al-Jassir 1992; Al-Gaby 1998; Ramadan and Mörsel 2004).

### 29.9.1 Lipids and Sterols

*N. sativa* seeds contain approximately 0.4–2.5% essential oil, more than 30% fixed oils, and 38% total lipids including phospholipids. Oleic and linoleic acids are the two major fatty acids in black seed oil, constituting 75% of total fatty acids. Other authors provide different values: the seeds would contain 26.6% oils, of which 64.6% linoleic acid and 20.4% palmitic acid. Sterols make up about 2% of the fixed oil and most of them are in esterified and free form. The major sterol, β-sitosterol, alone accounts for about 60% of sterols, followed by stigmasterol at about 20%. Cholesterol may be found in trace amounts (around 1%) (Nickavar et al. 2003).

### 29.9.2 Aromatic Compounds

It was believed that most of the pharmacological activities attributed to *N. sativa* originated from its essential oil. This is why as early as 1960 studies were undertaken on the constituents of this volatile oil. It was in 1963 that thymoquinone, an oxygenated monoterpene, was isolated from black seed oil by El-Dakhakhny, and other studies have shown the main constituents. Burits and Bucar detected 32 components, most of which are monoterpenes, in the analysis performed by GC-MS. The most important of these are p-cymene (38%), thymoquinone (30%), carvacrol (5–11%), α-pinene (5–14%), β-pinene (5%), limonene (4%), longifolene (1.2–8%), 4-terpineol (1.98–6.59%), and t-anethole (0.25–4.28%). The presence of thymohydroquinone, thymol, and oxidation products of thymoquinone, such as dithymoquinone, is also reported (Benkaci-Ali et al. 2006).

### 29.9.3 Saponosides

Saponosides are heterosides of sterols or triterpenes. These are compounds that are very widespread in the plant kingdom. They are soluble in water and can be hydrolysed to one or more doses and sapogenin by hydrolysis. The first saponin isolated by Greenisch in 1882 from the seeds of *N. sativa* is melianthin, the aglycone of which is heragenin. Recently, other saponosides have been isolated from an ethanolic extract of the seeds of

*N. sativa* including 3-O-[beta-D-xylopyranosyl-(1–3)-alpha-Lrhamnopyranosyl-(1–2)-alpha-L-arabinopyranosyl]-2, while many other saponosides could be determined from black seed oil. A study made it possible to isolate from the methanolic extract three other saponosides related to α-hederin, with the elucidation of their structures by chemical and spectral methods. These saponicides are 3-O-β-D-xyl (1-3)-α-L-rha-(1-2)-α-L-ara-28-O-α-L-rha (1-4)-β -D-glu (1-6)-β-D-glu–hederagenin, 3-O-α-L-rha- (1-2) α-L-ara-28-O-α-Lrha (1-4)-β-D-glu (1-6)-β-D-glu-hederagenin, and 3-O-β-D-xyl (1-3)-α-L-rha-(1-2)-α-L-ara-hederagenin (Taskin et al. 2005).

### 29.9.4 Polyphenols and Flavonoids

Flavonoids are aromatic compounds whose biosynthesis is one of the fundamental processes in phytochemistry. They are part of what are called phenolic compounds. Flavonoids are generally coloured substances very widespread in plants. Ranunculaceae are a group rich in flavonols and flavones. In 1997, three new triglycosylated flavonoids were isolated from seeds of *N. sativa*. These saponicides are quercetin 3-glycosyl (1→2) galactosyl (1→2) glucoside, kaempferol 3-glycosyl (1→2) galactosyl (1→2) glucoside, and quercetin 3-(6-feruloglucosyl) (1→2) galactosyl (1→2) glucoside (Merfort et al. 1997). In 2008, fourteen phenolic compounds were isolated from a methanolic extract of the shoots and roots of *N. sativa*. These compounds are gallic acid, para-hydroxybenzoic acid, chlorogenic acid, vanillic acid, para-coumaric acid, ferulic acid, trans-2-hydroxycinnamic acid, trans-hydroxycinnamic acid, epicatechin, catechin, quercetin, apigenin, amamentoflavone, and flavone (Bourgou et al. 2008).

### 29.9.5 Alkaloids

Alkaloids are substances with an alkaline character, containing nitrogen, most often included in a heterocycle. Alkaloids have, for the most part, physiological and therapeutic actions at low doses. However, they become very toxic in high doses. The most important alkaloids isolated from black seeds are nigellicin, nigellimine, nigellimine N-oxide, and nigellidine (Ali et al. 2008).

### 29.9.6 Proteins

*N. sativa* seeds are very high in protein (around 20%), with a dominance of glutamic acid (22.4%), aspartic acid (10.05%), and arginine (9.18%). The most studied protein to date is lipase, which catalyses transesterification reactions. Amino acid analysis of the hydrolysate of these proteins reveals the presence of 17 amino acids including the 8 essential amino acids (Al-Gaby 1998).

### 29.9.7 Vitamins and Minerals

The vitamin composition has been determined to reveal the presence of vitamins A, $B_1$, $B_2$, $B_6$, PP, and folic acid. Total tocopherols constitute 0.05% of the oil and consist mainly of α-tocopherol (48%) and γ-tocopherol (28%). Other fat-soluble vitamins, such as β-carotene (0.05%) and vitamin $K_1$ (0.1%), are also present in *N. sativa* seeds. Work on the mineral composition of the seed of *N. sativa* reported that its potassium content is high (1.18% of the total weight of the seed) and that calcium, iron, and sodium represent 0.188%, 0.0575%, and 0.0853%, respectively. The selenium content of the seeds was found as 0.27–0.54 mg/kg (Nergiz and Otles 2003).

## 29.10 Pharmacological Properties of *N. sativa* L.

Since 1960s, much work has focused on the study of *N. sativa*, particularly the effects due to extracts from the seed, as well as the main constituents, especially thymoquinone (Benkaci-Ali et al. 2006).

### 29.10.1 Antioxidant Properties

Studies carried out in vitro and in vivo have demonstrated the antioxidant activity of black seed and its various constituents.

#### In Vitro Studies

A study on the auto-oxidation of corn oil has determined the antioxidant power of *N. sativa*. Indeed, the ethanolic and aqueous extracts delayed the oxidation of triglycerides in corn oil at 100 ° C, the ethanolic extract having a stronger antioxidant power than the aqueous extract. The antioxidant activity of the ethanolic extract is comparable to that of tert-butylhydroquinone (2 - (1,1-dimethylethyl) -1,4-benzenediol), an antioxidant used in cosmetics, and used as a preservative of fatty acids unsaturated in food (Atta and Imaizumi 1998). Burits and Bucar (2000) investigated the antioxidant activity of volatile oil. They demonstrated an anti-free radical activity of thymoquinone, carvacrol, t-anethol, and 4-terpineol. They neutralized hydroxyl radicals in non-enzymatic lipid peroxidation. Thymol, thymoquinone, and dithymoquinone, constituents of *N. sativa*, act as reactive oxygen species (ROS) neutralizers.

#### In Vivo Studies

One study, investigating the toxicity of tetrachloromethane ($CCl_4$) in mice, showed that *N. sativa* oil restored the serum lipid profile and played a protective role against hepatotoxicity. Abnormally high potassium and calcium levels and lowered $CCl_4$ blood counts were restored by black seed oil. It decreased elevated liver enzymes and increased decreased antioxidant enzymes; *N. sativa* has been shown to control hepatic fibrosis by $CCl_4$ (Butt et al. 2017). Another study shows that black seed oil increases the concentration of glutathione and the antioxidant defence system in the renal cortex, in a biochemical and histological dose-dependent manner, which implies protection against nephrotoxicity (Salem 2005). Other research teams have focused on thymoquinone in particular. Pretreatment with thymoquinone showed hepatoprotective action in rats after $CCl_4$ injection, unlike p-cymene and α-pinene which had no protective antioxidant effect (Burits and Bucar 2000).

### 29.10.2 Antihistaminic Properties

El-Dakhakhny et al. (2002) isolated the dithymoquinone dimer, nigellone, from volatile black seed oil. Nigellone given orally to patients with asthmatic bronchitis had a beneficial effect in suppressing symptoms. Subsequently, it was given to children as well and showed no toxic effects. In a clinical study with allergic patients with rhinitis, asthmatic bronchitis, or atopic eczema as symptoms, a decrease in eosinophils, IgE, and endogenous plasma and urinary cortisol was observed after administration of volatile oil of *N. sativa* (El-Dakhakhny et al. 2002).

In vitro studies, on isolated and pre-contracted tracheal chains, have demonstrated the relaxing and antihistamine effect of aqueous extract of N. sativa; the experiment was performed without calcium and in the presence of the Krebs cycle. This shows that the muscle relaxant effect of black seed has no connection with its calcium channel blocker effect, even though its relaxing effect is identical to that of verapamil, a calcium channel blocker which decreases the transmembrane movements of calcium. When no contraction is caused by potassium chloride, no effect is observed (Ali and Blunden 2002).

### 29.10.3 Anti-inflammatory Properties

Three types of anti-inflammatory mechanisms have been demonstrated in the different studies, inhibition of eicosanoids production, inhibition of prostaglandin synthesis, and decrease in nitric oxide production.

#### In Vitro Studies

Leukocytes from the peritoneum of rats stimulated by a calcium ionophore were subjected to thymoquinone and black seed oil. They inhibited arachidonic acid metabolism pathways,

cyclooxygenase (COX), and 5-lipo-oxygenase (5-LO). In the respective order, thromboxane $B_2$ and leukotrienes $B_4$ and $C_4$ were inhibited in a dose-dependent manner. Thymoquinone showed a stronger effect than oil. The two products inhibited the non-enzymatic peroxidation of phospholipids constituting the liposomes of the brain; again thymoquinone is ten times more potent than oil. But the inhibition of eicosanoid production and lipid peroxidation is greater with fixed oil than with thymoquinone. Unsaturated fatty acids and other constituents of *N. sativa* are believed to have an antioxidant and anti-eicosanoid effect. Additionally, nigellone or thymoquinone, the essential oil constituents used to treat polymorphonuclear leukocytes (neutrophils), has shown concentration-dependent inhibition of 5-LO product synthesis and production of hydroxy-eicosa-tetraenoic acid (El-Dakhakhny et al. 2002).

#### In Vivo Studies

*Nigella sativa* has shown its anti-inflammatory effect in certain inflammatory diseases such as experimental allergic encephalomyelitis, colitis, and arthritis. In fact, animals with encephalomyelitis saw their glutathione level increase and had no pre-vascular inflammation after administration of thymoquinone. The therapeutic potential of thymoquinone observed in this experiment could be extrapolated to multiple sclerosis. Topical black seed oil used in one study reduced the effects of arthritis and was shown to be anti-inflammatory, and the same effects were seen with the seeds taken orally. In response to lipopolysaccharide, injection of *N. sativa* oil emulsion causes a decrease in endotoxin shock and inhibits oedema caused by carrageenans and croton oil (Salem 2005).

### 29.10.4 Immunomodulatory Properties

El-Kadi and Kandil (1987) published the first study on the subject; they have shown that black seed has immunomodulatory properties in vivo on T lymphocytes. Later studies confirmed that black seed affected both innate and acquired immunity, so that it could intensify the immune response. For acquired immunity, subjects were treated for four weeks with black seed oil; an increase in natural killer cell activity as well as an increase in the number of $CD_4$ and $CD_8$ T lymphocytes was observed (Salem 2005). Different studies carried out on black seed have shown the stimulating properties on cell-mediated immunity via T lymphocytes, and at the same time an inhibitory effect on humoral immunity mediated by B lymphocytes. Rats vaccinated with a typhoid antigen have had decreased antibody production after administration of *N. sativa* essential oil. On the specific antigenic response, *N. sativa* L. would therefore decrease the humoral response and, on the contrary, it would stimulate the cellular response (Islam et al. 2004).

### 29.10.5 Anti-infectious Properties

Numerous studies have measured the activity of different extracts of *N. sativa* L. against bacteria, fungi, and other microorganisms.

#### Antimicrobial Properties

**Essential Oil** *Nigella sativa* essential oil inhibited the growth of Gram-positive and Gram-negative bacteria in a study performed on several bacteria except certain strains of Pseudomonas aeruginosa. The phenolic compounds present in the oil are thought to be responsible for this antibacterial effect (Khan 1999). An in vitro study using the disk diffusion method demonstrated the strong inhibitory activity of essential oil diluted to one hundredth against several bacteria including *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi,* and *Vibrio cholerae*, with a stronger action on Gram (+) bacteria (Ali and Blunden 2002).

**Vegetable Oil** *Nigella sativa* vegetable oil is also credited with antibacterial properties, especially in food preservation. Khan (1999) showed that the use of black seed oil in food preservation at a level of 0.1% inhibits the growth of microor-

ganisms. A study was carried out to verify the action of black seed oil on twenty strains of *Listeria monocytogenes*. The antibacterial effect of *N. sativa* oil has been compared to that of gentamycin and a vegetable oil, by the disk diffusion method. Black seed oil showed the strongest antibacterial activity; it was active on all strains of *L. monocytogenes*, gentamycin had a less marked effect, and vegetable oil had no effect (Nair et al. 2005).

## Antifungal Properties

The different extracts studied on bacteria were also used to determine the antifungal activity. The test of essential oil diluted to one hundredth by the disk diffusion method, cited above, was carried out on fungi of the genus Aspergillus and Microsporum. The antifungal effect of black seed oil has been observed along with the antibacterial effect (Ali and Blunden 2002). A study comparing the antifungal properties of 16 essential oils, including *N. sativa*, evaluated their minimum inhibitory concentration (MIC) on different fungi. Black seed volatile oil has been shown to be the most effective against *Candida albicans* at an MIC of 2.5 mg/mL, and second against *Chaetomium olivaceum* at the same MIC. This oil could potentially be used in rice, wheat, and cotton crops frequently affected by *C. olivaceum*. *Nigella sativa* L. could have an interest in the agro-alimentary field, on the conservation of crops of cereals and of foodstuffs (Aboul Ela et al. 1996). A study on the growth of *Aspergillus flavus* and the production of aflatoxins highlights the role of black seed. Indeed, black seed powder at 10% concentration inhibited the production of aflatoxins and the growth of *A. flavus* from 85% to 90%. In addition, aflatoxin production was inhibited in a concentration-dependent manner by *N. sativa* oil (Kabli 2009).

## Antiviral Properties

An in vivo study of the action of black seed oil on mice infected with cytomegalovirus (CMV) showed the antiviral activity of *N. sativa*. After inoculation of CMV and intraperitoneal injection of black seed oil into mice, the observation focused on non-specific immunity, that is, on NK cells and macrophages, and on specific immunity constituted by T lymphocytes. Cytotoxic T lymphocytes constitute the delayed response with their mediators such as γ interferons, while NK cells and macrophages constitute the early response of immunity. In the organs studied, the liver and the spleen, a decrease in CMV was observed; at the same time an increase in IFN-γ and macrophages explains the antiviral effect. In viral infectious foci, a decrease in the number of lymphocytes by apoptosis is observed. Antioxidant agents can inhibit these cell deaths as many times as there are viral replications in the target cells. The antioxidant effect of *N. sativa* is therefore implicated in its antiviral activity (Salemal and Hossain 2000).

## Anti-parasitic Properties

Numerous studies have shown the effectiveness of black seed as an anthelmintic agent. Aggarwal et al. (1979) demonstrated the activity of *N. sativa* oil comparable to piperazine, an anti-roundworm, and anti-pinworm dewormer. An in vivo study on goats infested with intestinal nematodes showed the activity of the glycosides contained in black seed against these worms. For the goats having been infested for more than 15 days, increasing doses of 50, 150, and 200 mg/kg of glycosides were administered orally. The results obtained were compared with those obtained with oxyclosamide, the benchmark anti-parasitic in veterinary settings, at 15 mg/kg. After 10–15 days of treatment with black cumin glycosides at concentrations of 150 and 200 mg/kg, the results were close to those of oxyclosamide. And the results obtained after 15 days of treatment with glycosides at 150 mg/kg were identical to those of oxyclosamide (Akhtar and Aslam 1997).

The essential oil of *N. sativa* had an anti-parasitic activity comparable to piperazine against earthworms (*Pheritima posthuma*), tapeworms (*Taenia solium*), nematodes (*Bunostomum trigonocephalum*), and lumpworms (*Oesophagostomum colombionum*). Malaria has an important place in parasitic diseases, especially since certain strains of parasites are becom-

ing resistant to current treatments. In order to see the action of black seed on Plasmodium falciparum, an in vitro study was carried out. *Nigella sativa* extract, obtained from an equimolar mixture of chloroform and petroleum ether, inhibited the growth of *P. falciparum* schizonts. The antiparasitic effect is believed to be due to the flavonoids, tannins, sterols, and alkaloids of triterpenes and anthraquinones, contained in the extract (Khan 1999).

### Antidiabetic Properties

Treatment with various preparations of *N. sativa* L. consistently results in decreased blood sugar levels in various animal models. A mixture of five plants including *N. sativa* was used in Kuwait on streptozotocin-induced diabetic and normal rats. Glucose tolerance was improved in both groups. This mixture was subsequently thought to inhibit hepatic gluconeogenesis (Ramadan 2007). In hyperglycaemic and normal rabbits, the essential oil of black seed was injected intraperitoneally at a dose of 50 mg/kg. Four to six hours after administration, a decrease in blood sugar was observed (15–23%). Since the improvement in blood sugar is not accompanied by a change in insulinemia, this effect of black seed is independent of insulin mechanisms (Al-Hader et al. 1993).

## 29.10.6 Cardiovascular Properties

We have already seen the effect of black seed on diabetes, a disease that exposes the early onset of cardiovascular complications. Here we will see the action of *N. sativa* L. on other risk factors such as dyslipidemia and metabolic syndrome, direct action on blood pressure, as well as its role in the prevention of cardiovascular accidents.

### Direct Anti-hypertensive Action

El-Tahir et al. (1993) studied the activity of *N. sativa* essential oil and thymoquinone on the blood pressure and heart rate of anesthetized rats. Intravenous injection of these products causes a drop in the two parameters studied; it seems that the serotoninergic and muscarinic mechanisms are involved. Indeed, the results were reversed by the successive medullary injection of ciproheptadine (an $H_1$ antihistamine with anticholinergic and antiserotonergic properties), atropine (muscarinic anticholinergic), hexamethonium (nicotinic ganglionic anticholinergic), and reserpine (monoamine vesicular transport inhibitor). In addition, the unsaponifiable fraction of the fixed oil had a depressant effect on the heart by causing bradycardia (El-Tahir et al. 1993).

### Action on Hyperlipidaemia and Atherosclerosis

Black seed fixed oil was used in rats at a level of 1 mL/kg/day for 12 weeks to confirm its traditional use in hyperglycaemia and dyslipidemia. Discoveries on other blood parameters like haemostasis were made, and the weight gain was stopped. The serum values of haematocrit and haemoglobin were increased, while those of cholesterol, triglycerides, glucose, leukocytes, and thrombocytes were decreased. Based on the results, the conclusions were that black seed could be used in hyperglycaemia, hyperlipidaemia, and some forms of anaemia (Zaoui et al. 2002). A biochemical study showed inhibition of lipid peroxidation and increased membrane permeability of cultured leukocytes by fixed oil (Houghton et al. 1995).

## 29.10.7 Gastrointestinal Properties

The seed of *N. sativa* is widely used in disorders of the gastrointestinal system. The oil has a cytoprotective effect (Ali and Blunden 2002). In the aspirin-induced ulcer in rats, the aqueous extract of black seed had antiulcer activity. The volume of gastric acid secretion and total and free acidity were markedly reduced. Black seed vegetable oil administered twice daily for two weeks to rats at 0.88 g/kg/day causes an increase in mucin and glutathione, and a decrease in histamine production, stimulating the acid secretion by enterochromaffin cells (Akhtar et al. 1996). The peptic activity and free acid of the stomach were not affected, therefore black seed provided good protection against ethanol ulcer in rats (Kanter et al. 2006).

### 29.10.8 Antihepatotoxic, Hepatoprotective, and Antinephrotoxic Properties

Several in vivo and in vitro studies in rats have shown the protective effect of *N. sativa* on hepatotoxicity and induced nephrotoxicity.

#### Hepatoprotective Action

Black seed oil was administered for sixteen weeks, at 0.27 g/100 g of body mass/day, to rats to see its impact on structural and functional changes in the liver and kidneys, that is, say its action on the processes of cellular ageing. In the control group, an increase in nuclear DNA was observed, while the treated rats saw their levels of cholesterol, total lipids, gamma-glutamyl transferase, urea, uric acid, and nuclear DNA decreased. It was concluded that black seed causes a slowdown in ageing (Khan 1999).

#### Nephroprotective Activity

*Nigella sativa* with its antioxidant and anti-inflammatory properties would fight effectively against kidney damage. Black seed extract administered at 50 mg/kg 30 minutes before cisplatin, a DNA alkylating cytotoxic agent used in cancer chemotherapy, restores biochemical and physiological indicators of nephrotoxicity (Ali and Blunden 2002).

### 29.10.9 Neurological Properties

Numerous studies carried out on different animal models have determined the action of *N. sativa* L. on the nervous system. They have thus demonstrated antinociceptive, neuroprotective, sedative, anticonvulsant, anxiolytic, and antiepileptic properties.

#### Antinociceptive Properties

Black seed oil and thymoquinone have been used to determine their effects on the pain experienced by rats subjected to various nociceptive tests. The hot plate test, to measure the animal's reaction time, the tail straightening test after exposure to a heat source, the contraction test induced by the intraperitoneal injection of acetic acid, and the test of reaction to pain after injection of formaldehyde into a hind paw were used (Abdel-Fattah et al. 2000).

#### Neuroprotective Properties

To measure the pharmacological activities of black seed on the central nervous system (CNS), aqueous and methanolic extracts of seed oil of *N. sativa* L. were used. The results were such that the two extracts had a CNS depressant effect and a central analgesic effect (Al-Naggar et al. 2003).

#### Anticonvulsant and Sedative Properties

An in vitro study putting neurons in contact with a methanolic extract of black seed has demonstrated the action of *N. sativa* on the secretion of various excitatory neurotransmitters, such as aspartic and glutamic acid, and inhibitors such as glycine and GABA. After incubation, the amount of GABA increased, while that of amino acids decreased; this would explain the sedative and anticonvulsant properties of *N. sativa* (El-Naggar et al. 2010).

#### Anxiolytic Properties

Recent studies have demonstrated the anxiolytic effect of *N. sativa* L. on rats. Different tests are used to study animal behaviour, such as the raised cross maze, the light/dark preference test, and the social interaction test. An animal immobilization test combines emotional stress, through flight response, and physiological stress, through muscle work. From these tests, various biochemical parameters are measured (Perveen et al. 2009).

### 29.10.10 Properties on Reproductive and Fertility Functions

#### Actions on Spermatogenesis

Different fertility parameters are studied to determine the action of black seed on reproduction. The thickness and diameter of seminiferous

tubules, spermatogonia, primary and secondary spermatocytes, spermatids, free spermatozoa, Leydig cell diameter, sperm motility and density, secretory activity of seminal vesicles and the prostate, the arousal time linked to a stimulation of the libido, and male hormones level are the parameters used to conclude on male fertility. It has been observed that the application of *N. sativa* has a healing effect on all these parameters (Mukhallad et al. 2009).

#### Galactogenic Properties

Traditional usage mentions the galactogenic power of black seed; the mechanism is still not clear, although the action has been demonstrated. It is also known that vegetable oil is responsible for this effect and that the effect is greater than that of estrogen (Agrawala et al. 1971).

#### Estrogenic Properties

The estrogenic activity of *N. sativa* is assessed by a vaginal keratinization test. In ovariectomized rats, administration of black seed powder at 300, 600, and 1200 mg/kg was performed; the results showed keratinization due to estrogenic activity. Measurement of the estradiol level in the blood at the various powder strengths made it possible to determine the effective dose; an increase in estradiol levels was observed at 300 mg/kg. Black seed is thought to act through its unsaturated fatty acids on estrogen receptors, and we still do not know the nature of its phytoestrogens (Parhizkar and Latiff 2013).

#### Contraceptive Properties

In ancient Greece, black seed oil was already used for contraceptives. The pessaries were coated with oil, or else honey and then black seed. *Nigella sativa* oil is believed to be abortive during the first 10 days of gestation in the spleen, but after the tenth day no abortive, teratogenic, or duration of gestation effects could be observed. Other studies have shown the antioxytocic and muscle relaxant effect on the uterus of non-pregnant spleen of the essential oil of *N. sativa*. Muscle relaxation is thought to be via the calcium channel blocker effect (Keshri et al. 1995).

### 29.10.11 Antitumour Properties

Numerous in vitro and in vivo studies have shown the antitumour properties of *N. sativa* L. and its constituents. By studying the action of the essential oil of *N. sativa* on different human cancer cells, a cytotoxic effect was observed. *Nigella sativa* extract reduces the incidence of sarcomas and decreases the diameter of tumours induced by carcinogenic chemicals. This same group determined that *N. sativa* possesses an antitumour effect against several types of malignant cells. This action is due to inhibition of thymidine incorporation into DNA (Swamy and Tan 2000). *Nigella sativa* ethyl acetate extract also acts against proliferation in various cancer cell lines. Kumara and Huat (2001) isolated an active principle (α hederine) which has a strong antitumour activity in mice implanted with lung sarcoma and murine P388 lymphoma.

### 29.10.12 Anti-angiogenic Properties

Thymoquinone inhibited angiogenesis in vitro and in vivo; it inhibited tumour growth through activation of the two signalling pathways mentioned above in endothelial cells. However, no anti-VEGFR effect was observed, and there are other proangiogenic growth factors including fibroblast growth factor (FGF), placental growth factor (PGF), and platelet-derived growth factor (PDGF). All of these growth factors regulate angiogenesis through AKT and ERK signalling pathways. It was concluded in this study that thymoquinone would inhibit angiogenesis by suppression of the AKT and ERK signalling pathways, and not by direct inhibition of VEGFR activation (Jain 2003).

## 29.11 Toxicological Studies of *N. sativa* L.

The toxicity of black seed is well-known by most herbalists. In fact, it is only used at low doses, whether internally, externally, in fumigation, or in inhalation. An overdose of *N. sativa* seeds can

be fatal. Bellakhdar et al. (1991) reported in his book that therapeutic overdose can lead to abortions. This toxicity, like that of most species of the Buttercup family, is mainly due to the presence of high amounts of saponins and alkaloids in the seeds of black seed. Mahfouz et al. (1960) and Tennekoon et al. (1991) studied the toxicity of aqueous and alcoholic extracts of *N. sativa*. Plasma concentrations of γ-glutamyl transferase (GGT) and alanine aminotransferase (ALT) were increased in rats after oral treatment for 14 days; however, no histological abnormalities were observed in these rats (Tennekoon et al. 1991). Zaoui et al. (2002) reported that the fixed oils have an $LD_{50}$ of 28.8 mL/kg (po) and 2.06 mL/kg (ip). Likewise, the chronic toxicity of 2 mL/kg of oils for 12 weeks presents normal values for ALT, GGT, and aspartate aminotransferase (AST). Most of these studies clearly show that black seed has a high therapeutic index and excellent safety at doses below 4 g/kg/day.

## 29.12 Available Commercial Formulations of *N. sativa* L.

Although all of this potential has not yet materialized, there is a great deal of work supporting the possible use of *N. sativa* in therapy. Indeed, this plant is already showing applications, in particular in the form of fixed oil-based capsules claiming the claim "food supplement with immunomodulatory activity." Some commercial formulations of black seed found in European Union countries are summarized in Tables 29.1 and 29.2.

## 29.13 Gap Between Ethnomedicinal and Scientific Evidences

Formulations using *N. sativa* seeds have been used in the treatment of various diseases for centuries. The efficacy of a significant part of these formulations has been proven by various in vivo and in vitro studies conducted after the emergence of modern medicine. The most important diseases treated using *N. sativa* seeds in folk medicine and the preparation methods of *N. sativa* are given below (Toparslan 2012).

### 29.13.1 Diabetes Mellitus

**Necessary ingredients:** 1 glass of black cumin seed, 1 glass of *Inula helenium*, 1 glass of *Origanum syriaticum*, 1 glass of pomegranate fruit peel

**Preparation:** Finely grind the black cumin and elecampane, oregano, and pomegranate peel. Store in a dry place in a glass container.

**Usage:** Take a tablespoon of the mixture 15 minutes before each meal, in a liquid or honey. The cure should be continued for 4 weeks. We can then continue by slowly reducing the amount absorbed at each meal (Toparslan 2012).

### 29.13.2 Allergy, Hay Fever, Asthma

**Necessary ingredients:** One glass of powdered black cumin seed, 1 litre of boiling water

**Preparation:** Put the black cumin powder in a saucepan, add the boiling water, and let infuse for 5 minutes.

**Usage:** Inhale the vapour for 10 minutes (by covering the neck and the head with a towel, put the head above the bowl). Do this several times a day, starting early in the morning on an empty stomach (Toparslan 2012).

### 29.13.3 Common Cold

**Necessary ingredients:** Black cumin seed, olive oil

**Preparation:** Mix the pounded black cumin seeds with the olive oil.

**Usage:** Administer the drops by the nasal route, 3–4 times a day (Toparslan 2012).

**Table 29.1** Some commercial formulations of organic *N. sativa* vegetable oil

| | |
|---|---|
| Abiessence | 50 and 100 mL bottles |
| Centiflor | 100 mL bottle |
| Centifolia | 100 mL bottle |
| Emma Noel | 50 mL spray bottle |
| Ferme des peupliers | 250 mL bottle |
| Herbes et Tradition | 50 mL bottle |
| Hevea | 50 and 200 mL bottles |
| Huiles et baumes | 30 mL bottle |
| Hyteck | 100 and 250 mL bottles or 10 mL cartoons |
| Karawan | 50 mL bottle |
| Melvita | 50 mL bottle |
| Natessance | 50 mL bottle |
| Pranarom | 50, 100 mL and 1 L bottles |
| Sophery | 50 mL bottle |
| Terrocean | 200 mL bottle |

**Table 29.2** Some commercial formulations of *N. sativa* in solid forms and capsules

| | |
|---|---|
| Abc de la nature | Boxes of 60, 100, and 200 capsules in fish gelatin, virgin vegetable oil, first cold pressed, dosed at 500 mg |
| Bioluxe | Pill box of 120 oily capsules dosed at 500 mg of black seed oil |
| Biovedas | Box of 200 capsules containing 500 mg of black seed oil in each capsule |
| Boutique nature | Pill box of 90 capsules of marine origin dosed at 500 mg of black seed oil in each capsule |
| Chifa | Pill box of 60 capsules containing 500 mg of black seed oil |
| Dieti Natura | Boxes of 60 and 200 capsules containing 500 mg of black seed oil in each capsule |
| Emma Noel | 515 mg capsules comprising 73.25% virgin organic black cumin oil |
| Floralpina | Black seed oil capsules |
| Ombelle Nature | Boxes of 60 and 200 capsules containing 500 mg of black seed oil in each capsule |
| Terrocean | Boxes of 200 capsules of 782 mg of black seed oil in each capsule |

### 29.13.4 Bronchitis, Cough

**Necessary ingredients:** 1 clove of garlic, 2 tablespoons of honey, 1 teaspoon of black cumin seed powder

**Preparation:** After passing through boiling water to soften it, press the garlic in a garlic press, mix with honey (slightly warmed in a double boiler to liquefy it, if necessary) and black cumin powder.

**Usage:** Every morning at breakfast, take a teaspoon of this syrup and continue this treatment for 3 weeks (Toparslan 2012).

### 29.13.5 Acne

**Necessary ingredients:** 1 glass of cider vinegar, 1 glass of powdered black cumin, black cumin oil

**Preparation:** Let the black cumin macerate for 6 or 7 hours in the cider vinegar. Drain and express. Discard the juice. Keep the powder moist and add the same volume of black cumin oil to it. Mix well and heat briefly for 2–3 minutes. Mix one last time vigorously.

**Use:** Apply this paste several times a day on the affected areas. For an even more effective action, apply the paste at bedtime after a facial steam bath (Toparslan 2012).

### 29.13.6 Headache

**Necessary ingredients:** 1 glass of black cumin seed, 1 glass of anise, 1 or 2 cloves

**Preparation:** Grind and finely pulverize the plants, mix them, and store them in a glass jar, away from humidity and light.

**Usage:** 2 times a day (in breakfast and lunch) take a teaspoon of this preparation. Keep this powder in the mouth for a long time to soak it up with saliva, chew gently, then swallow it with a glass of water. This is the best way to make this remedy work because some of the active ingredients will already be absorbed by the oral mucous membranes (Toparslan 2012).

### 29.13.7 Insomnia, Gastric Acidity

**Necessary ingredients:** 200 mL of milk, 2 teaspoons of black cumin oil, 1 teaspoons of honey

**Preparation:** Slowly heat the milk in a saucepan. Before boiling, remove the pan from the heat and add the black cumin oil. Then add the

honey, stirring until all the ingredients are completely dissolved.

**Usage:** Take a tablespoon of this mixture 3 times a day, before the meals (Toparslan 2012).

## 29.14 Considerations for Using *N. sativa* Preparations

### 29.14.1 Drug Interaction and Other Interactions

There is no record of black seed-drug interaction to date.

### 29.14.2 Warnings and Adverse Reactions

There is no record of any adverse effects resulting from the use of *N. sativa* preparations. However, very sensitive individuals should not use it. In addition, individuals known to be hypersensitive to any of the herbal active substances and auxiliary substances contained in the black seed preparations sold in the market should be careful.

### 29.14.3 Pregnancy and Lactation

It should not be used during pregnancy. Studies on pregnancy, embryonal or foetal development, and parturition and postnatal development on animals are not available. For this reason, it is not recommended to use black seed oil internally, especially in pregnant women. *Nigella sativa* seeds are used in the literature as increasing milk secretion, but their use in lactation should also be consulted with the doctor.

### 29.14.4 Duration of Use

Tea prepared by putting a teaspoon of crushed seeds into a cup of boiling hot water can be drunk as a tonic twice a day. Infusion (2–5%) can be drunk 2–3 glasses per day. Externally, it can be applied as a thin layer where deemed necessary (Datta et al. 2012). Although there is no record about the duration of use, it is recommended that the black seed preparations should not be used for more than 2 months.

### 29.14.5 Overdose

No cases of overdose have been reported to date. Orally used black seed oil is well-tolerated, and no effects are expected due to overdose. However, if any symptoms occur after overdose, treatment should be symptomatic and supportive. There is no specific antidote or a method to increase its elimination.

### 29.14.6 Storage

Black seed preparations should be stored in their original packaging and at room temperature, away from heat, light, and moisture. It is recommended to keep it out of the sight and reach of children.

## 29.15 Challenges and Future Recommendations as Potential Drug Candidate

As it has been noticed, black seed has been neglected in the West for many years, but the marked use in the East has aroused considerable interest from medical research teams. During the last 20 years, several works have focused on the study of *N. sativa*, in particular on the effects due to extracts from the seed of this species as well as to the main constituents (in particular thymoquinone) on various in vitro and in vivo systems. Nigella being an aromatic spice, it regulates appetite and has digestive properties. There are many phytochemical and bioactivity studies on *N. sativa*, which has such important traditional uses. Since fixed and essential oil are more responsible for pharmacological effects, studies have focused on these two active ingredient groups. The fixed oil in the seed is particularly rich in polyunsaturated fatty acids, thus exhibit-

ing antioxidant, antiallergic, anti-inflammatory, immunomodulatory, antibacterial, antitumoural, antidiabetic, hepatoprotective, cardioprotective, and gastroprotective activities.

Studies on *N. sativa* mentioned in the literature have generally been carried out using seeds obtained from the plant grown in countries where it has widespread use or commercially available seed oil. In the studies conducted in Turkey, it is seen that the most studies are done by using *N. sativa* seeds, which have been cultivated, as in the world. It is thought that this plant will constitute a valuable resource for bioactivity studies to be conducted in further studies and the development of various dosage forms due to its high amount of thymoquinone (Toparslan 2012).

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# *Olea europaea* L.

# 30

Damla Kırcı and Fatma Ayaz

**Abstract**

*Olea europaea* L. is one of the most significant members of the medicinal plants belonging to Oleaceae family. *Olea europaea* and its cultivars, generally referred to "olive," grow in the regions of the Mediterranean. *Olea europaea* is a popular food and used as traditional medicines and for other needs in a lot of countries. In more than ten countries, *O. europaea* is frequently used in both internal and external applications as a traditional medicine for a large variety of diseases and complaints. It is primarily used in the treatment of cardiovascular disorders and diabetes mellitus when taken by mouth, as well as in the cure of wounds and burns together with the aim of antiseptic when used externally. Phytochemical studies on many different parts or products of *O. europaea* including fruits, leaves, stems, barks, as well as oil and extra virgin olive oil (EVOO) have extensively been examined until now. There were also much research on diverse biological activities, especially antioxidant, anti-inflammatory, antidiabetic, anticancer, and antimicrobial associated with the compounds, such as phenolics, iridoids, flavonoids, secoiridoids, bisphenols, and triterpenes isolated from different parts of *O. europaea.* In addition, the plants extract samples and their phytochemicals have been investigated in in vitro and in vivo bioassays, as well as clinical studies up to date. Otherwise, there are restricted toxicity research on the extracts from leaves of *O. europaea* and their main components. As a consequence of this report, many herbal products derived from olive leaves will need to be studied further in clinical trials.

**Keywords**

*Olea europaea* · Olive · Oleuropein · Hydroxytyrosol · Olive oil · Olive fruit

## 30.1 Introduction

*Olea europaea* L. (Oleaceae), a medicinal plant, grows in warm and tropical landscapes worldwide. *O. europaea* tree, commonly called as olive, is popular because of its fruit, and oil. *O. europaea* is known with many different names, such as "olivo, aceituna" in Spain, "azeitona, oliveira" in Portugal, "elia" in Greece, "oliven" in Denmark, "al-aotem" in Saudi Arabia, "zeytin, zeytun" in Turkey, "zolive" in Rodrigues Island, and "woira" in Ethiopia (Ghanbari et al. 2012;

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Amuamuta and Na-Bangchang 2015; Hashmi et al. 2015).

The genus *Olea* L. consists of plants in the form of a shrub and tree with green leaves throughout the year. The plants from the genus can also grow up to 10–15 m during their lifespan (Davis 1978). The botanical properties of the genus are summarized in Table 30.1. Among the species, the most popular one is *O. europaea* and the photography of Ankara University Herbarium sample from *O. europaea* (AEF 25196) is presented in Fig. 30.1.

*Olea europaea* has been growing in various regions by many cultivators in Turkey, such as Gemlik, Ayvalik, Erkence, Çakir, Uslu, Çilli, Domat, Çelebi, and Edinciksu. Especially in these regions, *O. europaea* is preferred because of its fruit and olive oil. In addition, two varieties of the plant, known as *O. europaea* var. *sylvestris* (Mill.) Lehr. and *O. europaea* var. *europaea* (synonyms: *O. europaea* var. *sativa* (Weston) Lehr), are growing in Turkey. The size of the fruit is the most notable difference between the two varieties. *Olea europaea* var. *europaea* has large fruits to 35 mm, while the fruits size of *Olea europaea* var. *sylvestris* is 15 mm (Davis 1978).

In this present work, the distribution of *O. europaea* with its history, traditional uses, phytochemicals, pharmacological activities and clinical research, as well as toxicity and commercial products with bioavailability, were evaluated.

**Table 30.1** Botanical properties of *Olea* genus (Davis 1978)

| Plant parts | Botanical properties |
|---|---|
| Leaf | Simple, opposite, coriaceous, lanceolate to obovate |
| Twigs | Quadrangular or terete |
| Flowers | Polygamous or hermaphrodite, in axillary branching fascicles or panicles |
| Calyx | 4 toothed and short |
| Corolla | 4-valvate lobes and short tube |
| Stamens | Shorter than lobes, anthers large, epipetalous, filaments short |
| Fruit | Ovoid drupe or oblong |

## 30.2 Distribution

The origins of *O. europaea* are traced back to Asia Minor, including Palestine and Syria. It was first grown in the Mediterranean regions, and many religions regard the olive tree, its fruit, and oil as sacred. Moreover, olives are distributed around the Mediterranean area by Romans and the Arabs. Nowadays, approximately 97% of grown olives are produced in Spain, Greece, Italy, Turkey, Morocco, France, Tunisia, Algeria, Israel, Syria, Portugal, Yugoslavia, Jordan, Egypt, and Libya. In addition, olives are grown in Chile, Argentina, the USA, Mexico, Australia, Japan, South Africa, and Peru. The cultivation areas for various types of olives can differ from each other. *Olea europaea* subsp. *oleaster* grows throughout the Mediterranean zone, *O. europaea subsp. europaea* is found in tropical regions, and *O. europaea* subsp. *cuspidate* occurs in Africa (Rugini and Lavee 1992; Ghanbari et al. 2012; USDA-ARS 2016). The world map showing the regions where olives are grown is given in Fig. 30.2.

*Olea europaea* varieties are identified and classified by the International Olive Oil Council. There are about 2500 of them as established. Besides, 250 varieties are commercially defined. The main cultivators are demonstrated in Fig. 30.3.

Traditionally, table olives and olive oil are manufactured using these olive cultivars and they are commercially important in the region of Mediterranean. Spain is the highest olive producer in the world, followed by Italy, Greece, and Turkey that mostly produce olives (Ghanbari et al. 2012).

## 30.3 Traditional Uses

The olive tree has a long history, dating back to 6000 BC, and is revered by many religions for its fruits and olive oil. *Olea europaea* is commonly used as a folk medicine for a large variety of disorders in more than ten countries,

**Fig. 30.1** *Olea europaea* L. Ankara University Herbarium (AEF 25196)

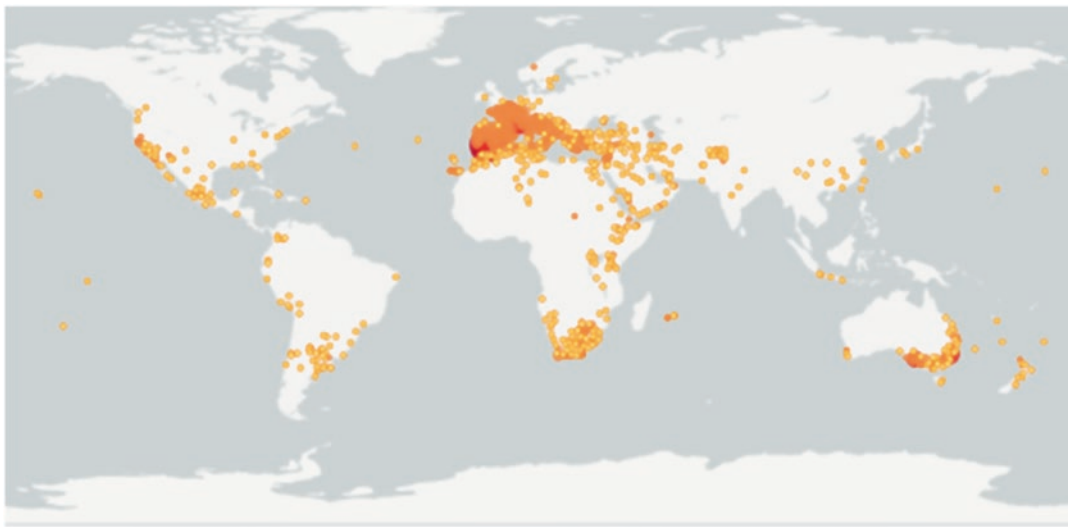


**Fig. 30.2** Regions where olives are growing (USDA-ARS 2016)

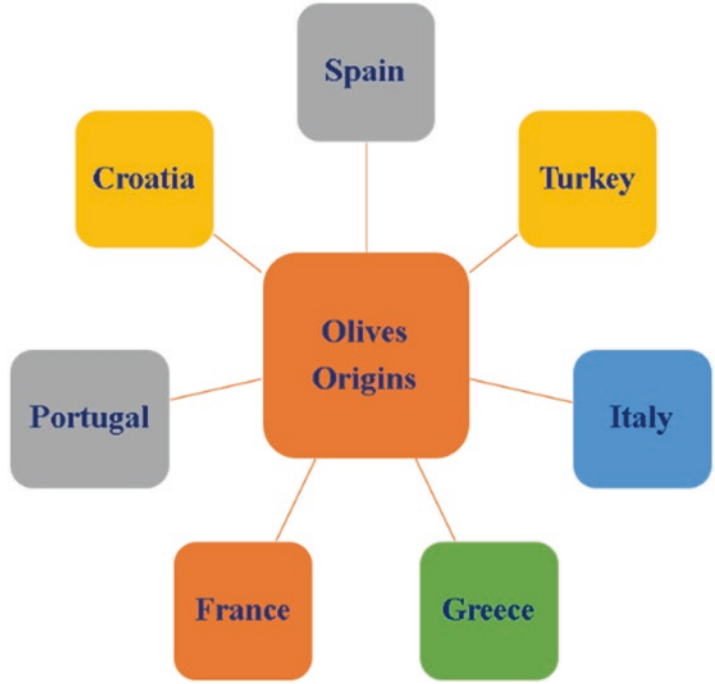



**Fig. 30.3** Main cultivators of olives origins

both internally and externally. *Olea europaea* has generally been used as olive oil, essential oil, tincture, balm, and gum using infusion, decoction, and pressing methods. The plant has also been used in separate parts of olives, including leaves, fruits, barks, and seeds. The leaves of the olives are known as the most typically used part according to the reports (Lawrendiadis 1961; Pieroni et al. 1996; Benítez et al. 2010; Yeşil and İnal 2019).

In Greece, Italy, Spain, and Turkey, there are similar usages as traditional medicine. The infusion method is mainly preferred for the preparation of the folk medicine from *O. europaea* leaves. It is mostly used to treat diabetes mellitus and cardiovascular disorders orally, as well as for the wounds and burns externally. It has also been reported in the literature about cardiovascular system that it causes hypotension or hypertension, which is found inconsistent with these knowledges (Benítez et al. 2010; Amel 2013). The traditional use of *O. europaea*, the countries where it grows, and used parts, with preparation methods is shown in Table 30.2.

## 30.4 Phytochemicals

Phytochemical studies have been carried out in many separate parts and products of *O. europaea*, including fruits, stems, leaves, and barks, as well as oil and extra virgin olive oil (EVOO). Their several secondary metabolites have also been isolated up to date. These compounds are mainly found as iridoids, flavonoids, secoiridoids, bisphenols, and triterpenes (Jerman et al. 2010; Obied 2013; Hashmi et al. 2015).

### 30.4.1 Fruit

Secoiridoids, flavonoids, and polyphenolic constituents are abundant in the fruits of *O. europaea*. Oleuropein, a secoiridoid glycoside, is the dominant compound present in *O. europaea* fruits and leaves (Fig. 30.4). Oleuropein is a very significant compound due to its biological activities and is also used as a standard compound to evaluate quality of the olive leaves extract. When the extracts contain a minimum of 16% oleuropein, these are appropriate with European Pharmacopoeia 9.0

**Table 30.2** Traditional uses of *Olea europaea* in different countries

| Countries | Parts | Preparation | Traditional uses | References |
|---|---|---|---|---|
| Italy | Fresh leaves | Infusion | Anti-inflammatory | Pieroni et al. 1996 |
| | Leaves | Tincture | Febrifuge, epithelium restorer, and ingrown nails | De Feo and Senatore 1993 |
| | Fruit | Essential oil | Treatment of renal lithiasis (orally), Sores, promote circulation, burn, and rheumatism (externally) | De Feo et al. 1992 |
| Spain (Granada) | Leaves | Infusion | Treatment of hypertension and hyperglycemic | Benítez et al. 2010 |
| | Olive oil | Fresh ingested | Constipation, food poisoning, and hernia | |
| | Olive oil | – | Cough, hemorrhoids | |
| | Fruit | – | Warts, heartburn | |
| Japan | Leaves | – | Internal and stomach diseases (orally) | Bellakhdar et al. 1991 |
| | Leaves | Essential oil | Liver pain, constipation (orally) | |
| Canary Islands | Leaves | Infusion | Treatment of hemorrhoid (rectum) and hypertension (orally) | Darias et al. 1986 Darias et al. 1996 |
| Iran | Leaves | Infusion | Headache, liver pain, toothache | Mikaili et al. 2012 |
| Jordan | Olive oil | Balm | Anti-inflammatory and laxative (orally) | Al-Khalil 1995 |
| Turkey (Batman) | Leaves | Infusion | Defused | Yeşil and İnal 2019 |
| Turkey | Fruit | – | Skin cleanser | Fujita et al. 1995 |
| Turkey | Leaves, bark | Infusion | Diuretic, antipyretic, and antidiabetic, to treat constipation (orally) Antiseptic (externally) | Baytop 1999 |
| Turkey | Fruit and seed | Pressing | Rheumatism, pain, and swelling | Tuzlacı 2006 |
| Morocco | Fruit | – | Diarrhea, internal and stomach diseases, respiratory infections, liver disorders, mouth health, tonic, to treat constipation, haircare | Bellakhdar et al. 1991 |
| Greece | Fresh leaves | Boiled extract | Treatment of high blood pressure and asthma (orally) | Lawrendiadis 1961 |
| Saudi Arabia | Leaves | Chew | Antidiabetic and to treat hypertension | Ali et al. 2017 |
| | Katran | Liniment | Skin diseases of camels | |
| | Almahel | Mouth wash | Inflamed gums | |
| Arabia (Oman) | Fruit | Olive oil | Broken limbs | Ghazanfar and Al-Al-Sabahi 1993 |
| Algeria | Leaves and fruit | Infusion, Maceration | Hypotension and hypoglycemic | Amel 2013 |
| Palestinian | Leaves and fruit | Infusion, decoction | Antidiabetic | Ali-Shtayeh et al. 2012 |
| Palestinian (West Bank) | Fruit | Olive oil | Cleanser in soap | Zaid et al. 2017 |
| Brasil | Dried leaves | Boiled | Hypotension | Hashmi et al. 2015 |
| Armenian | Leaves | Extraction (hot water) | Diuretic | Hashmi et al. 2015 |
| Rodrigues Island | Leaves | Infusion | Hypotension and to treat hypercholesterolaemia | Samoisy and Mahomoodally 2015 |

–: no knowledge

**Fig. 30.4** Oleuropein

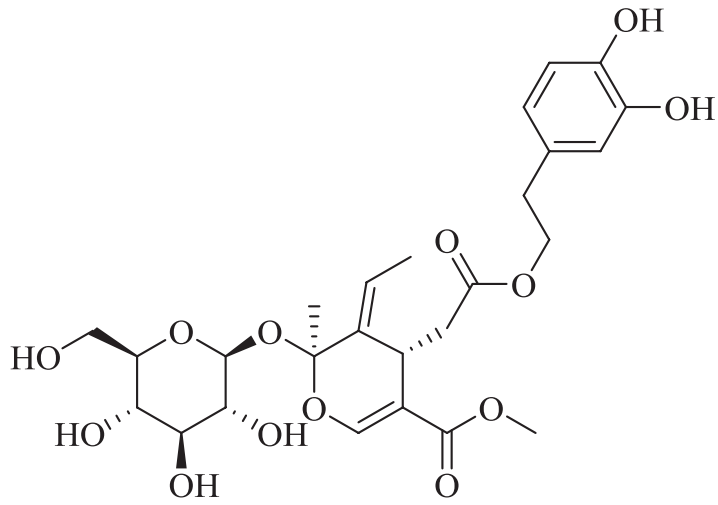
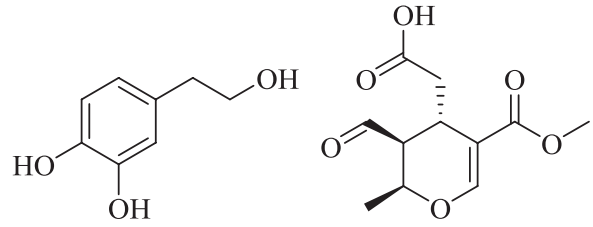



**Fig. 30.5** Hydroxytyrosol and elenolic acid




standard (Procopio et al. 2009; Haloui et al. 2011; Hashmi et al. 2015; PhEur 2017).

The oleuropein contains glucose, and it loses glucose at the end of the hydrolysis reaction, giving hydroxytyrosol and elenolic acid (Fig. 30.5). Hydroxytyrosol, namely "3,4-dihydroxytyrosol or 3,4-dihydroxyphenylethanol," is colorless and liquid. The compound can also be miscible with oily or aqueous matrices (Heilman et al. 2015).

The major compounds of the chloroform extract of *O. europaea* fruits skin are shown as maslinic and oleanolic acids (Fig. 30.6), which are pentacyclic triterpenes (Juan et al. 2006).

### 30.4.2 Olive Oil

The oil of *O. europaea* has extremely essential constituents in terms of diet and health. Olive oil can be obtained from *O. europaea* fruit using many different methods. Olive pomace oil is a mixture of refined olive oil and olive pomace. No refined oil can be found in extra virgin olive oil or virgin olive oil. Olive oil is a mixture of refined olive oils and virgin olive oils. Although these oils are similar in contents, their effects against diseases vary due to the different rates of the compounds in their chemical composition (Mateos et al. 2020).

Olive pomace oil has included in fatty acids, and its major compound is oleic acid (C18:1) (Fig. 30.7), a monounsaturated fatty acid. Olive oil also contains squalene, polyphenolics, tocopherols, pentacyclic triterpenes, sterols, and fatty alcohols as its minor components. The chemical compositions of olive oil have constructive effects, particularly in the prevention of cardiac problems (Mateos et al. 2020).

**(-)-**Oleocanthal, secoiridoid (mono-phenolic), has only been established in EVOO (Fig. 30.8) (Siddique et al. 2019).

### 30.4.3 Leaves

Various research has been carried out on the leaves of *O. europaea* until today. In these studies, several components were isolated using sol-

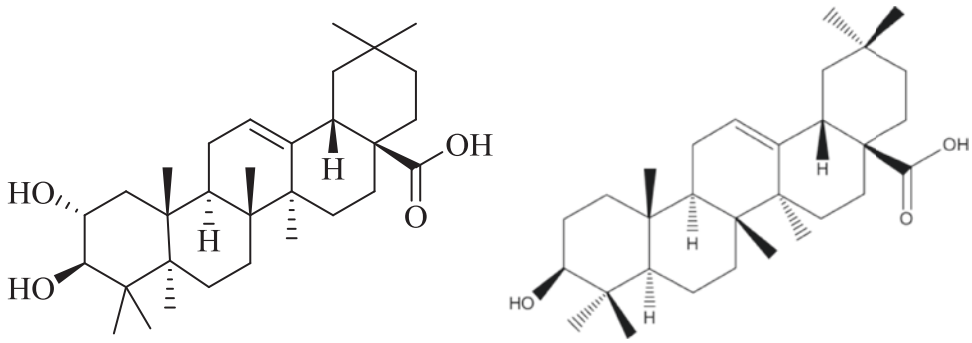
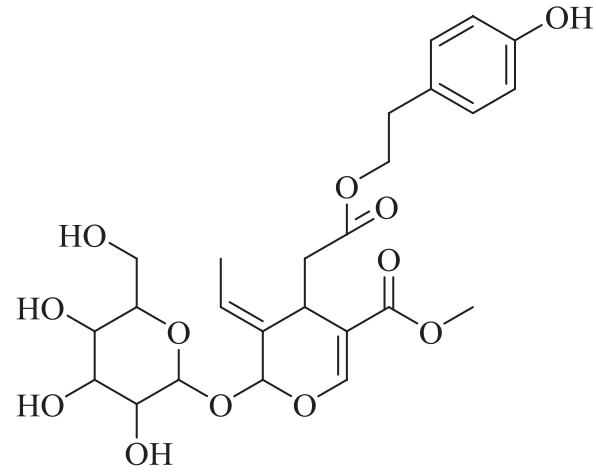



**Fig. 30.6** Maslinic and oleanolic acids

**Fig. 30.7** Oleic acid




vents and possess different polarities. The chemical structures of these compounds are composed of secoiridoids, triterpenoids, the other terpenes, lignans, flavonoids, and phenolics (Schumacher et al. 2002; Bouaziz et al. 2005; Karioti et al. 2006; Peralbo-Molina et al. 2012; Hashmi et al. 2015).

Secoiridoid derivatives, such as oleoside, comselogoside, and oleuropein, are purified from the methanol extract of olive leaves. Oleoside is detected in the water extract of olive leaves and fruits (Maestro-Duran et al. 1994; Karioti et al. 2006; Hashmi et al. 2015).

### 30.4.4 Stem

Ligstroside, mainly found in olive seeds and fruits, is found in the olive stem (Fig. 30.9). The ethyl acetate extract of olive stems yielded ligstroside-3′-O-β-D-glucopyranoside, 7-deoxyloganic acid, isojaspolyoside A, jaspolyanoside, and oleuropein-3″-methyl ether. Oleanolic acid demethyl has also been discovered as a novel compound (Servili et al. 1999; Pérez-Bonilla et al. 2011; Hashmi et al. 2015).

### 30.4.5 Bark

Lignanglycosides,suchas(+)-l-acetoxypinoresinol-4′-β-D-glucopyranoside,(+)-l-acetoxypinoresinol-4″-methyl ether-4′-β-D-glucopyranoside, and (+)-1-hydroxypinoresinol-4′-β-D-glucopyranoside, and lignans, such as (+)-1-acetoxypinoresinol, (+)-1-hydroxypinoresinol, (+)-1-hydroxypinoresinol-4″-O-methyl ether, (+)-1-acetoxypinoresinol-4″-O-methyl ether, (+)-cycloolivil, and (−)-olivil, as well as oleuropein, were purified from the ether extract of olive barks

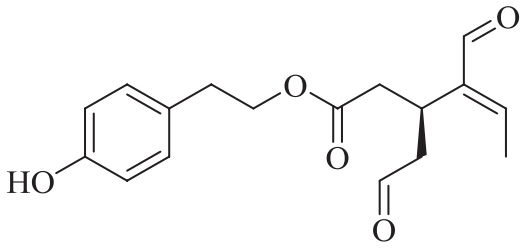



**Fig. 30.8** **(-)-**Oleocanthal

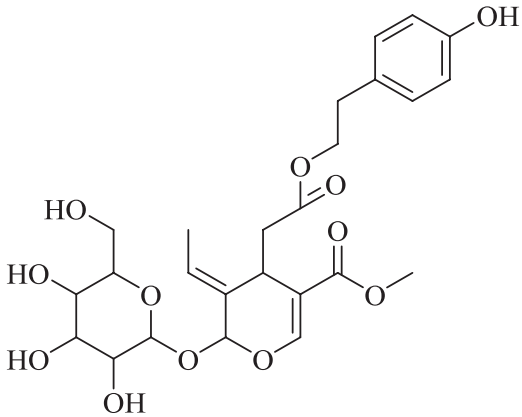



**Fig. 30.9** Ligstroside

(Chiba et al. 1979; Tsukamoto et al. 1984; Hashmi et al. 2015).

## 30.5 Pharmacological Activities

*Olea europaea* has long been investigated on anticancer, enzyme inhibition, antimicrobial, antioxidant, neuroprotective, gastroprotective, antihypertensive, cardioprotective, and antidiabetic effects using in vitro and in vivo bioassays (Al-Azzawie and Alhamdani 2006; Juan et al. 2006; Arsić et al. 2010; Teng et al. 2010; Diad et al. 2020).

The biological activities of the main compounds, especially oleuropein, hydroxytyrosol, and (-)-oleocanthal, isolated from olives have been examined by diverse researchers. These activities of oleuropein (Table 30.3), hydroxytyrosol (Table 30.4), and (-)-oleocanthal (Table 30.5), supported by in vitro and in vivo tests, are briefly summarized below.

Hydroxytyrosol is widely detected in olive oil and fruits. It is well-known for its potent antioxidant properties. Therefore, it has also a protective effect against high LDL (Raederstorff 2009; Heilman et al. 2015).

The other compound found in olive oil is **(-)-**oleocanthal which also has been researched on various biological activities against different diseases.

## 30.6 Clinical Research

Several clinical trials have been reported regarding the main ingredient oleoresin and the fruit, oil, tea, and tree of *O. europaea* (Table 30.6). These studies are compatible with their ethnobotanical applications, and the results indicate that it has meaningful use in conventional medicine. It has also been found to be safe to use during pregnancy (SoltaniPoor et al. 2012).

## 30.7 Toxicity

There are limited toxicity studies on the extracts and main components of *O. europaea* leaves. Antiviral activity and cytotoxicity of olive leaf extract have been carried out. While an antiviral effect was observed at 1 mg/mL and high concentration, the cytotoxic effect against Vero cells was detected at 1.75 mg/mL concentration (Motamedifar et al. 2007).

Olive leaves extract, prepared with 10% decoction, was investigated for hypocholesterolemic effect in rats. According to the findings, the hypocholesterolemic effect was observed low, and there was no toxic effect (Bennani-Kabchi et al. 2000).

Oleanolic and maslinic acids, purified from the chloroform fractions of olive fruits, their cytotoxicities against colon cancer cell lines, were investigated. Consequently, oleanolic (55.5 μmol/L) and maslinic (150 μmol/L) acids inhibited the cell proliferation at nontoxic concentrations. In this study, it was suggested that colon cancer cells are restored apoptosis at without toxic effects (Juan et al. 2006).

**Table 30.3** Biological effects of oleuropein

| Biological effects | References |
|---|---|
| Antioxidant activity | Visioli et al. 1998; Al-Azzawie and Alhamdani 2006; Jemai et al. 2009 |
| Anti-inflammatory activity | Procopio et al. 2009; Haloui et al. 2011; Larussa et al. 2017 |
| Antidiabetic activity | Al-Azzawie and Alhamdani 2006 |
| Analgesic activity | Haloui et al. 2011 |
| Antiulcerogenic activity | Romero et al. 2007; Larussa et al. 2017 |
| Stimulation of nitric oxide synthase | Visioli et al. 1998 |
| Anticancer against human colorectal cancer | Cárdeno et al. 2013 |
| Immunomodulatory activity | Randon and Attard 2007 |

**Table 30.4** Biological effects of hydroxytyrosol

| Biological effects | References |
|---|---|
| Antioxidant activity | Visioli et al. 2001; Jemai et al. 2009; Bayram et al. 2012 |
| Anti-inflammatory activity | Bitler et al. 2005; Richard et al. 2011; Bernini et al. 2013 |
| Maintains mitochondrial function and biogenesis | Hao et al. 2010 |
| Prevents the risk of metabolic syndrome | De Bock et al. 2013 |
| Inhibits apoptosis | Yang, et al. 2002 |
| Inhibition of platelet aggregation | Petroni et al. 1995 |
| Stimulation of nitric oxide synthase | Visioli et al. 1998 |
| Antithrombotic activity | Leger et al. 2005 |
| Ameliorate osteoarthritis | Bitler et al. 2007 |

**Table 30.5** Biological effects of (-)-oleocanthal

| Biological effects | References |
|---|---|
| Antioxidant | Siddique et al. 2019 |
| Antibacterial | Siddique et al. 2019 |
| Anti-inflammatory | Beauchamp et al. 2005; Parkinson and Keast 2014 |
| Analgesic activity | Haloui et al. 2011 |
| Anti-Alzheimer | Abuznait et al. 2013 |
| Antiulcerogenic activity | Romero et al. 2007 |
| Anticancer activity against breast and prostate cancers | Shattuck et al. 2008; Elnagar et al. 2011; Siddique et al. 2019 |
| Anticancer activity against gastric cancer | Chen et al. 2012 |
| Anticancer activity against lung cancer | Engelman et al. 2007 |
| Anticancer activity against human hepatocellular carcinoma | Pei et al. 2016 |

The water extract of *O. europaea* leaves was tested on the genotoxicity in vitro and in vivo bioassays. While no genotoxicity was observed in in vitro studies, the genotoxic concentration limit was found to be 2000 mg/kg in in vivo studies with mice (Clewell et al. 2016).

Leaves of *O. europaea* have been published in an assessment report by the European Medicines Agency (EMA). According to the report tested on rats, it was reported that $LD_{50}$ value of *O. europaeae* leaves extract is >3000 mg/kg with oral dose, and its $LD_{50}$ value is 1300 mg/kg i.p. use (EMA 2017). In mice, $LD_{50}$ value of *O. europaea* subsp. *africana* leaves extract with methanol is detected as 3475 mg/kg (p.o. administration) (Amabeoku and Bamuamba 2010).

## 30.8 Commercial Products

Olive oil is commercially used as both nutrition and medicine. When considered as nutrition, the first country in olive oil production is Spain. The other countries with the most production are Italy and Greece (Ghanbari et al. 2012). Olive oil is also found in products used for intravenous nutrition. One of these products is ClinOleic 20% (Baxter Healthcare Ltd). Olive oil is used as a medicine to remove and soften earwax. Patients apply it as drop and spray forms. The drop has been licensed by at least nine companies. The commercial name of the spray form is Earol olive oil ear spray (HL Healthcare Ltd). The products are recommended to be used twice a day for children and adults (MedicinesComplete 2021).

Bonolive® and Olecol®, clinically been developed as an antidiabetic product, consist of the extract of olive leaves (Kerimi et al. 2019). There must be followed certain requirements for the extracts obtained from *O. europaea* that complies with pharmacopoeia standards. According

**Table 30.6** Clinical studies of *Olea europaea*

| Disease | Participants number | Product | Dose of administration | Therapy (days) | Effects | References |
|---|---|---|---|---|---|---|
| Coronary heart disease | 94 | Olive oil | 50 g daily<br>Virgin olive oil | 28 | HDL-C ↑<br>LDL-C ↓<br>TC/HDL-C ↑ | Khaw et al. 2018 |
| Cardiovascular disease | 125 | Dietary supplement (BruMeChol™) | Fruit of *Olea europaea*, vitamin K2 and *Citrus bergamia* fruit<br>Twice a day | 84 | Total cholesterol levels ↓<br>Inflammatory biomarkers ↓ | Bonfigli et al. 2020 |
| Hypertension | 60 | Leaf extract | 250 mg | 84 | Interleukin-6 ↓<br>Interleukin-8 ↓<br>Inflammatory biomarkers (Tumor necrosis factor-α) ↓ | Javadi et al. 2019 |
| Post-episiotomy pain | 73 (Women) | Olea ointment | 2.5 and 4 g | 28 | Episiotomy pain ↓ | Jafarzadeh-Kenarsari et al. 2019 |
| Rhinoconjunctivitis | 47 (Women) | Extract | 20–1000 (TSU/mL) | 119 | SIgG and sIgG4 ↑ | De San Pedro et al. 2020 |
| Pre-hypertension | 60 | Leaf extract | 136 mg oleuropein | 28 | LDL cholesterol<br>Plasma total cholesterol<br>Triglycerides | Lockyer et al. 2017 |
| Upper respiratory illness | 32 (Men) | Olive leaf extract | 100 mg daily oleuropein | 63 | Sick days (28%) ↓ | Somerville et al. 2019 |
| Diabetis mellitus | 90 | Leaf extract (Bonolive®, Olecol®) | 125 mg–100 g orally | – | Inhibited Caco-2 monolayers, sucrase, maltase | Kerimi et al. 2019 |
| Hematological disease | 31 (Women) | Olive leaf tea | 5 mg/mL daily | 84 | Hematocrit ↑ | Ferdousi et al. 2019 |
| Rheumatoid arthritis | 56 | Olive oil and fruit | Olive:olive oil:fig oil (2:5:1 w/w)<br>15 g daily | 10 | Total cholesterol (TC) ↓<br>Triglyceride (TG) ↓<br>Low-density lipoprotein cholesterol (LDL-C) ↓ High-density lipoprotein cholesterol (HDL-C) ↑ | Bahadori et al. 2016 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Fattening performance | 36 Male Lambs | Olive cake | 12.5 and 25% | 56 | Total polyunsaturated fatty acids (Σ PUFA) ↑<br>Total monounsaturated fatty acids (Σ MUFA) ↑<br>Total saturated fatty acids (Σ SFA) ↑ | Ozdogan et al. 2017 |
| Ulcerative colitis | 14 | Oleuropein | 3 mM | – | CD3, CD4, CD20 cells ↓<br>CD68 cell ↑<br>Cyclooxygenase (COX)-2 ↓<br>Interleukin (IL)-17 ↓ | Larussa et al. 2017 |
| Burn | 30 | Ointment olive | (8.5%) Ointment olive | 12 | Tissue repair ↑ | Zahmatkesh et al. 2015 |
| Osteoporosis | 64 | Olive extract | 250 mg/day | 12 months | LDL-C ↓<br>TC ↓ | Filip et al. 2015 |
| Striae gravidarum (SG) (during pregnancy) | 100 | Olive oil | 1 cc topically olive oil twice a day | 18–20th gestational week to 38–40th week | SG severe ↓ | SoltaniPoor et al. 2012 |

↓: decrease
↑: increase

to the monograph, European Pharmacopoeia 9.0, the dried extract of *O. europaea* leaf prepared by using ethanol (65–96% v/v), need to possess oleuropein with minimum of 16.0% (PhEur 2017).

As for the bioavailability of the olive phytoconstituents, polyphenolic compounds from olives are absorbed from the intestinal lumen. ADME is eventually excreted as innocuous metabolites (EFSA et al. 2020). ADME of phenolic compounds has been studied in products containing oil, fruit, or leaf of *O. europaea*. Phenolic components of olive oil are absorbed in 55–66% from the intestines. Hydroxytyrosol, which is a phenolic compound, is 99% bioavailable when taken orally with olive oil and 75% when taken with water. In a study, it was found that the bioavailability of oleuropein is weak in the intestinal system (Kendall et al. 2009; Heilman et al. 2015).

## 30.9 Conclusion

In more than ten countries, *O. europaea* has commonly been used as a traditional medicine for a wide variety of diseases, both internally and externally. *Olea europaea* leaves and fruits have generally been used in folk medicine against various diseases, such as hypertension, diabetes, rheumatism, and hypercholesterolaemia. *Olea europaea* is investigated for biological activities as in vitro and in vivo such as anticancer, enzyme inhibition, antimicrobial, antioxidant, neuroprotective, gastroprotective, antihypertensive, cardioprotective, and antidiabetic activities. Also, numerous clinical trials and studies have been reported regarding the main ingredient oleoresin and the fruit, oil, tea, and tree of *Olea europaea*. It was also known that their findings have been supporting the traditional uses of *O. europaea*.

In connection with the studies carried out, there are many licensed products on the market regarding olive leaf and oil. There are also clinical studies on these products. The pharmaceutical formulations from olive products have clinically been developed due to having an antidiabetic effect.

Although there are several studies on the clinical trials for the usages of olives, they are still not safe and effective products on the market enough today. Considering the importance of olive due to presenting the bioactive components, we suggest that it still need performing research on olives to develop pharmaceutical formulations.

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# *Papaver somniferum* L.

# 31

Ömerül Faruk Tavlı

**Abstract**

*Papaver somniferum* L., opium poppy, (Papaveraceae) has been used for several purposes since ancient times. *P. somniferum* L. is an annual herb that bears alkaloids such as morphine, codeine, noscapine, papaverine, etc., especially in its capsule. Thanks to these bioactive compounds, it has several therapeutic effects. Because of that, it has also been used against several illnesses for centuries. Until today, countless studies have been carried on *P. somniferum* L. and its bioactivities. These studies are focused on the isolation of bioactive alkaloids and synthesizing their various semi-synthetic and synthetic derivatives. Along with identification and bioactivity tests of alkaloids of opium poppy, their clinical behaviors were also examined by researchers from the whole world. Today, opium poppy, especially its alkaloids, became an indispensable part of medicine.

The objective of this chapter is to discuss *Papaver somniferum* L. with all aspects.

**Keywords**

*Papaver somniferum* L. · Opium poppy · Opiate · Morphine · Codeine · History of opium

## 31.1 Introduction (Occurrence/Habitat, Importance, Objective of This Chapter)

*Papaver somniferum* L., opium poppy, (Papaveraceae) is one of the oldest medicinal plants and has been used for medicinal purposes since ancient times. This annual plant is approximately 150 cm in height. Its stems and leaves are greyish-blue; the leaves are approximately 10 cm in length, entire, sessile, and amplexicaul. Fruits are characteristic spherical capsules. These capsules bear at its apex a flat disc formed by the union of the radiating stigmas. The hairless capsule contains latex and plenty of seeds. According to cultivars, botanical features such as margin of leaves, flower color, capsule shape, or seed color of the plant may differ. The margin of leaves is usually dentate; the flower color may be attractive white, red, or purplish; the seed color usually greyish-black, and the capsule shape is usually egg-shaped (Wyk and Wink 2004; Evans 2009).

It is postulated that the word "opium" is derived from the Greek words opos (juice) and opion (poppy juice). There is yellowish-white

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latex in the anastomosing system of latex vessels of the capsule. In spring, while the opium poppy capsules are still raw, shallow incisions are made horizontally early in the morning. When the latex contacts the oxygen, its color turns from white to brownish-black and it hardens. The exuded latex is scraped off with a special knife before the sunset. The hardened and brownish-black latex is called raw opium. The collected raw opium is kneaded by hand, sun-dried, wrapped with poppy leaves, and then presented to commerce. 20–30 mg raw opium corresponding to 2–5 mg of morphine are obtained from per capsule (Sandberg and Corrigan 2001; Schiff 2002).

*P. somniferum* has historical importance for pharmaceutical science and Anatolia. Anatolia is the gene center of *P. somniferum*, which is also an important portion of the Anatolian culture since it has been cultivated in Anatolia for centuries. The most ancient written source on *P. somniferum* is Sumerian cuneiform tablets and they referred it as "the joy plant". The clay tablets of Hittites found in Boğazköy (Hattuşaş) showed that Hittites also cultivated *P. somniferum* and referred to it as "hassikka." "Hassikka" means "to sleep" and "to tranquilize" in the Hittite language; besides, it is probably the origin of the Turkish name "Haşhaş". Materia Medica written by Dioscorides in first century A.D. is the first comprehensive book about Anatolian medicinal plants. The cultivation of *P. somniferum* and preparation of opium and meconium for therapeutic purposes are mentioned in this book. In the Ottoman Empire period, travelers such as P. Belon, J. P. de Tournefort, G. A. Olivier, and Evliya Chelebi also mentioned its cultivation, traditional use, and trade in Anatolia in their itineraries (Ertem 1974; Mat 2010a; Baser and Arslan 2015).

In 1933, the International Opium Convention was signed by Turkey and the cultivation areas of *P. somniferum* were restricted and opium production was controlled. Additionally, opium production has also been forbidden in Turkey since 1972 (Mat 2010a; Baser and Arslan 2015).

Nowadays, various varieties and subspecies of *P. somniferum* are cultivated to obtain edible seeds and seed oil and to extract bioactive opium alkaloids such as morphine, codeine, papaverine, noscapine (narcotine), and narceine (Pushpangadan and Singh 2000).

The objective of this chapter is to discuss *Papaver somniferum* L. with all aspects.

### 31.1.1 Vernaculars

***Arabic:*** Abou En Noum, Abunom, Afiun, Bazrul Khash-Khash, Bizrul Khashkhash**;** ***Chinese:*** Ying Suhk, Ying Tzu Su**;** ***English:*** Opium Poppy, Peony Poppy, White Garden Poppy, White Poppy**;** ***French:*** Pavot, Pavot blanc, Pavot des jardins, Pavot à opium. Pavot somnifère**;** ***German:*** Gartenmohn, Mohn, Ölmohn, Opiummohn, Schlafmohn**;** ***Greek*****:** Aphioni, Agria, Mekon**;** ***Hindi:*** Afeem, Afim, Afin, Afyun, Kashkash,Tukhm Khashkash**;** ***Japanese*****:** Keshi, Papi**;** ***Korean*****:** Apyeon, Apyon, Popi**;** ***Portuguese:*** Dormideira, Papoila**;** ***Russian****:* Mak Snotvornyj, Opijnyj Mak**;** ***Spanish:*** Ababa, Amapola, Amapola Real, Semillas De Amapola**;** ***Turkish:*** Haşhaş, Haşşaş, Haşikeş, haşgeş, haşeş, Afyon Haşhaşı, Gelincik çiçeği (Baytop 2007; Lim 2016; Akbar 2020).

### 31.1.2 Taxonomical Classification

***Kingdom:*** Plantae**;** ***Subkingdom:*** Tracheobionta**;** ***Superdivision:*** Spermatophyta**;** ***Division:*** Magnoliophyta**;** ***Class:*** Magnoliopsida**;** ***Subclass:*** Magnoliidae**;** ***Order:*** Papaverales**;** ***Family:*** Papaveraceaae**;** ***Genus****: Papaver* L.**;** ***Species:*** *Papaver somniferum* L.

## 31.2 Distribution and Status of Species

*Papaver somniferum* is not generally found wild, but it can be cultivated in such diverse areas as South and North America, Northeast Africa, Australia, Europe, and Japan. The plant is generally distributed in north temperate and subtropical regions. (Kapoor 1995; Pandey et al. 2019).

Today, *P. somniferum* is cultivated by only legal cultivator countries such as Turkey, India, Australia, Spain, France, and Hungary under the supervision of the United Nations due to its narcotic nature (Pandey et al. 2019; Yazici and Yilmaz 2021).

There are two subspecies in Anatolia, namely, *P. somniferum* subsp. anatolicum M. Veselovs and *P. somniferum* subsp. subspontaneum M. Veselovs, each of these subspecies has white and purple varieties (Mat 2010a).

## 31.3 Comparison of Traditional/Ethnomedicinal/Local Uses: In Turkey and Throughout the World

*Papaver somniferum* L. has been in use as remedy since ancient times. Antique Egyptians used it to help children stop crying and to relief pain caused by worms. The narcotic effect of opium was mentioned by the Greek biologist Theophrastus for the first time. Hippocrates, the father of medicine, remarked on its soporific effect. Galen, the father of pharmacy, prescribed a kind of suppository that contained an aqueous infusion of opium, against intestinal pain and diarrhea. Avicenna mentioned various effects of opium such as analgesic, hypnotic, cognitive, antitussive, etc. Paracelsus referred to it as the "stone of immortality" and he prepared various drugs containing opium. In Ottoman Empire, it was used as sleep-inducing pastes for children as well as a kind of lollipop made of opium fruit was used for the same purposes. In ottoman medicine, it was used as an analgesic drug in some tinctures or extracts. Thomas Sydenham, the father of clinical medicine, developed Laudanum, which is a mixture of opium, saffron, cinnamon, clove, and sherry, as an analgesic drug to use during surgery. Sydenham's student named Thomas Dover introduced opium power which is diaphoretic to be used against febrile illnesses and pain. Throughout history, various preparations including opium were produced for various purposes. These are mainly Theriac, Paracelsus pills of laudanum, laudanum tincture, Quaker's black drop (namely black drop or Lancaster), paregoric elixir, Godfrey's cardial and Dalby's carminative, Poppy tea, pills of opium, etc. (Booth 1996; Mat 2010a; Presley and Lindsley 2018).

In addition to its historical use, various parts of *P. somniferum* L. have been reported to have ethnopharmacological uses for numerous healing purposes. Ethnobotanical records of *P. somniferum* L. are summarized in Table 31.1.

Numerous uses have been reported in different complementary and alternative medicine systems as well.

In homeopathy, it is used as a remedy against insomnia, narcolepsy, some respiratory problems, constipation, shock as well as used to recover stroke paralysis, brain injuries, delirium tremens, and alcohol withdrawal (Lockie 2006; Balkrishna and Misra 2018).

In ayurvedic medicine, it is used against insomnia, epilepsy, psychosis, paralysis, fatigue, unconsciousness, mental weakness, meningitis, delirium, asthma, diarrhea, anemia, chest pains, dysentery, and fever. It is used also as an analgesic, digestive, aphrodisiac, antitussive, deliriant, excitant, intoxicant, astringent, fattening, stimulant, and tonic. Purified opium is used in such formulations as Ahifenasav (liquid preparation), Karpur Ras, Nidroday Vati, etc. (Savithramma et al. 2007; Mani and Dhawan 2014; Lim 2016; Balkrishna and Misra 2018).

In Unani medicine, it is used against diarrhea, dysentery, influenza, cough and dry cough, asthma, insomnia, leucorrhea, burning in bladder, fever, anemia, headache, conjunctivitis, and bilious diarrhea (Masihuddin et al. 2018; Chaudhary et al. 2019).

*P. somniferum* L. is used for not only medicinal but also nonmedicinal purposes. Its seeds have been used as a food ingredient in cuisines as well as obtainment of seed oil. The oil is used as a massage oil in aromatherapy, the oil cake is used as animal feed, and the fresh leaves are used as salad ingredient as well (Baser and Arslan 2015; Kujawska et al. 2017).

**Table 31.1** Ethnobotanical records

| | Location | Part used | Therapeutic effect | Preparation | Administration | Reference |
|---|---|---|---|---|---|---|
| 1 | Turkey | Fruits | Against diarrhea | Decoction | Internal | Bulut et al. (2017) |
| 2 | Turkey | Fruits | Sedative | Decoction | Internal | Bulut et al. (2017) |
| 3 | Turkey | Seeds | Wound healing | Pounded | External | Honda et al. (1996) |
| 4 | Turkey | Fruits | Analgesic | Decoction | Internal | Fakir et al. (2009) |
| 5 | Turkey | Fruits | Antitussive | Dried | Internal | Kültür (2007) |
| 6 | Turkey | Seeds | AgainstPeptic Ulcer | Dried and mixed with sugar | Internal | Yeşilada et al. (1999) |
| 7 | Greece | Seeds | Calmative | Decoction | Internal | Valiakos et al. (2015) |
| 8 | Italy | Fruits | Sedative | Infusion | Internal | Tuttolomondo et al. (2014) |
| 9 | Uzbekistan | Fruits; latex | Against cough, cold, flu | A piece of crushed fruit or a small piece of latex | Internal | Sezik et al. (2004) |
| 10 | Pakistan | Seeds; fruit; pericarp | Against Cough, diarrhea, menstrual problems, high blood pressure | Decoction | Internal | Bibi et al. (2014) |
| 11 | Pakistan | Fruits; seeds; latex; flowers | Antidiabetic | Boiled | Internal | Ozturk et al. (2018a) |
| 12 | Pakistan | Fruits; seeds | Antihypertensive | Decoction | Internal | Ozturk et al. (2018b) |
| 13 | India | Seeds | Against asthma | Powder | Internal | Savithramma et al. (2007) |
| 14 | India | Latex | Abortifacient; against pain, cholera, and dysentery | – | – | Rao and Jamir (1982) |
| 15 | India | Seeds | Against diarrhea, dysentery irritating cough | Infusion | Internal | Chinnappan (2012) |
| 16 | Thailand | Latex | Analgesic | Dried | Internal | Anderson (1986) |
| 17 | China | Seeds | Against cough | – | Internal | Lee et al. (2008) |
| 18 | Catalonia | Flower; fruit; seeds | Analgesic, sedative | – | – | Gras et al. (2019) |
| 19 | Bosnia and Herzegovina | Fruit | Against diseases of the nervous system and psyche | Infusion | Internal | Savić et al. (2019) |
| 20 | Spain | Fruit | Against insomnia | Decoction | Internal | Benítez et al. (2010) |

## 31.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques

### 31.4.1 Opium

The major alkaloid in *P. somniferum* L. is morphine, whose isolation is a milestone for pharmacognosy. Morphine is the first isolated active ingredient from a plant. German pharmacist Friedrich Sertürner isolated it in 1805 and called it "morphium" as a tribute to the Greek god of dreams, Morpheus (Beyer et al. 2009; Mat 2010b).

Morphine, phenanthrene derivative, is classified as morphinan type alkaloid as well as codeine and thebaine. Another group is benzylisoquinoline type alkaloids such as papaverine, noscapine, and narceine. Morphinan type alkaloids are strong base and highly toxic molecules, while benzylisoquinoline type alkaloids are weak bases and mildly toxic molecules. Apart from these important groups, opium also contains relatively fewer quantities of different groups of alkaloids: benzyltetrahydroisoquinoline type (e.g., laudanine and laudanosine), aporphine type (e.g., isoboldine and corytuberine), ptotoberberine and tetrahydroberberine type (e.g., canadine and berberine), protopine type (e.g., protopine and cryptopine), phthalide-isoquinoline type (e.g., narcotine and narcotoline), rhoeadine type (e.g., glaudine), benzophenanthridine type (e.g., sanguinarine), morphinandienone type (e.g., salutaridine), and tetrahydroisoquinoline type (e.g., hydrocatarinine), respectively. The alkaloids occur as salts of organic acids such as lactic, fumaric, oxaloacetic, and most of all meconic acid (more than 5%). Opium also contains water (approximately 10–15%) and sugars (approximately 20%) (Bruneton 1993; Kapoor 1995).

There are basically three techniques which are used to obtain alkaloids from opium. The methods are based on extraction with ethanol in the acidic environment, extraction with organic solvent in the alkaline environment, or ion exchange resin method (Baytop 1986; Bruneton 1993).

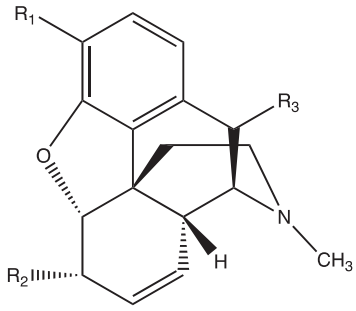
The chemical structures of major alkaloids are shown in Fig. 31.1.

### 31.4.2 Seed and Seed Oil

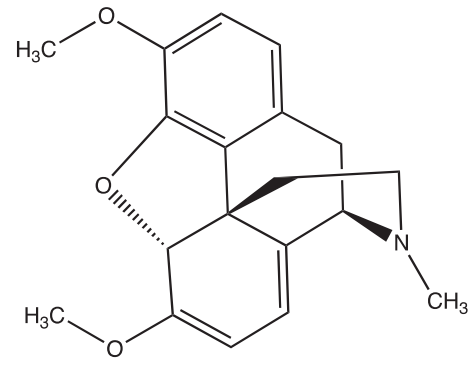
The edible seed has a great deal of nutrition value and energy yield. According to a study on seven cultivars in Turkey, the seeds contain moisture (3.4–4.8%), crude protein (11.9–13.6%), crude ash (4.92–6.25%), crude fiber (22.6–30.1%), crude energy (6367.0–6740.5 kcal/100 g), crude oil (32.4–45.5%), HCl-soluble ash (0.72–1.68%), respectively. Additionally, they reported that all cultivars were rich in P, K, Ca, Mg, Na, and Fe contents, while poor in Cd, Cr, Ni, and Pb contents (Musa Özcan and Atalay 2006; Muthukumaran et al. 2019).

The poppy seeds are rich in oil, containing approximately 50% of edible oil with a pleasant odor and almond-like flavor (oil yield depends on the cultivar, cultivation location, etc.). The poppy seed oil is rich in polyunsaturated fatty acids such as linoleic acid (53–74%), oleic acid (13–24%), palmitic acid (8–19%), stearic acid (less than 1%), and linolenic acid (less than 1%). It contains also phenolics (quercetin, apigenin, vanillic acid, ferulic acid, *p*-hydroxybenzoic acid, cinnamic acid, *p*-coumaric acid, and protocatechuic acid, etc.), tocopherols (γ-tocopherol, ß-carotene, lutein, etc.), phytosterols (β-sitosterol, campesterol, δ-5-avenasterol, stigmasterol), and minerals (manganese, copper, magnesium, and zinc). Because of its nutrient value, it is a good alternative for sunflower oil in dietary (Pushpangadan et al. 2012; Rahimi et al. 2015; Aksoylu Özbek and Günç Ergönül 2020; Dąbrowski et al. 2020).

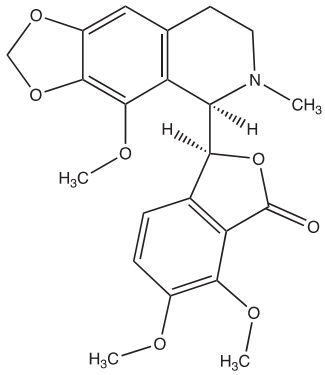
The poppy seed oil can be obtained via the cold or hot press. Additionally, it can also be extracted through the use of such organic solvent as petroleum ether (Baytop 1986; Bruneton 1993).



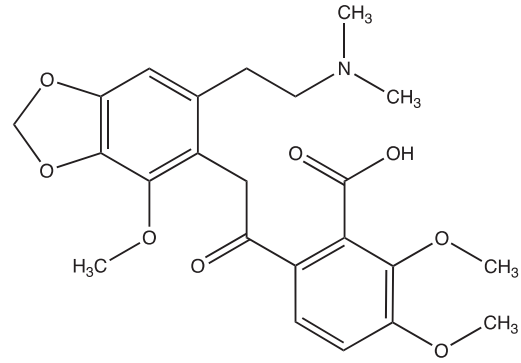

Morphine : $R_1$= OH, $R_2$=OH, $R_3$= H
Codeine. : $R_1$= OH, $R_2$=OH, $R_3$= H



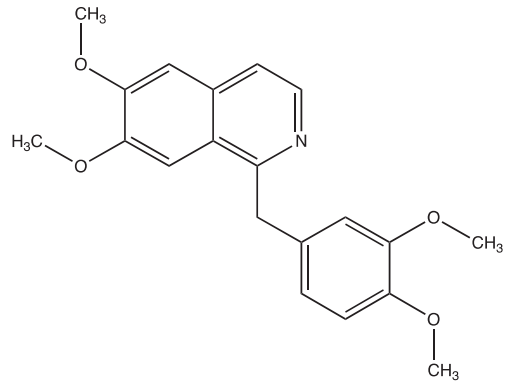

Thebaine




Noscapine (Narcotine)




Narceine




Papaverine

**Fig. 31.1** Chemical structures of major alkaloids of *P. somniferum* L.

## 31.5 Scientific Evidences: Pharmacological Activities

### 31.5.1 Analgesic Effect

As analgesic agent, opium use dates to ancient times but the first references on analgesic effect of morphine, which is the major alkaloid responsible for analgesic effect, began in the 1820s (Devereaux et al. 2018).

Morphine, morphine-6-phosphate and morphine like molecules have agonist effect at μ, κ, and *δ* opioid receptors (namely, MORs, KORs, DORs, respectively). When morphine binds the MORs, analgesia, euphoria, respiratory depression, myosis, reduced gastrointestinal motility, nausea, and sedation occur. Morphine also binds other receptors, but the affinity of morphine for MORs is approximately ten folds of other two receptors. KORs are responsible for peripheral analgesia and dysphoria (sometimes cause hallucinations); on the other hand, DORs are responsible for supraspinal and spinal analgesia and reducing gastrointestinal motility and secretion (Hosztafi 1998; Sverrisdóttir et al. 2015).

Codeine has analgesic activity; however, its activity and its affinity on μ opioid receptor are less than that on morphine. Codeine which is structurally close to morphine shows this effect via converting to morphine and its metabolite morphine-6-phosphate in human (De Craen et al. 1996; Schiff 2002; Presley and Lindsley 2018).

### 31.5.2 Antitussive Effect

Various findings show that the opiates such as morphine and codeine which have binding ability to MORs and KORs cause not only analgesia, but also relief from cough. Especially, codeine is used as a cough suppressant drug. Molecules affect respiratory center and cause decrease in secretions and bronchoconstriction on smooth muscles by binding to MORs and KORs (Kamei 1996; Reynolds et al. 2004).

Recent studies carried out on noscapine after the discovery of its antitussive effect in 1930 showed its highly efficacious antitussive and, unlike codeine, lacking analgesic, sedative, hypnotic, and euphoric effects. Its nonaddictive nature makes it safer than codeine. Unfortunately, its mechanism is not crystal clear, but it is demonstrated that the molecule shows the effect via DORs and B2 receptor bindings (Chen et al. 2015; Rida et al. 2015).

### 31.5.3 Antispasmodic Effect

Papaverine is discovered to be effective against pathological spasms of smooth muscles by in vivo tests in 1914. Some studies carried on papaverine showed that papaverine has antispasmodic effect on especially pulmonary and coronary artery and great vessels. These hypotensive and smooth muscle relaxation effects are systemic and nonspecific. Papaverine, which inhibits phosphodiesterase, has been postulated to show relaxing effect through upregulation of intracellular cAMP levels. It was also discovered to show selective inhibitor effect ($EC_{50}$ = 36μM) on phosphodiesterase PDE10A subtype which is mainly found in brain striatum. Additionally, papaverine was discovered to stimulate vascular L-type $Ca^{2+}$ channel via a PKA-dependent mechanism, thus antagonizing its main vasodilator activity ($pIC_{50}$ of 5.99 ± 0.05, n = 13(3); $P < 0.05$) (Hosztafi 1998; Fusi et al. 2016; Kang et al. 2018).

### 31.5.4 Anticancer Effect

Noscapine was reported to inhibit the progression of various cancer types in vitro and in vivo such as lymphoma, breast cancer, melanoma, ovarian carcinoma, glioblastoma, colon cancer, human nonsmall cell lung cancer, and prostate cancer after the discovery of its antitumor effect in 1998. Recent studies have revealed that noscapine shows its anticancer effect by the activation of different apoptotic pathways. Noscapine binds to tubulin stoichiometrically like tubulin-targeted antimitotic agents such as taxanes, vincas, and colchicine. Having low toxicity on normal cells and a unique binding site on ß-tubulin make noscapine and its analogs impor-

tant molecules for cancer studies (Zhou et al. 2002; Newcomb et al. 2006; Mahmoudian and Rahimi-Moghaddam 2008; Alisaraie and Tuszynski 2011; Ghaly et al. 2016; Mir et al. 2019).

Ke et al. discovered that noscapine inhibited in vitro growth of E.G7-OVA lymphoma cells ($IC_{50}$ = 10μM) as well as noscapine at 3 mg/day inhibited in vivo growth of E.G7-OVA lymphoma cells on C57BL/6 mice in comparison with the control group ($P < 0.001$). They also revealed oral administration of noscapine to more tolerable than parenteral administration. Landen et al. discovered that noscapine inhibited in vitro growth of murine melanoma B16LS9 cells ($IC_{50}$ = 50μM) as well as noscapine inhibited in vivo growth of Murine B16LS9 melanoma cells on C57BL/6 mice. At the end of 17 days in this study, tumor growth was inhibited by noscapine at 300 mg/kg/day by 85% of tumor volume compared with taxol and combination of taxol and noscapine. Landen et al. discovered that noscapine at 300 mg/kg/day inhibited in vivo growth of C6 glioma cells on eight-week-old athymic female mice (nu/nu) ($P \leq 0.01$). At the end of 21 days in this study, tumor growth was inhibited by noscapine at 300 mg/kg/day by 85% of tumor volume compared with the control group (1510 ± 237 and 3739 ± 586 $mm^3$, respectively; n = 12 and 11 respectively). Yang et al. discovered that noscapine inhibited in vitro growth of HT-29, LoVo, and SW480 colon cancer cells ($IC_{50}$ = 95μM, 75μM, 207μM, respectively) as well as noscapine inhibited in vivo growth of LoVo colon cancer cells on nude mice in a dose-dependent manner ($P < 0.005$). At the end of 36 days in this study, tumor growth was inhibited by noscapine at 10, 20, and 40 mg/kg/day by 32%, 44%, and 68% of tumor volume, respectively, compared with the control group (1480 $mm^3$). Jackson et al. discovered that noscapine inhibited in vitro growth of H460 human nonsmall cell lung cancer cells ($IC_{50}$ = 34.7 ± 2.5μM) as well as oral noscapine at 300 mg/kg/day inhibited in vivo growth of H460 human nonsmall cell lung cancer cells on nude mice ($P < 0.05$). At the end of 28 days in this study, tumor growth was inhibited by noscapine at 300, 450, and 550 mg/kg/day by 49%, 65%, and 86% of tumor volume, respectively. Xu et al. discovered that noscapine inhibited in vitro growth of HepG2 and Huh7 hepatocellular carcinoma cells ($IC_{50}$ = 50.53μM, 74.14μM, respectively) as well as noscapine at 300 mg/kg inhibited significantly in vivo growth of HepG2 hepatocellular carcinoma cells in mouse. At the end of 2 weeks in this study, none of the mice that were treated with noscapine died (Ke et al. 2000; Landen et al. 2002, 2004; Jackson et al. 2008; Yang et al. 2012; Xu et al. 2016).

Additionally, noscapine was also discovered to inhibit in vitro growth of MCF-7 breast cancer cells ($IC_{50}$ = 42.3μM); Renal 1983 bladder cancer cells ($IC_{50}$ = 39.1μM); 1A9, 1A9PTX10, and 1A9PTX22 ovarian carcinoma cells ($IC_{50}$ = 18.2μM, 22.7μM, and 15.4μM, respectively); U87MG, U118MG, LN229, and T98G glioma cells ($IC_{50}$ = 131μM, 91μM, 86μM, 97μM, respectively); and A-431 human skin cancer cells ($IC_{50}$ = 71.42μM); (Jackson et al. 2008; Newcomb et al. 2008; Yang et al. 2012; Maurya et al. 2019).

Recent in vitro studies showed that papaverine has selective and potential antitumor activity against breast cancer, prostate cancer, colorectal carcinoma, hepatocarcinoma, fibrosarcoma, and glioblastoma. It is also discovered that papaverine sensitizes A549 lung and EO771 breast tumor cells to radiation therapy. In addition, Gaber et al. indicated that Au(III) complex of papaverine has anticancer activity against both breast cancer MCF-7 and Human HepG-2 cell lines plus the Au(III) complex of papaverine is more active than cisplatin and papaverine alone (Afzali et al. 2015; Inada et al. 2019; Gaber et al. 2020).

Afzali et al. showed that narceine and papaverine have selective cytotoxic effect on cancer cell lines comparing to doxorubicin on HT29 colon cancer cells, T47D breast cancer cells, and HT1080 human fibrosarcoma cells. The $IC_{50}$ values of papaverine were calculated as 17.4 ± 2.07μM, 55.66 ± 16.28μM, and 209.64 ± 7.63μM, respectively. Sajadian et al. showed papaverine to inhibit in vitro growth of MDA-MB-231 and MCF-7 breast cancer cells; $IC_{50}$ values are 6.06 ± 1.98μM, and 6.16 ± 0.84μM, respectively. Noureini et al. discovered papaver-

ine to inhibit in vitro growth of HepG-2 hepatocarcinoma cells; $IC_{50}$ value is 120μM (Noureini and Wink 2014; Sajadian et al. 2015; Afzali et al. 2015).

Morphine is a well analgesic molecule. Because of its analgesic activity, it is used commonly to relieve pain in cancer patients. Recent studies showed that morphine has dose-dependently anticancer activity through different pathways (Sueoka et al. 1998; Li et al. 2020).

### 31.5.5 Antimicrobial Effect

Aqueous, ethanolic, and hydroalcoholic extracts of *P. somniferum* L. seeds were discovered to show antimicrobial effect against *Propionibacterium acnes* and *Staphylococcus epidermidis*. Zones of inhibition shown by aqueous and ethanolic extracts against *P. acnes* were measured as 13 ± 1.04 mm and 14 ± 1.8 mm, respectively, while zones of inhibition shown by hydroalcoholic and ethanolic extracts against *S. epidermidis* were measured as 15 ± 1.09 mm and 13 ± 1.6 mm, respectively (Hao et al. 2015).

Many studies showed papaverine to have antiviral effect against measles virus, human immune deficiency virus, cytomegalovirus, influenza virus, paramyxovirus, and ß-coronavirus. Papaverine was discovered to inhibit in vitro measles virus strain (the Edmonston strain); human immune deficiency virus strains [HIV strain 3b ($CD_{50}$ = 32μM and $ED_{50}$ = 5.8μM), HTLV-IIIB]; cytomegalovirus strain [AD169 ($ED_{50}$ < 1μM)]; influenza virus strains [A/WSN/33 ($IC_{50}$ = 16.77μM), A/Udorn/72 ($IC_{50}$ = 36.41μM), A/Equine/2/Miami/1/63 ($IC_{50}$ = 27.36μM), A/PR/8/34 ($IC_{50}$ = 24.54μM), B/Lee/40 ($IC_{50}$ = 14.34μM), B/MD/59 ($IC_{50}$ = 2.63μM)]; paramyxovirus strains [RSV strain ($IC_{50}$ = 2.02μM), PIV5 ($IC_{50}$ = 5.5μM), HPIV3 ($IC_{50}$ = 2.6μM)]; ß-coronavirus strains [HCoV-OC43 ($EC_{50}$ = 11.61μM), HCoV-NL63 ($EC_{50}$ = 7.32μM), MERS-CoV ($EC_{50}$ = 9.45μM), MHV-A59 ($EC_{50}$ = 11.46μM), SARS CoV-2 ($IC_{50}$ = 1.1 ± 0.39μM)] (Miller and Carrigant 1982; Yoshikawa and Yamanouchi 1984; Albrecht et al. 1987; Turano et al. 1989; Nokta et al. 1993; Shen et al. 2019; Aggarwal et al. 2020; Jafarova Demirkapu and Raci Yananli 2021; Ellinger et al. 2021).

## 31.6 Clinical Studies

There are three recently completed clinical studies on *P. somniferum* L. extracts in the literature.

Phase I clinical study conducted by De Moraes et al. showed that the liquid alcoholic extract of P. somniferum L., Elixir paregorico®, is safe, tolerable, and free of any unwanted toxicity in healthy male and female volunteers when administered four times a day during 10 days (De Moraes et al. 2008).

Untoro et al. compared the efficiency of iodized peanut oil with iodized seed oil of *P. somniferum* L. that is used to control iodine deficiency in poor of iodized salts areas. In the study carried on schoolchildren, they showed the iodized peanut oil to be more effective than iodized seed oil of *P. somniferum* L. (Untoro et al. 2006).

Morphine was added in the IOC list of banned substances since it can be misused by athletes to overcome pain during strenuous exercises. It was indicated that morphine was detected in urine until 12 hours after administration of herbal teas in the study conducted on two herbal teas containing fruit of *P. somniferum* L. and five healthy male volunteers (Van Thuyne et al. 2003).

In addition to the clinical studies on *P. somniferum* L. extracts, there are also countless clinical studies on its secondary metabolites separately.

## 31.7 Toxicological Studies

Opioids can cause numerous expected or unexpected side effects. Different organ systems can be affected by these side effects.

That is, nervous system (delirium, hallucination, sedation, hyperalgesia, seizure, headache), cardiovascular and respiratory systems (noncardiogenic pulmonary edema, bradycardia, hypotension, cardiac dysrhythmia), digestive system

(nausea, constipation, xerostomia, gastroesophageal reflux disease, obstruction of the common bile duct), urinary system (altered kidney function, urinary retention, peripheral edema), endocrine system (sexual dysfunction, osteoporosis), and immune system (immune suppression) (Harris 2008; Benyamin et al. 2008).

The aforementioned effects vary in severity and incidence, and they may be associated with any opioid, dosage, and route of its administration (Harris 2008).

Opioids are indispensable and legitimate drugs; however, they should not be neglected for risks of misuse, abuse, diversion, and addiction. Thousands of deaths, economic losses, and social harms occur due to opium addiction every year. Opioid addiction is one of the chronic mental illnesses which could begin with recreational and experimental use, or unfortunately, after the using for medicinal purposes legally. It is a severe case that obliges humans to suffer such drastic problems as tolerance development and withdrawal symptoms such as muscle and bone pain, abdominal cramps, runny nose, diarrhea, agitation, anxiety, sweating, etc.. Development of addiction may differ depending on such factors like age (incidence in adolescence or early adulthood is higher than other periods), genetic predisposition, and social circumstance, etc. Methadone (full agonist on MORs, some agonist on the KORs, and is also a possible weak antagonist on DORs and NMDA receptors), buprenorphine (partial agonist with a high affinity on the MORs, a partial agonist on KORs), naloxone (nonselective and competitive opioid receptor antagonist), and naltrexone (opioid antagonist) are used for the treatment of opium addiction. It is aimed to decrease withdrawal syndromes and improve psychosocial function in day-life and social relations with this therapy (Shepard 2010; Salsitz 2016; Eitan et al. 2017; Wang 2019).

There are many morphine-related in vivo toxicity studies in the literature. In Sprague-Dawley rat pups, morphine was discovered to cause profound respiratory depression and hypothermia dose-dependently; besides, reduced respiratory rate and induced prolonged respiratory arrest at all doses attempted (2, 10, or 20 mg/kg). In mice, rats, and guinea pigs; morphine caused reversible lens opacities. A study conducted on male SD rats pointed that morphine may upregulate expression of Bax and Caspase-3; thus, it may cause increasing testicular cell apoptosis and reducing sperm concentration. Morphine was observed to induce impaired luminal epithelial differentiation, decreased stromal cell proliferation, and weak angiogenesis through the study in which morphine was spatiotemporally expressed in the uterus of mouse during the peri-implantation period. In Sprague-Dawley rats, morphine was stated to have no teratogenic effect up to 35 mg/kg/day, but cause other adverse fetal effects and increased postnatal mortality. In another study in which rats were pretreated with morphine, the fetuses of rats exhibited significant but temporary growth retardation that was not eliminated by cross-foster feeding (Grant 1986; Fujinaga and Mazze 1988; Kesavan et al. 2014; Liu et al. 2014; Tang et al. 2015).

There are also many toxicological studies and case reports related to morphine, which has a long-standing clinical use. Many deaths related to morphine overdoses, abuses, and drug interactions were reported in literature (Lötsch et al. 2006; Monteil-Ganiere et al. 2014; Brokjær et al. 2015; Steinhorn et al. 2015; Baillif-Couniou et al. 2015).

The toxicity value of morphine was calculated as therapeutic blood concentration 1–7μg/dL; toxic blood concentration 10–100μg/dL; lethal blood concentration >400μg/dL in human (Gossel and Bricker 2001).

In vivo toxicological studies showed that codeine doesn't show teratogenic effect. Respiratory malformations (8 cases), genitourinary tract defects other than hypospadias (7 cases), Down's syndrome (1 case), tumors (4 cases), umbilical hernia (3 cases), and inguinal hernia (12 cases) were observed in 563 cases who used codeine first trimester, while hydrocephaly (7 cases), pyloric stenosis (8 cases), umbilical hernia (7 cases), and inguinal hernia (51 cases) were observed in 2522 cases who were exposed to codeine anytime in pregnancy. Codeine shouldn't be used by children, since there are

many case reports associated with respiratory arrest, coma, and death occurred in children (Young et al. 1995; Shepard 2010; Friedrichsdorf et al. 2013).

There are many toxicological studies and case reports related to codeine. Its toxicity value is calculated as therapeutic blood concentration: 1–12μg/dL; toxic blood concentration 20–50μg/dL; lethal blood concentration >60 ug/dL in human (Gossel and Bricker 2001).

## 31.8 Available Commercial Formulations/Products, Uses, Administration Methods and Pharmacokinetic Studies

Morphine, which is the major alkaloid in opium, is the oldest well-known opioid agonist used as an analgesic drug in the clinic. Many combined and alone medications involve morphine or its various derivatives. These medications are to be applied by oral, rectal, parenteral, neuraxial, submucosal, transdermal, etc. (Hamilton and Baskett 2000).

The bioavailability of morphine is approximately 80–100% after the oral administration since its absorption in the alkaline medium of the digestive tract is well. The maximum plasma concentration occurs 24–48 hours after the oral administration. After the intravenous administration, the onset of analgesic effect is slow (6–30 min) since lipid solubility of morphine and rate of penetration through the blood-brain barrier of morphine are partly low. Due to the significant first-pass metabolism, the oral dose should be six times higher than the parenteral dose to achieve the same effect. Ninety percent of a dose of morphine is metabolized by UGT2B74 to morphine-3-glucuronide (57.3%) and morphine-6-glucuronide (10.4%). It may be converted to codeine, normorphine, and morphine ethereal sulfate as well. Even though it is generally eliminated in the urine; 2–10% of a dose is recovered as an unchanged drug, while 7–10% of a dose is eliminated in the feces. The elimination half-life is 2–3 hours, but it may differ according to age-like parameters (Hoskin and Hanks 1990; Lötsch 2005; Klimas and Mikus 2014; Beltrán-Campos et al. 2015; Pacifici 2016).

Codeine is used to relieve mild pain and cough. It can be combined with acetaminophen; it can also be found in some cough medications that are generally liquid (Pratt et al. 2012).

Codeine is absorbed in the digestive tract; it reaches maximum plasma concentration approximately 60 min after administration. Codeine is metabolized to codeine-6-glucuronide (by CYP2D6, 70–80%), to morphine (by CYP2D6, 5–10%), and to norcodeine (by CYP3A, 10%) in the liver. The elimination half-life is about 3 hours. It is generally eliminated in the urine; approximately 10% of the drug is eliminated as an unchanged drug (Dart 2004; DrugBank 2021b).

Papaverine is used against such diseases as ischemia, myocardial infarction, angina, embolism, hypertension, cerebral vasospasm, visceral spasms, urinary incontinence, prostate hyperplasia, and erectile dysfunction. Papaverine is to be applied by oral, intramuscular, intravenous, intraarterial, and topical (Liu and Tu 2002; Porst et al. 2013; Kang et al. 2018; Jafarova Demirkapu and Raci Yananli 2021).

Papaverine is absorbed in the digestive tract. Fifty-four percent of a dose is metabolized through first-pass metabolism; thus, its bioavailability is relatively high. Papaverine is metabolized to 6-Desmethylpapaverine (6-DMP, major metabolite) and $4^0$,6-didesmethylpapaverine (4,6-DDMP) in the liver. The elimination half-life is about 0.5–2 hours. It is generally eliminated in urine. Although the oral median dose in rate is observed to 360 mg/kg, there is no data in humans (Jafarova Demirkapu and Raci Yananli 2021).

Noscapine is generally used for common cold, cough, and respiratory diseases. There are tablet and liquid forms to be applied by oral route (DrugBank 2021a).

Recent studies revealed that noscapine is absorbed rapidly, and it reaches maximum plasma concentration 1 hour after the oral administration. The elimination half-life is calculated

as about 2.5 hours. Additionally, it is discovered that noscapine may be converted to nor-noscapine (Dahlström et al. 1982; Karlsson et al. 1990).

## 31.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

*P. somniferum* L., whose different parts are used for many therapeutic purposes, is a well-known medicinal plant for centuries. Recent studies scientifically illuminated not only its biological effects, but also its chemical content responsible for these effects. On the other hand, various ethnobotanical uses have also been shown to be incorrect.

There are many cases of poisoning related to misuse of folk remedies and use as a recreational substance, addiction, drug, or food interaction in the literature. It is crucial to the correct usage of P. somniferum L. due to the magic nature of the plant as well as the beneficial effects of the chemical components in the plant. Otherwise, many serious side effects may be observed. (Haber et al. 2019; Martínez and Ballesteros 2019; Bishop-Freeman et al. 2020).

## 31.10 Challenges and Future Recommendations as Potential Drug Candidate

*P. somniferum* L., a medicinal plant famous for its alkaloid content, has been subject to numerous studies to date. Its bioactive compounds were discovered and brought to medicine through these studies. Besides, morphine and codeine were granted FDA approval in 1941 and 1950, respectively (DrugBank 2021b, c).

Today, *P. somniferum* L. and its alkaloids are still indispensable despite their narcotic nature. Besides, various semisynthetic and synthetic derivatives of its alkaloids were invented to prevent drug addiction and adverse effects, prolong the half-life of drug increase bioavailability, etc.

*P. somniferum* L. and its chemical content, contrary to all studies and clinical use, still have unknown aspects. Morphine and codeine remain the gold standard among analgesics and antitussives, despite their hitherto unavoidable narcotic effects. In addition, further studies are needed on the toxicity of chemicals and other pharmacological activities on diseases such as cancer or erectile dysfunction of its alkaloids (Bolser and Davenport 2007; Ruiz-Garcia and Lopez-Briz 2008).

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# *Rheum ribes* L.

# 32

Ceyda Sibel Kılıç

**Abstract**

*Rheum ribes* L. is a species of the Polygonaceae (Buckwheat) family. The plant has been used traditionally in various parts of the world, and since it has various medicinal usages, it is known as "the wondrous drug" all through the world. In this chapter, ethnobotanical and clinical usages, composition, and biological activities of this well-known plant are focused on.

**Keywords**

*Rheum ribes* · Rhubarb · Syrian rhubarb · Polygonaceae · Buckwheat family

## 32.1 Introduction

*Rheum ribes* L. is a herbaceous plant bearing short and thick rhizomes. The plant has big leaves that have long and fleshy petioles. Flowers are small but they form large, compound inflorescences (Mohammed et al. 2018). Shoots of the plant can grow up to 40 cm; both these shoots and the stalks are eaten as raw (Özyurt et al. 2021).

The name of the plant comes from Greek language; "rha barbaron" means "foreign rhubarb" that is associated with the word "barbarian" meaning "foreign, of another nation or culture" (www.etymonline.com/word/rhubarb). Vernacular names of the plant in different languages are given in Table 32.1.

## 32.2 Distribution and Status of the Species

The species is a member of the Irano-Turanian phytogeographical region (Özyurt et al. 2021) and thus native to Turkey, Iran, Lebanon,

**Table 32.1** Vernacular names of *R. ribes* in different languages

| Language | Vernacular name | References |
|---|---|---|
| English | Rhubarb | Adham and Naqishbandi (2015) |
| Arabic | Rawand | Adham and Naqishbandi (2015) |
| Turkish | Işgın, Işkın, Eşğı, Rives, Gavalak, Gavalat, Revas, Yemlik, Eşgin, Uçgun, Uşkun | Kadıoğlu et al. (2021), Erbay and Sarı (2018), Bulut et al. (2016), Üstün et al. (2019), Taşkın and Bulut (2019) |
| Kurdish | Rewas | Adham and Naqishbandi (2015) |

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Pakistan, India, and China (Zahedi et al. 2015; Khiveh et al. 2017; Kök et al. 2020).

According to the Plant List, the following taxa are found naturally throughout the world:

- *Rheum acuminatum* Hook.f. & Thomson
- *Rheum alexandrae* Batalin
- *Rheum altaicum* Losinsk.
- *Rheum australe* D. Don
- *Rheum compactum* L.
- *Rheum cruentum* Siev. Ex Pall.
- *Rheum delavayi* Franch.
- *Rheum forrestii* Diels
- *Rheum glabricaule* Sam.
- *Rheum globulosum* Gage
- *Rheum hotaoense* C.Y. Cheng & T.C.
- *Rheum x hybridum* Murray
- *Rheum inopinatum* Prain
- *Rheum kialense* Franch
- *Rheum laciniatum* Prain
- *Rheum lhasaense* A.J. Li & P.G Xiao
- *Rheum likiangense* Sam.
- *Rheum lucidum* Losinsk.
- *Rheum macrocarpum* Losinsk.
- *Rheum maculatum* C.Y. Cheng & T.C. Kao
- *Rheum moorcroftianum* Royle
- *Rheum nanum* Siev. Ex Pall.
- *Rheum nobile* Hook. f. & Thomson
- *Rheum officinale* Baill.
- *Rheum palmatum* L.
- *Rheum przewalskyi* Losinsk.
- *Rheum pumilum* Maxim.
- *Rheum racemiferum* Maxim.
- *Rheum reticulatum* Losinsk.
- *Rheum rhabarbarum* L.
- *Rheum rhaponticum* L.
- *Rheum rhizostachyum* Schrenk
- *Rheum rhomboideum* Losinsk.
- ***Rheum ribes* L.**
- *Rheum spiciforme* Royle
- *Rheum subacaule* Sam.
- *Rheum sublanceolatum* C.Y. Cheng & T.C. Kao
- *Rheum tanguticum* Maxim. ex Balf.
- *Rheum tataricum* L.f.
- *Rheum tibeticum* Maxim. ex Hook. f.
- *Rheum turkestanicum* Janisch.
- *Rheum uninerve* Maxim.
- *Rheum webbianum* Royle
- *Rheum wittrockii* C.E. Lundstr.
- *Rheum yunnanense* Sam.

## 32.3 Traditional/Ethnomedicinal Uses

Rhubarb is known to be one of the oldest remedies in the oldest books of Chinese medicine (Zahedi et al. 2015) and thus used in Traditional Chinese Medicine (TCM) (Roghani-Shahraki et al. 2020). According to traditional Persian medicine, the plant is good for fever and dysentery and was included in Canon of Medicine by Avicenna (Khiveh et al. 2017). Furthermore, *R. ribes* is reported to be included in a remedy called "*teryagh*" which was used in the treatment of some epidemics like plague and cholera (Mahroozade et al. 2021). It is also reported to be used in Iran as a mood enhancer and as sedative (Naemi et al. 2014). It is used as a traditional remedy in Turkey for various ailments and as food, as well, where it is the only species of the genus growing naturally in the country (Cakilcioglu and Turkoglu 2010; Korkmaz and Karakuş 2015). Some examples for ethnobotanical/traditional uses of the species are as tabulated in Table 32.2 below:

Though the plant has various medicinal usages, it is mostly known and consumed as food in the countries where it grows naturally. Young stalks and leaves of the plant are consumed as vegetable and mostly eaten as raw due to its acrid taste (Altundağ Çakır 2017; Üstün et al. 2019; Kök et al. 2020; Çalışkan et al. 2020; Akoğul and Aksakallı Bayraktar 2020; Demir 2020; Yerebasan et al. 2021; Kawarty et al. 2021). In East Anatolian region of Turkey, the leaves of the plant are reported to be used in the preparation of *sarma*, a dish from Ottoman and Turkish cuisine (Dogan et al. 2017). The plant does not grow in European countries naturally; however, it was reported that it is used in cakes in some European countries such as Germany, England, and Sweden (Okcu and Kaplan 2018).

The plant is involved in other applications related to foodstuff, as well. In a study by Doğan and Meral (2016), *R. ribes* was added to biscuit formulations and it was determined that function-

**Table 32.2** Ethnomedicinal usages of *R. ribes*

| Plant part | Preparation method | Usage/Activity | Country | References |
|---|---|---|---|---|
| NA | Raw, pulverized, decoction, mixed herb, heated on embers | Stomach disorders, joint pains, kidney ache, hair loss, boil, ulcers | Iran | Maleki and Akhani (2018) |
| Leaf, flower, stem | NA | Antianxiety, depression | Shahrekord, Iran | Teimouri et al. (2019) |
| Stem, leaf | NA | Anti-diarrhea | Shahrekord, Iran | Anbari et al. (2019) |
| NA | NA | Constipation | Shahrekord, Iran | Karami et al. (2020) |
| Leaf, stem | Brewed, fresh | Hepatoprotective | Shahrekord, Iran | Ghanadi et al. (2019) |
| Leaf, stem | NA | Jaundice | Shahrekord, Iran | Basati et al. (2019a, b) |
| NA | NA | Stomachache | Iran | Ghaneialvar et al. (2020) |
| Roots | Oral consumption | Antibacterial (related to respiratory system) | Iran | Iranzadasl et al. (2021) |
| NA | NA | Stomachic, emmenagogue, astringent, anti-lithiasis | Iran | Zeidali et al. (2021) |
| Fruit-petiole | NA | Jaundice, urinary antiseptic, diuretic, depurative, liver tonic, antiseptic, hair tonic | Iran | Buso et al. (2020) |
| NA | As kohl | Vision impairment | Iran | Shayanfar et al. (2019a) |
| NA | NA | Eye health | Iran | Shayanfar et al. (2019b) |
| Whole plant | Syrup | Nausea, vomiting | Iran | Darvishpor et al. (2018) |
| Root | Cold and dry | Appetizer | Iran | Javan et al. (2017) |
| NA | NA | Appetizer | Iran | Hamidi et al. (2017) |
| Stems | NA | Joyful and cooling | North Khorasan, Iran | Farouji and Khodavari (2016) |
| NA | Na | Hypertension | Ilam, Iran | Baharvand-Ahmadi et al. (2016) |
| Fruit-Petiole | NA | Liver disorders | Khorasan, Iran | Moradi et al. (2016a) |
| Stems | NA | Hypertension | Iran | Moradi et al. (2016b) |
| Fruit | Fresh | Kidney and urinary stones | Iran | Bahmani et al. (2016) |
| Root | Decoction | Jaundice, liver diseases, cardiac tonic, antilithiasis | Mashhad, Iran | Amiri et al. (2014) |
| Roots | Drying (+ Infusion) | Diabetes | Hakkari, Turkey | Kaval et al. (2014) |
| Aerial parts, roots | Infusion (one cup is drank on an empty stomach in the mornings), raw | Asthma, diabetes, kidney stones, cardiac disorder | Bingöl, Turkey | Polat (2019) |

(continued)

**Table 32.2** (continued)

| Plant part | Preparation method | Usage/Activity | Country | References |
|---|---|---|---|---|
| NA | Eaten fresh, tea-decoction | Diabetes, hemorrhoids | Bayburt, Turkey | Kadıoğlu et al. (2021) |
| NA | NA | Cholesterol lowering | Elazığ, Turkey | Yerebasan et al. (2021) |
| Roots, seeds | Decoction, crude mixed with honey | Diabetes, hemorrhoids, constipation | Erzurum, Turkey | Karakaya et al. (2020) |
| Root, shoots | Decoction | Hypertension | Turkey | Olcay and Kültür (2020) |
| Aerial parts | NA | Breast cancer | Turkey | Bozyel et al. (2019) |
| Root | Decoction | Diabetes | Van, Turkey | Dalar (2018) |
| Root | Crushed + *Lawsonia inermis* | Analgesic for headache | Turkey | Erbay et al. (2018) |
| Root | Decoction | Hemorrhoids | Turkey | Erbay and Sarı (2018) |
| Shoot and root | Internal as decoction or crushed | Hemorrhoids | Turkey | Koca Caliskan et al. (2017) |
| Root and stem | NA | Diabetes, hypertension | Hakkari, Turkey | Oğuz and Tepe (2017) |
| Root | Decoction | Stomach ulcer | Turkey | Kültür et al. (2018) |
| Seeds, aerial parts, roots | Decoction, infusion | Asthma | Turkey | Melikoğlu et al. (2015) |
| Aerial parts | As tea | Kidney stones | Hatay, Turkey | Güzel et al. (2015) |
| NA | NA | Headache, diabetes | Van, Turkey | Mükemre et al. (2015) |
| NA | Aqueous extract | Diabetes | Jordan | Issa et al. (2019) |
| Root | Infusion | Diabetes | Azerbaijan | Jafarirad and Rasoulpour (2019) |

*NA* not available

ality of the biscuits increased due to the antioxidant effect of the plant via the inhibition of free radicals without having an impact on the flour properties. Furthermore, some plants are added to meat products for their antioxidant effects, and thus, they provide resistance against oxidative deterioration. *R. ribes* is among the ones used for this purpose due to the antioxidant compounds that it contains (Yıldız Turp et al. 2018).

There are also other recorded ethnobotanical uses. For example, flowers of the plant are used as dye in Markazi province of Iran (Moghadam et al. 2016). And as for ethnoveterinary medicine, stems and roots of the plant are used in wounds, hoof and mouth disease, against intestinal parasites around Elazığ Province, Turkey (Özen and Doğan 2017); against diarrhea (as dried, grounded and added to tar) in Antalya Province of Turkey (Avcı and Özen 2016); against coughing (the root is boiled in water); and against exhaustion (the root is dried and given to the animals as fodder either alone or with Keven – an *Astragalus* L. species) (Çavuş Alan et al. 2021). It is also recorded to be used in animal husbandry around Diyarbakır Province of Turkey, as well (Özen 2021).

## 32.4 Composition

The plant has important secondary metabolites which make it beneficial in the prevention and treatment of diseases. And since it is also consumed as fresh and also cooked as a vegetable dish, phytochemical composition of the plant is worth mentioning.

The phytochemical composition of the plant is given in Table 32.3 along with the plant parts that contain these phytochemicals, minerals, etc.

Essential oil compositions of the flowers were investigated in a study by Naemi et al. (2014) and palmitic acid (27.08%), m-tetracosane (17.81%), n-eicosane (9.9%), linoleic acid (6.56%), and

**Table 32.3** Phytochemical composition of *R. ribes*

| Plant part | Phytochemical and/or mineral composition | References |
|---|---|---|
| Leaves | Phosphorous (10.53 mg/100 g), potassium (1490 mg/100 g), sulfur (79.92 mg/100 g), calcium (437 mg/100 g), magnesium (42.11 mg/100 g), sodium (17.76 mg/100 g), Iron (1.36 mg/100 g), manganese (0.17 mg/100 g), zinc (0.18 mg/100 g), copper (0.032 mg/100 g) | Turan et al. (2003) |
| Stems (collected from Ağrı/ Turkey) | Silver (190.54 ± 14.02 mg/kg), aluminum (99.61 ± 13.7 mg/kg), boron (31.18 ± 3.37 mg/kg), barium (7.25 ± 1.05 mg/kg), calcium (337.18 ± 139.43 mg/kg), cobalt (0.28 ± 0.08 mg/kg), chromium (1.48 ± 0.38 mg/kg), copper (2.93 ± 0.44 mg/kg), Iron (56.11 ± 8.43 mg/kg), gadolinium (1.52 ± 0.7 mg/kg), potassium (34,693 ± 702.52 mg/kg), lithium (0.25 ± 0.02 mg/kg), magnesium (2,030.58 ± 24.66 mg/kg), manganese (0.24 ± 0.09 mg/kg), Sodium (2,050 ± 215.99 mg/kg), nickel (2.88 ± 0.83 mg/kg), phosphorous (4,570.13 ± 153.09 mg/kg), strontium (13.09 ± 0.55 mg/kg), vanadium (0.09 ± 0.01 mg/kg), zinc 22.95 ± 3.8 mg/kg) | Özcan et al. (2007) |
| Stems (collected from Elazığ/Turkey) | Silver (1,271.26 ± 14.88 mg/kg), aluminum (210.8 ± 5.7 mg/kg), boron (33.93 ± 3.58 mg/kg), barium (9.55 ± 2.07 mg/kg), calcium (1,647.16 ± 118.2 mg/kg), cobalt (0.15 ± 0.08 mg/kg), chromium (6.37 ± 1.57 mg/kg), copper (2.77 ± 0.04 mg/kg), Iron (147.01 ± 9.11 mg/kg), gadolinium (2.39 ± 0.85 mg/kg), potassium (32,730 ± 586.55 mg/kg), lithium (0.30 ± 0.02 mg/kg), magnesium (2,250.25 ± 21.03 mg/kg), manganese (1.27 ± 0.50 mg/kg), sodium (1,993.9 ± 226.5 mg/kg), nickel (1.63 ± 0.25 mg/kg), phosphorous (4,114,76 ± 175.14 mg/kg), strontium (38.17 ± 1.26 mg/kg), vanadium (0.21 ± 0.05 mg/kg), zinc 16.87 ± 1.26 mg/kg) | |
| Rhizomes | Copper (2.584%), cadmium (3.513%), manganese (35.03%), potassium (0.0388%), iron (126.85%), cobalt (1%), titanium (0.02%), nitrogen (0.59%) | Jalill et al. (2015) |
| Aerial parts | Calcium (4,020.51 mg/100 g), potassium (6,150.25 mg/100 g), magnesium (280.69 mg/100 g), sodium (40.31 mg/100 g), cadmium (0.07 mg/100 g), cobalt (0.04 mg/100 g), copper (0.20 mg/100 g), iron (6.04 mg/100 g), manganese (0.80 mg/100 g), nickel (0.19 mg/100 g), zinc (0.80 mg/100 g) | Jalali and Fakhri (2021) |
| Rhizomes | Anthraquinones (chrysophanol, physcion, aloe-emodin, emodin) | Alaadin et al. (2007) |
| Roots | Aloe-emodin, emodin, chrysophanol, physcion, rhein, chlorogenic acid, gallic acid, kaempferol, tannic acid, rutin | Abdulla et al. (2014) |
| NA | β -sitosteryl-3β-glucopyranoside-6′-*O*-fatty acid ester, β-sitosterol, triacylglycerol, chlorophyllidine, phytyl fatty acids | Ragasa et al. (2017) |
| NA | Flavonoids (quercetin, 5-desoxy-quercetin, quercetin 3-*O*-rhamnoside, quercetin 3-*O*-galactoside, quercetin 3-*O*-rutinoside), anthraquinones (chrysophanol, physcion, emodin) | Raafat and El-Lakany (2018) |
| Roots | Aloe-emodin (29.9056 μg/g), emodin (252.880 μg/g), Chrysophanol (76.8493 μg/g), physcion (56.1317 μg/g), rutin (49.2098 μg/g) | Al-Samarrai et al. (2018) |
| NA | Aloe-emodin, emodin, quercetin, physcion, chrysophanol, rhein, glucoside, stilbene | Mahmood (2020) |
| NA | Anthraquinones, malic acid, funic acid, sulfuric acid, resin, oxalic acid, tannin, anthocyanin | Zeidali et al. (2021) |
| Aerial parts | Resveratrol, 6-*O*-methylalaternin, emodin, aloe-emodin, β-sitosterol, rutin | Gecibesler et al. (2021) |
| Whole plant | L-ascorbic acid (1,286.92 ± 342.4 mg/kg), gallic acid (132.06 ± 53.66 mg/kg), catechin (55.37 ± 18.89 mg/kg), luteolin (52.77 ± 3.77 mg/kg | Alaca et al. Ahead of print (2021) |

ethyl linoleate (4.76%) were found to be the major components.

Structures of some secondary metabolites found in the plant are given in Fig. 32.1.

## 32.5 Pharmacological Activities

The plant has a long history of traditional usages in the countries where it grows naturally. These traditional usages were justified with some scientific studies as well, and in this section, these studies and/or bioactivities are focused on.

### 32.5.1 Acetylcholinesterase Inhibitory Activity

Acetylcholinesterase (AChE) is responsible for the rapid hydrolysis of acetylcholine at the cholinergic synapses and thus increases the cholinergic function in the brain for the treatment of Alzheimer's Disease (AD). In a study by Gholamhoseinian et al. (2009) some Iranian plants were screened for their AChE inhibitory activities and it was stated that *R. ribes* demonstrated potent inhibitory activity and considered to be a promising agent in AD. Moreover, in a study by Zahedi et al. (2015) performed on rat model of AD, hydroalcoholic extract of *R. ribes* was found to improve spatial and passive memory impairments which was induced by the destruction of NBM nucleus of rats and was considered to be used in some neurological diseases such as AD.

### 32.5.2 Antibacterial Activity

In a study by Alaadin et al. (2007), total ethanol extract was prepared from the roots of the plant and then chloroform and aqueous fractions were obtained and tested for their antibacterial activities against *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 9027, *Escherichia coli* ATCC 11229, *and Bacillus subtilis* ATCC 6633 along with four anthraquinone compounds (chrysopahnol, physcion, aloe-emodin, emodin) isolated from the plant. The extracts, aloe-emodin and emodin, were found to be active against *Staphylococcus aureus*; however, they had no effect on other microorganisms.

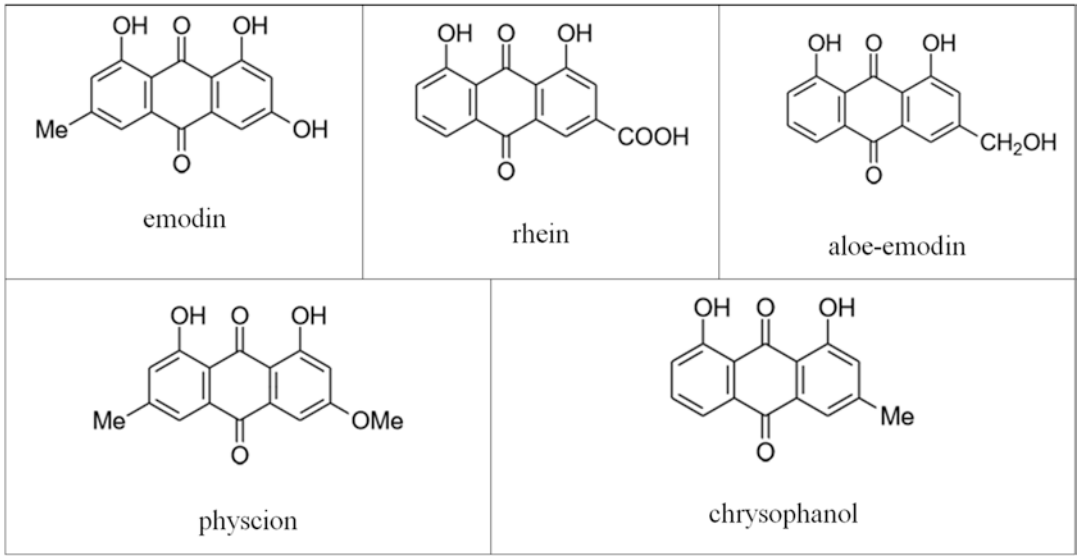


**Fig. 32.1** Structures* of some secondary metabolites found in *R. ribes*. (*All structures were drawn by Reaxys®-ChemDrawJS editor – version 20.0.0-CDJS-20.0.x.7+b59aa09e8)

Tartik et al. (2015) tested the antibacterial activity of the extract of the roots on four bacteria, and at the end of this study, the extract was found to inhibit the growth of *Enterobacter aerogenes* and *E. coli* at low doses and *Staphylococcus aureus* and *Saccharomyces cerevisiae* at high doses.

Antibacterial activity of the plant was also tested on some microorganisms in another study. Methanol extract prepared from the roots, stalks, and leaves of the plant was used against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa,* and *Shigella flexneri,* and while the extract was found to be effective against all of these microorganisms, highest activity was observed against *S. flexneri* and *K. pneumoniae*. However, conflicting results are also present. For example, in a study that examined the antimicrobial activity of hydroalcoholic extract of *R. ribes*, *K. pneumonia* was reported to be resistant to plant extract but was active against *S. aureus* (Gheisari et al. 2019).

Fighting with these food-borne pathogens is important since they result in food-borne diseases in humans. Aqueous and ethanol extracts of the leaves and stalks were tested against some of these pathogens and were found to be effective especially against *S. aureus* and *E. coli*. Therefore, the plant has the potential to be used for the inhibition of these bacteria and can be used to improve the quality and safety of foodstuff (Salehi et al. 2016). Antibacterial activity of the methanolic extract of the plant was demonstrated against *S. aureus*, *E. coli*, *B. cereus,* and *P. aeruginosa* and was found to inhibit their growth (Sayyahi et al. 2019).

In an effort to elucidate the mechanism of action of antibacterial activity of the plant, methanol, methanol-chloroform, and aqueous extracts of the roots were prepared and tested against *B. cereus*, *Enterococcus faecalis*, *Listeria monocytogenes*, *S. aureus*, Methicillin resistant *S. aureus*, *Chronobacterium violaceum*, *E. coli,* and *P. aeruginosa*. At the end of the study, it was understood that the plant had inhibitory effect on the swarming motility, which is considered to be one of the important virulence factors. It was also demonstrated that antibacterial activity of the plant was more significant on Gram (+) bacteria (Önem et al. 2020). This phenomenon was explained in a study by Mahmood (2020) in which bacterial cell wall was reported to be responsible for the antibacterial susceptibility of the bacteria. Gram-negative bacteria were reported to have a self-barrier consisting of lipopolysaccharides along with complex proteins that prevent the transmission of some antibacterial agents into the cell.

In Iran, the plant is traditionally used for dysentery, and in a study by Khiveh et al. (2017), a syrup is prepared from the fruits of the plant and this syrup was considered to be a complementary treatment to conventional antibiotic treatment in the diarrhea and fever seen in children during dysentery caused by *Shigella* spp. The syrup both alleviates the severity of the disease and reduces the duration of the disease, fever, and abdominal pain.

Biofilm production is also an important health problem since bacteria associated with biofilm production are sometimes hard to eradicate with antibiotics. Among these bacteria, biofilm-producing *E.coli* strains are the main causes of infections seen in patients having indwelling bladder catheters. Methanol extract of the rhizomes was demonstrated to inhibit biofilm formation significantly (60–80%) and thus, has the potential to be used as an antibacterial agent (Obaid et al. 2017).

*Acetobacter baumanii* is an opportunistic pathogen, which is usually found in hospital environment and is associated with important skin infections and infections of the central nervous system. Unfortunately, this microorganism is resistant to some drugs and has the ability to survive in various environments. In the search for more effective antibacterial agents, hydroalcoholic and aqueous extracts of *R. ribes* were prepared and tested against this bacterium, and it was determined that both extracts had potent inhibitory activity, aqueous extract being the most active among them (Bagheri et al. 2019).

Edible methylcellulose films are a new type of packaging materials that are considered to be eco-friendly since they are biodegradable.

Furthermore, edible films having antibacterial additives or coatings also enable us reduce the proliferation of microorganisms, and for this purpose, natural antimicrobials are preferred to synthetic ones in order to avoid their toxic properties. When ethanol extract of *R. ribes* was tested for its utility in edible films, it was understood that methylcellulose polymer containing plant extract possessed antimicrobial activity against some important pathogens, and it also had antioxidant effect, which also rendered it an important alternative to food packaging (Kalkan et al. 2020).

Antimicrobial agents used in foodstuff are important since they can affect human health directly when consumed; therefore, phytochemicals having antimicrobial activities are started to be preferred in foodstuff since they are considered to be safe. Meat is among the foodstuff that requires the addition of antimicrobial agents since meat products can be spoiled by saprophytic and pathogenic microorganisms and constitute an important economic burden because 20% of total meat production is lost due to the spoilage by these microorganisms every year. When fresh juice of *R. ribes* was added to raw beef packed under vacuum, the juice was observed to exert antibacterial activity against *L. monocytogenes*, *E. coli,* and *S. thyphimurium* and could be used as an accidulant against contamination of meat products and in the preparation of marinades for meat, as well (İncili et al. 2021).

### 32.5.3 Anticancer Activity

Cancer is an important health problem with a high ratio of mortality. Though chemotherapy is among the standard treatments administered to cancer patients, it has many side effects and complications, thus safer alternatives are being sought and medicinal plants nearly constitute the number one alternative. In a study that evaluated the efficacy of *R. ribes* methanol extract in different cancer cell lines, the extract was found to be inhibit K562 (leukemia cell line) cell growth significantly (Esmaeilbeig et al. 2015).

Ethanol extract of the roots were tested against prostate cancer cells (PC3) in an in *vitro* study and it was understood that the extract fragmented PC3 cells' DNA and increased reactive oxygen species (ROS) and lipid peroxidation (LPO) levels and this might contribute to the inhibition of PC3 cell viability as a prooxidant according to the authors (Tartik et al. 2015).

MCF-7 is a breast cancer cell line and the effect of the plant was also tested on these cell lines, which is an important and common type of cancer seen in women. Ornithine decarboxylase enzyme (ODC) was increased due to the expression of ODC1 gene and the expression of this gene was observed to decrease with the administration of the extract and also cell line mortality was increased in a concentration-dependent manner. Since the proliferation of cancer cells was inhibited with the administration of the extract via ODC1 gene, the plant is considered to have beneficial anticancer activity in breast cancer (Noori and Afshar 2019).

Effect of the plant was tested on MCF-7 cell lines in another study, as well. In this study, methanol extract of the whole plant was prepared and then n-hexane, aqueous, and butanol fractions were prepared. Consequently, butanol fraction was found to be active against MCF-7 cell line with fewer side effects and less toxicity, while the other fractions were found to be inactive (Achakzai et al. 2019).

In a study by Kirmit et al. (2020), ethanol extracts of the roots, barks, and stems of the plant were prepared individually, and the cytotoxic and apoptotic efficacies of these extracts against malign melanoma (B16F10) cell lines were examined. The highest activity was observed for the root extract in a dose-dependent manner and was considered to be a promising agent in anticancer studies.

Methanol extract of the plant was examined in another study in which the efficacy of the extract was tested for its influence on miR-200 family expression in human colorectal cell line. The results of this study showed that the extract increased miR-200a/b/c and miR-141 expressions and also suppressed BCL-2, EB1, and GATA4 expressions. Consequently, it was concluded that the extract might be used in the aforementioned cancer cell line either alone, or better

yet in combination with fluorouracil (5-FU) to yield a better response (Çınar Ayan et al. 2020).

The plant was examined for its combinatorial effect in other cancer types, as well. For example, methanol extract prepared from the rhizomes of the plant was tested for its additional effect in cancer virotherapy, which was performed with oncolytic Newcastle disease virus. This virus is reported to provide DNA fragmentation and thus induces apoptotic cell death; therefore, it is considered to be a promising anticancer agent. Combination of this virus with the plant extract was observed to increase the efficacy of the therapy five to ten folds and reported to be a novel promising administration in the management and treatment of tumors (Al-Shammari et al. 2020).

In addition to these studies performed with different extracts prepared from different parts of the plant, some compounds isolated from the plant, or known to be present in the plant, were also tested for their anticancer effects. For example, parietin is an anthraquinone, which is known to be present in *R. ribes* and was found to be active against human liver cancer cell line (HepG2), and since it was cytotoxic at low dose but not genotoxic for HepG2 cells, it could be used in combination with other agents (Demirkaya et al. 2019).

Similarly, the efficacy of emodin and aloe-emodin that were isolated from the plant against human glioblastoma (U373), human breast carcinoma (MCF-7), and human colorectal cancer (HT-29) cancer lines was also investigated in a study. The compounds were determined to have potent antiproliferative activity against these cancer cell lines and reported to be considered in the prevention and treatment of cancer (Erdoğan et al. 2020).

### 32.5.4 Anti-diabetic Activity

*Rheum ribes* is traditionally used in various countries in the treatment of diabetes, thus many studies have been carried out to support this traditional usage. In a study by Naqishbandi et al. (2009) performed on mice, total ethanol extract of the roots of the plant was prepared and then partitioned between chloroform and water and the aqueous extract was observed to display marked hypoglycemic activity. The mechanism of action was also examined in this study and it was determined that insulin release was stimulated from INS-1E cells with the administration of the aqueous extract. When the active extract was examined phytochemically, it was found to contain anthraquinone glycosides of aloe-emodin, emodin, physcion, and chrysophanol derivatives.

Anti-diabetic activity of the underground parts of the plant was confirmed with another study in which aqueous extracts were tested both with in vitro enzymatic starch digestion assay and studies on rats. At the end of these experiments, plant extract was found to inhibit α-amylase and α-glucosidase enzymes and the plant was reported to be potential candidate in management of type 2 diabetes having ameliorative effect on the disease (Kasabri et al. 2011).

In addition to its anti-diabetic activity, aqueous extract of the plant also improved peripheral nerve function and protected the mice against developing diabetic neuropathy. This activity was reported to be due to rutin that the plant contains, which prevented oxidative stress in animals with diabetes (Raafat et al. 2021).

When powdered roots were administered to patients with type 2 diabetes in a study performed by Adham and Naqishbandi (2015), it was observed that the root powder was able to reduce blood glucose levels in diabetic patients both alone and also in combination with conventional drugs like glibenclamide and metformin. Quercetin was identified in the plant via HPLC and considered to be responsible for the activity.

Aqueous extract of the plant was tested in another study on Swiss-Webster mice in combination with metformin and it was found that blood glucose, HbA1c, α-glucosidase, and lipid peroxide levels were reduced significantly. Painful hyperalgesia and allodynia were also improved with the administration of this combination as observed with increased tail flick, hot plate latency, and paw withdrawal threshold. Thus, the combination was reported to have better antinociceptive activity in addition to its anti-diabetic effect with less side effects (Raafat and El-Lakany 2018).

In addition to its anti-diabetic activity, aqueous extract of the roots significantly increased beta-cell activity and then decreased alpha-cell activity, as well. And results of both histological examinations and serum biochemistry estimations led to the conclusion that the extract had regeneration and reparation effects in pancreatic tissues (Dizaye et al. 2019).

In most studies, generally aqueous extracts were reported to be active or more active compared to extracts prepared with other solvents. However, in a study by Ghafouri et al. (2020), ethanolic extract was found to be more active compared to aqueous extract in diabetic patients. Nevertheless, both extracts were able to reverse metabolic impairments of the disease and this was achieved by the elevation of insulin sensitivity, improvement of oxidant, and inflammatory status. Thus, the plant was concluded to be an important agent in the prevention and treatment of complications that are usually seen in diabetes.

Roots of *R. ribes* and leaves of *Urtica dioica* L. were powdered, soaked in normal saline, and tested for their anti-diabetic activities in Sprague-Dawley male rats and it was determined that both the extracts were effective in lowering blood glucose levels. Their combinations also had the same effect; however, synergistic or antagonistic effect was not in question (Hussaini et al. 2021).

### 32.5.5 Anti-inflammatory Activity

In a study by Ghafouri et al. (2020) in which anti-diabetic activity of the plant was examined, the plant was found to decrease inflammatory factors such as hs-CRP and therefore reported to have anti-inflammatory activity. The mechanism of action was specified to involve the reduction of pro-inflammatory production of cytokines.

### 32.5.6 Antioxidant Activity

Superoxide anion radicals, hydroxyl radicals, hydrogen peroxide, and singlet oxygen are important oxygen derivatives that are responsible for reactive oxygen species (ROS)-associated effects that are harmful in respect to human health. Antioxidants delay or inhibit oxidation and plants are among sources that provide antioxidant compounds such as free radical inhibitors, active oxygen scavengers (Oktay et al. 2007) since phenolic compounds that are present in plants have hydroxyl groups which make them good antioxidants (Abdulla et al. 2014).

In the study by Oktay et al. (2007), ether, ethanol, and aqueous extracts of the stems, flowers, and roots of the plant were prepared and the extracts were found to have stronger antioxidant activity compared to butylated hydroxyanisole (BHA) which was used as the standard antioxidant agent; however, the activity of ether extract was weaker compared to other extracts. Anthraquinones that are known to be present are considered to be responsible for the antioxidant activity of the extracts (Oktay et al. 2007).

Methanol extract of the flowers was tested for its antioxidant activity in another study in which butylated hydroxytoluene (BHT) was used as the standard and the extract was determined to have significant activity compared to BHT. Moreover, the extract with a concentration of 250 ppm was found to be equivalent to 200 ppm of BHT and considered to be an alternative for synthetic antioxidants like BHA and BHT that have hazardous side effects (Shahi et al. 2016).

In another study by Abdulla et al. (2014), ethanol and aqueous extracts of the roots of the plant were tested for their antioxidant activities via DPPH scavenging method and the high antioxidant effect of the extracts was attributed to the phenolic compounds found in the extracts.

Antioxidant activity studies are numerous and all confirm that different parts of the plant possess antioxidant components, which make it an important alternative for synthetic antioxidants (Mohammed et al. 2018; Al-Samarrai et al. 2018; Bilgiç Alkaya et al. 2019; Taşkın and Bulut 2019; Ceylan et al. 2019; Keser et al. 2020; Eefan and Rahim 2020; Yildirim et al. 2020; Gecibesler et al. 2021; Mercimek Takci et al. 2021; Alaca et al. Ahead of print 2021; Özyurt et al. 2021; Yildirim et al. 2021).

### 32.5.7 Antiparasitic Activity

Trichomoniasis is a sexually transmitted disease caused by *Trichomonas vaginalis* and generally treated by a conventional drug named metronidazole. However, some strains are resistant to the drug, and furthermore, the drug has some side effects, and thus, new remedies are being sought for this parasitic disease. Essential oil and methanol extract of the aerial parts of *R. ribes* were tested against this protozoan and it was observed that the extract and fractions obtained from it possessed anti-trichomonas activity (Naemi et al. 2014).

Hashemi et al. (2021) attributed this activity to the presence of flavonoids, especially to quercetin and quercitrin that are known to be present in the plant.

Anti-trichomonas activity of the plant was reported in other studies, as well (Rahmani et al. 2021), and furthermore, emodin, an anthraquinone found to be present in the plant, was reported to decrease the number of trichomonads that are present in the vagina and cure the abscesses caused by the parasite (Hashemi et al. 2021).

*R. ribes* extract was also tested against cystic echinococcosis caused by *Echinococcus granulosus* for its protoscolicidal activity and it was determined that the plant was able to completely kill the parasite after an exposure to a dose of 900 mg/ml in less than 15 minutes (Mahmoudvand et al. Ahead of print).

### 32.5.8 Antiviral Activity

In a study by Hudson et al. (2000) in which antiviral activities of ethanol extracts of 16 medicinal plants growing naturally in Turkey were evaluated, *R. ribes* rhizome extract was found to have the highest activity and this activity was attributed to photosensitizers that were present in the extract. This attribution was justified with the finding of the presence of three-fold activity in the presence of light compared to dark reaction, and the plant was concluded to be a promising antiviral agent.

The plant was also recommended to be consumed to boost the immune system during COVID-19 pandemic; however, this effect was not attributed to the antiviral content of the plant, but to the vitamins and minerals found in the plant's composition (Biçer 2020).

### 32.5.9 Dermatological Usage

Parietin is an alkaloid that is found in various plant species along with *R. ribes*, which is known to induce cell proliferation at low doses that is seen in dermal fibroblast loss. In a study in which parietin isolated from the plant was tested in wound healing model on human dermal fibroblast cells, this anthraquinone was demonstrated to be used in wound healing as an alternative to zinc (Gundogdu et al. 2019). Furthermore, another anthraquinone derivative, emodin, which is also found in *R. ribes*, was demonstrated to increase type I collagen levels in Hs27 cells, and thus, the compound can be considered to be a candidate against skin aging and wrinkles (Song et al. 2021).

### 32.5.10 Hepatoprotective Activity

The plant is traditionally used for its hepatoprotective effect in Iran (Basati et al. 2019a, b). In a study in which antibacterial activity against *Burkholderia mallei*, a Gram-negative bacterium causing livers disorders, was examined, root extract of the plant was found to inhibit the toxicity of the bacterium in adult male albino rats (Saleh 2020).

### 32.5.11 Obesity

Obesity is an important health problem, which is defined as abnormal adipose tissue accumulation in the body; it has become a worldwide health problem that results in deterioration of well-being. Some plants are traditionally being used against obesity in different cultures, for example,

*R. ribes* is used for this purpose in Turkey (Sargin 2021). The plant is also reported to be among plants that reduce total and LDL cholesterol levels (Roghani-Shahraki et al. 2020). In a review by Seyedan et al. (2015), the plant was listed among plants that inhibit pancreatic lipase and methanol extract of the rhizome was reported to provide 25–50% inhibition. This finding is important since pancreatic lipase inhibitory effect is considered to determine the efficacy of an agent/extract, etc., as an anti-obesity agent (Seyedan et al. 2015; Mhatre et al. 2016).

In another study, lyophilized extract of the roots was prepared and tested on Wistar albino male rats with obesity due to high-calorie diet and it was reported that the extract halted weight gain possibly due to the secondary metabolites that it contains (Bati et al. 2020).

### 32.5.12 Renoprotective Activity

Renal dysfunction is one of the secondary complications of diabetes. In a study, in which hydroalcoholic extract of the roots of *R. ribes* was tested for its renoprotective effect, the extract was observed to improve renal dysfunction in diabetes that was induced in rats by alloxan. The extract also prevented the depletion of antioxidants in the kidneys (Hamzeh et al. 2014).

Renoprotective effect of the plant was also demonstrated in lead-acetate-induced nephrotoxicity. Lead is a toxic heavy metal that is accumulated in the kidneys at an early stage. Powdered plant was mixed with 70% ethanol and used in the experiment and it was determined that the extract was able to prevent nephrotoxicity induced by lead acetate in male Wistar rats. Though this effect was not confirmed with studies performed on humans, people exposed to lead acetate are recommended to consume the plant (Asgharian et al. 2018).

### 32.5.13 Other Activities/Usages

The plant is traditionally used for its urease inhibitory activity in Iran. Urease is the most prominent feature of *Helicobacter pylori*. Infection caused by the bacterium leads to chronic gastritis, gastroduodenal ulcer, and gastric mucosa-associated lymphoid tissue lymphoma. In a study in which commonly used Iranian traditional medicinal plants were screened for their urease inhibitory activities, *R. ribes* was found to be the second most active medicinal plant with an $IC_{50}$ value of 92 μg/ml. Plants having this activity can be used to accelerate the treatment in gastrointestinal diseases when combined with conventional medicines (Nabati et al. 2012).

Polycystic ovary syndrome (PCOS) is an important endocrine disorder seen in women of reproductive age, causing ovary dysfunction and problems related to reproduction. *R. ribes* roots were examined for their activities against PCOS and aqueous extracts prepared from the roots and anthraquinones such as emodin, aloe-emodin, quercetin, rutin, and also gallic acid present in the plant were considered to be responsible for the beneficial effect on some hormonal and biochemical parameters that were induced in PCOS (AbdulWahed et al. 2018).

*R. ribes* stem capsules were administered to type 2 diabetic patients and were found to decrease systolic and diastolic blood pressure. The hypotensive effect of the plant was attributed to its antioxidant effects (Shojaei-Shad et al. 2019).

The plant was also involved in a nanotechnological study. In this study, ethanolic extract of the plant was used to obtain silver nanoparticles via green synthesis. The extract was used as a stabilizing and reducing agent in the synthesis of the nanoparticles. As a result of this study, it was found that silver nanoparticles administered at a low dose had antibacterial activity against *S. aureus*, *MRSA*, *B. subtilis*, and *E. coli* and also

was found to be effective against breast carcinoma cell line (MDA-MB-231) (Aygün et al. 2020).

The plant is used as a mood enhancer and sedative in traditional Iranian medicine, and in a study to justify this activity of the plant, fresh stalks were extracted with methanol and tested for its antidepressant activity on humans. The extract exerted significant effect in reducing symptoms of depression; however, the study had some limitations, and thus, additional studies were concluded to be required (Sayyah et al. 2009).

## 32.6 Side Effects

The plant is consumed as raw and as cooked where it grows naturally; therefore, it is considered to be safe. However, topical exposure to the plant also has the potential to cause irritant contact dermatitis, which is a type of phytodermatitis (An and Ozturk 2019).

## 32.7 Toxicity

*Rheum ribes* is used for medicinal purposes and consumed in various countries and considered to be safe. In efforts to elucidate the toxicity of the plant, a study was carried out by Abudayyak (2019) and it was understood that the plant might cause cell death and DNA damage on human hepatocytes, and thus, might have negative effects.

In another study examining the acute and subchronic toxicity of *R. ribes,* aromatic water prepared from the aerial parts had no observed adverse effect level (NOAEL) at a concentration less than 250 mg/kg for male rats and 500 mg/kg for female rats. However, coagulated necrosis was observed in cardiac muscles cells, thus the plant might lead to some abnormalities in the heart. Nevertheless, this toxic effect has to be confirmed with additional clinical toxicological examinations (Mojarrab et al. 2015).

## 32.8 Commercial Formulations

### 32.8.1 Commercial Preparations Related to Well-Being

Rhubarb preparations are usually found as food supplements; however, the exact plant origin is not mentioned in the formulations. Members of the *Rheum* genus are generally known as rhubarb, so it is not possible to tell the name of the exact species.

### 32.8.2 Cosmetic Preparations

There are some cosmetic products in the market that contain Rhubarb extract; however according to their formulations, these extracts belong to *R. officinale*, not *R. ribes.*

## 32.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

The plant is being used for a long time in different countries for the treatment and/or prevention of various diseases/disorders, and according to the studies found in the literature, it can be concluded that ethnomedicinal usages of the plant/plant extract are usually justified with various studies performed on the composition and/or pharmacological activities of the plant.

## 32.10 Challenges and Future Recommendation

*R. ribes* is a plant that grows as wild in the nature in various countries, and it is also cultivated in some countries having temperate climate since the red stalks of the plant are eaten as raw and as cooked (Sayyah et al. 2009). Since the plant is also cultivated, we can say that there would not be any problem related to the survival of the plant.

The plant has been used for a long period as a traditional remedy and important activities of the plant have been demonstrated with various studies. Studies on the plant elucidating the exact mechanism of action of these activities and the responsible secondary metabolites should be increased in the near future and different bioactivities of the plant should be investigated in more detail.

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# *Rosa canina* L.

# 33

Kübra Öğüt

**Abstract**

Traditionally, *Rosa canina* L. is used in drink, food, and medicine form in many countries. *R. canina* contains great amounts of pharmacologically active compositions; flavonols, carotenoids, tannins, and organic acids. So *R. canina* has been utilized to cure disorders of the kidneys urethra and viral infections, anxiety, osteoarthritis, hypertension, immunomodulatory and antidiabetic, antimicrobial, etc. When clinical studies, toxicity, and side effects about *Rosa canina* were investigated as pharmaceutical preparations, further clinical trials are needed to confirm the reported promising experimental effects in clinical use.

**Keywords**

*Rosa canina* L. · Rosaceae · Rose hip · *Antioxidant, Anticancer, Antidiabetes, Osteoarthritis*

## 33.1 Introduction

The genus *Rosa* includes 200 species 200 cultivars that are widely distributed in Asia, Europe, North America, the Middle East, and the Northwest of Iran (Khazaei et al. 2020). Turkey is one of the most important origins. Twenty-five rose species have so far been announced to grow up in Turkey (Ercisli 2005). *Rosa canina* L. is one of the most widespread members of the Rosacea family (Davis 1970). *R. canina,* also known as the dog rose, is a deciduous shrub normally ranging in height from 1 to 5 m and fragrant pink or white flowers from May to June. Its branches are curved or arched, and fruits which ripen late (Roman et al. 2013) mature into an oval 1.5–2 cm red-orange fruit, or hip (Fujii et al. 2011) and plucked during autumn (Kizil et al. 2018). Its stems are covered with sharp, small, hooked prickles. Leaves are pinnate with 5–7 leaflets (Demir and Özcan 2001).

Traditionally, fruits of *Rosa canina* are used in drink, food, and medicine form in many countries (Demir and Özcan 2001; Guimarães et al. 2010). In many European countries, the rose hips have been used for the treatment and prevention of chill, influenza, and diabetes mellitus (Chrubasik et al. 2008a). In Austria, *R. canina* fruits have been used internally as a tisane for the cure disorders of the kidneys and urethra and viral infections (Miraj 2016). In Morocco, its leaves are used to treat stomachic, headaches, and erectile

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dysfunction by the inhabits (Benlamdini et al. 2014). As a food supplement, rose hips are used to prepare jam and pickle by Iranian people (Asghari et al. 2015). In Slovenia, fruits are used as a flavoring in soft drinks made (Miraj 2016).

*R. canina* seeds include palmitic, linoleic, oleic, linolenic, stearic, and arachidonic acid (Özcan 2002). *R. canina* fruit includes flavonoid contents and high phenolic (Montazeri et al. 2011). And all rose hips include tocopherols, vitamins, carotenoids, and sugars (Chai and Ding 1995; Ercisli 2007).

Investigations showed that the use of *R. canina* can be useful in the prevention and treatment of several ailments, for instance, gout, arthritis, sciatica, rheumatism, and gastrointestinal disorders (Tayefi-Nasrabadi et al. 2012; Nojavan et al. 2008; Orhan et al. 2007; Gürbüz et al. 2003). Worldwide, the hips have been used as an anti-inflammatory and antinociceptive (Orhan et al. 2007), anticarcinogenic (Trovato et al. 1996), antimicrobial agent (Shiota et al. 2000), antioxidant (Daels-Rakotoarison et al. 2002), immunosuppressive, cardioprotective, and gastroprotective agent (Demir et al. 2014; Ogah et al. 2014).

Currently, *R. canina* extracts are frequently used in the cosmetic, food, and pharmaceutical industries (Sardarodiyan and Sani 2016; Jiménez et al. 2017).

## 33.2 Origin and Distribution

The genus *Rosa* L. (Rosaceae) comprises roughly 200 reported species and as a whole, grow in Asia, North America, the Middle East, and northern hemisphere in Europe (Ercisli 2005), particularly in the temperate and subtropical regions of the northern hemisphere (Khazaei et al. 2020).

*Rosa canina* L. is widely grown in the yard for its fruits and flowers. The plants demonstrate strong resistance to formidable environmental conditions. Turkey is one of the most important germplasm centers for rose species (Ercisli 2005).

Roughly 27 rose species have been notified in Turkey (Rosa species [Internet] 2021). These 27 species are widely expanding along the region from the sea level to altitudes as high as 3000 m. Thus, this is proper to define Turkey as a "native rose museum." *Rosa canina* L. and *Rosa damascena* Mill are the species with the highest economic value in Turkey (Ercisli and Güleryüz 2004).

## 33.3 Ethnomedicinal/Local Uses

In different parts of the world, several species of *Rosa* plants have a deep-rooted history of conventional utilization in folk medicine. *R. canina* fruits, the most well-known species of the *Rosa* genus, have significant ethnobotanical and traditional medicinal specifications. The utilization of *Rosa canina* as a medicinal plant traces back to the time of Hippocrates in ancient Greek. Along with the second World War, Britain soldiers used fruits and the syrup of *Rosa canina* fruits for preventing scorbutic (Haas 1995).

*R. canina* pseudo-fruits are conventionally used in preventive therapy and for the preparation of some foods such as tea, syrup, flour substitute, jam, jellies, beverages, probiotic, and soft drinks (Montazeri et al. 2011). Besides, *R. canina* has been used in the therapy of some conditions such as influenza, pain infections, and inflammatory diseases (Demir et al. 2014). The rose hips extensively known as "Stropacui" are used as a cure for diarrhea, in Romania (Pieroni et al. 2012). In Turkish folk medicine, the hips are known as the most efficient cure against diabetes mellitus and hemorrhoids (Orhan et al. 2007). The leaves of Rosa plant boiled in water are utilized for diuretic ingredients in prevalent cold cures (Coruh and Ercisli 2010). In some other parts of the world, *R. canina* leaf decoctions and flowers are applied in ophthalmia as an eye lotion (Tuttolomondo et al. 2014). The fruit juice of *R. canina* is internally consumed as an antidiarrheic, diuretic, antiscorbutic, and adstringent (Arnold et al. 2015). *R. canina* fruits have been utilized as a diuretic, the treatment of high blood pressure and urinary calculus, and in Iranian folk medicine (Amiri and Joharchi 2013; Emami et al. 2012). In Denmark folk medicine, rose hips have been used as a rem-

edy for arthritis (Jäger et al. 2007). Consumption of *R. canina* fruits, go by the name of Hakeputten, is believed to prevent influenza and chill in Germany (Pieroni and Gray 2008). In traditional Chinese medicine, the leaves of some Rosa species are used in the treatment of burn diseases, blain, and inflamed sore (Fenglin et al. 2004).

Currently, in traditional European folk medicine, *Rose canina* extracts are used as urinative, nephropathy, eccoprotic, arthritis, podagra, chill, and for lack of vitamin C (Chrubasik et al. 2008a).

## 33.4 Bioactive Nutraceutical and Nutritional Composition

Considering the phytochemical investigations for *Rosa canina*, many classifications of phytochemicals have been defined, the most commonly known are carotenoids (Horváth et al. 2012), phenolic acids, fatty acids (Ercisli et al. 2007), tannins (Fecka 2009), flavanols (Guimarães et al. 2010), vitamins (Barros et al. 2011), flavonoids (Hodisan et al. 1997), organic acids, stilbenoid (Cunja et al. 2016), chlorins (Horváth et al. 2012), tocopherols, and galactolipid sugars (Kharazmi 2008).

Carotenoids are responsible for the colors of *R. canina* hips and are known to show antioxidant activity (Kaur and Kapoor 2001). Further research showed that the extraction techniques influence the carotenoid content of *R. canina* oils. Provides propane and SC-$CO_2$ are more extracted than any other conventional method. By Soxhlet extraction, the oil of rosehip seeds obtained the carotenoids in the highest concentrations all over other methods (Szentmihályi et al. 2002) and recent studies showed that β-carotene was determined as the major carotenoid (Fromm et al. 2012).

HPLC analysis has demonstrated fruits of *R. canina* extract to become particularly rich in the polyphenols hyperoside, astragalin, rutin, (+)-catechin, (−)-epicatechin, gallic acid, and polyhydroxylated (Ayati et al. 2018; Wenzig et al. 2008). The phenolic compounds phloridzin, gallic acid, rutin, astragalin, vanillin, (+)-catechin, (−)-epicatechin, and defined in *R. canina* extract, have been notified as strong scavengers of the radical (Marino et al. 2014).

The essential oil *R. canina*, as examined utilizing the gas chromatography (GC)/mass spectrometry (MS) method (Nowak 2006), comprised 97 chemical components that have contained vitispiran (isomer), α-*E*-acaridial, dodecanoic acid, hexadecanoic acid, docosane (C22), β-ionone, 6-methyl-5-hepten-2-one, myristic acid, and linoleic acid primarily (Wanes et al. 2020).

In some other studies, GC–MS analysis showed that volatile compounds of *R. canina* are a complicated mixture of ketones, aldehydes, alcohols, sesquiterpenes, and monoterpenes. Two ketones have been defined: 6-methyl-5-hepten-2--one and 4-octen-3-one. Among aldehydes, 2-hexenal is the main aldehyde, and among alcohols, 2-Hexen-1-ol and 1-hexanol were determined to be dominant. Among sesquiterpenes, α-humulene and β-elemene were found to be the major compounds. Additionally monoterpenes, limonene is the main monoterpene followed by α-pinene (Demir et al. 2014).

The rosehip oils contain minor bioactive lipid constituents such as carotenoids, tocols, and sterols. The levels of constituents have many functional characteristics in human health despite observed to become the minör compounds in the oils. In Bulgaria, the tocopherol content of *R. canina* oils was detected as 89.4 mg/kg. α-Tocopherol, β-tocopherol, γ-tocopherol, δ-tocopherol, α-tocotrienol, β-tocotrienol, γ-tocotrienol, and δ-tocotrienol were obtained from hexane-extracted oil (Zlatanov 1999). From Turkey, another research was obtained to be 1124.2 mg/kg amount of tocopherol for the cold-pressed *R. canina* oils. Respectively, tocopherols of *R. canina* oils contain α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol for cold-pressed in Turkey (Topkafa 2016). α-Tocopherol, γ-tocopherol, and δ-tocopherol are obtained from *R. canina* oils from Poland (Grajzer et al. 2015).

Potentially, other polyphenols are healthful for people such as ellagic acid, salicylic acid, vanillic acid, ferulic acid, and cateic acid have

been notified in trace amounts in *R. canina* hips extracts (Haas 1995; Pieroni et al. 2012).

Analyses of fatty acids demonstrate that *R. canina* contains nine major fatty acids. Respectively, α-linolenic acid, palmitic, and linoleic acid are the major fatty acids.

*R. canina* includes some elements such as Ca, K, Mg, N, P, and Zn (Dubtsova et al. 2012). Besides, *R. canina* is known as a rich source of vitamin C (Ziegler et al. 1986). High amounts of ascorbic acid, carotenoids, and vitamin E make rose hip a good antioxidant.

However, various factors including harvesting time, altitude, genotype, climate, and the district can be in charge of diverse chemical composition and activities (Ghazghazi et al. 2010).

## 33.5 Pharmacological Activities

Fruits of *R. canina* extracts have antibacterial, antifungal, antioxidative activity, and anti-inflammatory properties (Trovato et al. 2000; Gao et al. 2004). *R. canina* contains great amounts of pharmacologically active compositions; flavanols (Chrubasik et al. 2008a), carotenoids (Ercisli et al. 2007), tannins (Barros et al. 2011), and organic acids (Kharazmi 2008).

Many different in vitro studies have shown antioxidant activities of *R. canina* due to the high amount of vitamin C (Ghazghazi et al. 2010), rich content of carotenoids (Ercisli et al. 2007) and vitamin E (Hodisan et al. 1997), flavonoids (Cunja et al. 2016), polyphenols, and proanthocyanidins (Wenzig et al. 2008). Antioxidant activity of aqueous: methanol extracts (50:50) of *R. canina* has been notified, primarily as hydrogen peroxide scavenging activities and free radical scavenging (Serteser et al. 2008).

Especially, fruits of *R. canina* have been subjected to some pharmacological studies researching the gastro-protective impacts. Several studies have demonstrated the anti-ulcerogenic activity of *R. canina* fruit that was more efficient than the reference compound misoprostol in the animal models (Gürbüz et al. 2003). Carotenoids of *R. canina* can protect gastric mucosa in peptic ulcer disease and gastroduodenal mucosal inflammation. In vitro study demonstrated that carotenoid from *R. canina* exerted against *H. pylori* which were equiparable to that of metronidazole (Horváth et al. 2012).

*Rosa canina* methanolic extract has a significant amount of phenol and flavonoid contents and investigations are on about starch digestion via digestive enzyme inhibition. Consequences showed that *R. canina* methanolic extract was very effective in inhibiting α-amylase (Asghari et al. 2015).

Several in vitro studies have shown that inhibitory activities of fruits extracts of *R. canina* on α-glucosidase were analyzed. Using column chromatography, D-glucono-1,4-lactone and daucosterol were determined as active compositions, so fruit of *R. canina* was possibly utilized for the cure of diabetes mellitus because Rose hips include efficient α-glucosidase inhibitors (Asghari et al. 2015).

Several studies have demonstrated that medication of *R. canina* may decrease the hazard of cardiovascular diseases (Andersson et al. 2012). *R. canina* reduced cholesterol and attenuated atherosclerotic plaque formation in a hypercholesterolemic animal model. In animal models, using *R. canina* extract to the diet could enhance atherosclerotic plaque volume, liver expression LDLR genes, oxidized LDL, total cholesterol levels, RCT genes, and decreased blood pressure (Cavalera et al. 2017).

For osteoarthritis, the effect *R. canina* extracts have on the expression of collagen type II, CSPG, β1-integrin, SOX-9, COX-2, MMP-9, and MMP-13 in the primary canine articular chondrocytes model was analyzed. The herb extract of *R. canina* suppressed interleukin-1β-induced NF-κB activation by inhibition of IκBα phosphorylation, p65 nuclear translocation, p65 phosphorylation, and IκBα degradation. In some studies, everyday use of Rose hips for four weeks showed reduced serum C-reactive protein levels and chemotaxis of peripheral blood neutrophils. For his reason, *R. canina* dried fruits can be used as a dietary supplement in osteoarthritis patients. The clinical studies of *R. canina* have been confirmed for osteoarthritis (Winther et al. 1999).

An in vivo study examined the analgesic activity of the aqueous preparation using animal models of pain. The analgesic activity was analyzed with a hot plates model of visceral pain in mice. *R. canina* extracts increased the lead time using animal models in a dose-dependent manner. The precuring enhanced the antinociceptive activity of *R. canina* and that was more effective than sodium salicylate (Zhang et al. 2015).

*Rosa canina* has attracted notice as a possible anticarcinogenic plant thanks to its plenty of ingredients of antioxidant integrated like glutathione, β-carotene, phenols, tocopherol, and anthocyanins (Guimarães et al. 2013). Also, studies showed that extracts of *R. canina* prohibit tumor cell line growth. Based on an in vitro investigation, on colon cancer cells, the effect of several fractions of Rose hips was analyzed. The knowledge achieved from that investigation had determined that extracts of *R. canina* are effective antioxidants able to have an antiproliferative effect. On human colon, adenocarcinoma cell lines confront with normal colon cells; *Rosa canina* extract efficacy has been approved in a different study which is described selective cytotoxic activity (Turan et al. 2018). These studies showed that *R. canina* has the potency for the evolvement of anticancer compounds.

The antimicrobial activity of *R. canina* against some microorganisms has been informed. By RP-HPLC analysis, *R. canina* seeds extracts produced kaempferol 3-O-(6.-O-Z-p-cou maroyl)-b-D-glucopyranoside and kaempferol 3-O-(6.-O-E-pcoumaroyl)-b-D-glucopyranoside that showed antibacterial activity. Also, these composites demonstrated that the growth of some Staphylococcaceae, Enterobacteriaceae, and Lactobacillus species (Kumarasamy et al. 2003). *R. canina* water extract showed toxicity activity against bacteria of gram-(+) and gram-(−). *R. canina* acetone extract demonstrated antibacterial activity against some Enterobacteriaceae, Staphylococcaceae, and Saccharomycetaceae species. *R. canina* n-hexane and chloroform extracts didn't demonstrate inhibition against analyzed microorganisms. Some studies showed that about antimicrobial activity *R. canina* methanolic extract was more efficient than other extracts. So *R. canina* extracts can be beneficial for antimicrobial activity (Montazeri et al. 2011). Using the agar well diffusion method, *R. canina* flowers, methanolic, and ethanolic extracts showed activity against some Trichocomaceae, Nectriaceae, Pleosporaceae species and two gram-(−) bacteria, comprising some Enterobacteriaceae and Pseudomonadaceae species (Rovná et al. 2021).

In animal models of nephrolithiasis, some studies showed that *R. canina* extracts possess the possibility to be utilized for urinary calculus prevention (Tayefi-Nasrabadi et al. 2012). Besides, extracts of Rose hips have protective effects on function of kidney disturbances and histological injuries caused by reperfusion damage (Ashtiyani et al. 2013).

Rose hips's hepatoprotective activity against CCl4-induced hepatotoxicity in animal models was researched. Results showed *R. canina* fruit extracts' hepatoprotective effects on CCl4-induced hepatic damage in animal models. Hepatoprotective effects can be originated from decreasing oxidative stress (Miraj 2016).

In animal models, about the antianxiety activity for flowers of *R. canina* was analyzed by the EPM test. The behavior of animal models in the test was recorded; indices belonging to the apprehension grade were given points. In this study, in a dose-dependent manner, *Rosa canina* flowers extracts open arm entries, and besides at a high dose, enhanced residence time in the open arms. Closed arm entries explicated to associate the mobility consistency did not differ from the control (Nemati et al. 2015).

Extracts of *R. canina* made improved recognition memory and depression risks in animal models. Based on an in vivo investigation, novel object recognition and swimming experiments were utilized. In the brain of animal models, homogenate to assess oxidative stress parameters' antioxidant effectivity and malondialdehyde levels was quantified. In this study, results demonstrated that *R. canina* attenuated debilitation of recognition memory and depression risks with modulation of oxidative stress in the brain of animal models (Farajpour et al. 2017).

As an immunomodulatory agent, *R. Canina,* of efficacy on the immune system, some biochemical properties were analyzed in animal models. Extract of *R. canina* enhanced phagocyte efficiency, neutrophil and monocyte quantity, and gammaglobulin degree. In *R. Canina,* extract-treated animal models hadn't been observed having important alteration about aminotransferase, alanine aminotransaminase, and alkalane phosphates. Extracts of *Rosa canina* augmented thiobarbituric acid reagent objects and reduced glutathione quantity. So, *R. canina* has immunomodulatory effects (Sadigh-Eteghad et al. 2011).

## 33.6 Clinical Studies

When clinical studies investigated *Rosa canina,* lots of them are about a rose hip and seed powder.

Investigations showed that studies searching in people with osteoarthritis revealed that two of studies were subgroup analyses. However, recent investigations on the efficiency of *R. canina* in osteoarthritis (Rossnagel et al. 2007) contained some studies by the scientists (Rein et al. 2004; Warholm et al. 2003); other reviews didn't determine the subgroups and exhibited meta-analysis with all investigations (Christensen et al. 2008).

In vivo experience was implemented to people with inflammatory rheumatic and backache. Demonstration of the efficiency is moderately effective for osteoarthritis and insufficiently effective for rheumatoid arthritis and backache (Chrubasik et al. 2008b).

In this in vivo experiences implemented on healthful human voluntary have demonstrated that extract of *Rosa canina* decreased chemotaxis of peripheral blood neutrophils, the serum acute phase C-reactive protein, and level creatinine (Kharazmi and Winther 1999)

In this study, some animal models nourished by ad libitum diets that range from 5% to 15% *R. canina* oils along 15 or 60 days demonstrated the parallel consequences for nourished animal models by triglycerides. In addition to this, the plasma total and high-density lipoprotein cholesterol levels for some animal models nourished in the range of 15% R. canina oil were observed to be higher than others (Lutz et al. 1993).

The pharmaceutical preparation of *Rosa canina* was researched in a double-blind randomized study containing 60 people with IBS. Researchers made a record of patient's intestinal disorders 2 weeks before the administration of the products by a questionnaire. People who receive the officially registered *Rosa canina* beverage as a placebo benefited insufficiently than those taking supplementation Lactobacillaceae species, and stomach ache was decreased in all of the groups (Nobaek et al. 2000).

The external use of *Rosa canina* seed oil for cheilitis, exanthesis, neurodermititis, venous ulcer, etc., can be making a promise, as of research in an investigation study with 75 people testing external use of *R. canina* seed oil, in conjunction with an internal use of fat-soluble preparations vitamins (Shabykin and Godorazhi 1967).

More preclinical and clinical studies are required to elucidate effects on muscle tone and blood glucose, anti-inflammatory and lipid lowering, antimutagenic, anticancerogenic, and antiulcerogenic effects.

## 33.7 Toxicity and Side Effects

In animal models taking 0.5–1.5 mL group into the back cell fluid, sac did not demonstrate any unusual indications. In animal models, crude *R. canina* or an apozema of seeds of *R. canina* was suitably tolerated, as were subdermal medication of *R. canina* ethanol and aqueous extracts. In addition to this, an intensified ethanol extract of *R. canina* leads to the death of some animal models which were a little susceptible.

In the interest of the ethanol fluid extract of *R. canina*, a minimum lethal dosage could not be identified in some animal models. The dosage was identified as 0.7–0.9 mL in rats and 0.9–1.1 mL in mice.

Preclinical and clinical studies demonstrated that for seeds of *Rosa canina,* a minimum lethal dose could not be specified.

Some animal models demonstrated that ethanol and aqueous of *Rosa canina* ready-made drugs give rise to cardiovascular problems. Washing out the heart of animal models with *R. canina* solutions, a 3/10 contractility was an observation correlated with efficiencies.

The heart failure was recyclable in all cases by washing the isolated heart with isotonic saline, in a short time. Some extracts and apozem of rose hip seed brought about diastolic cardiac cease at some of the different doses. Besides heart failure was recyclable, even after several minutes of heart failure.

*Rosa canina* ready-made drug brought about hemolysis on insulated erythrocytes in dilutions of various doses (Chrubasik et al. 2008a).

In some studies, an amount of nonserious events of gastrointestinal discomfort have (Warholm et al. 2003) made patients experience gastric acid regurgitation (Rein et al. 2004).

## 33.8 Available Commercial Formulations/Products, Uses, Administration Methods and Pharmacokinetic Studies

Fruits of *R. canina* are a potential medicinal plant to be utilized for functional food, drug, and cosmetic production. The oils that are usually cold-pressed from the seeds of *R. Canina,* thanks to its derm healing property, are a substantial material for the evolution of skincare products and herbal medicines. *R. canina* oil has ameliorating power to treat dermatological diseases. Oils of *R. canina* are one of the most prosperous sources of EFAs. Additionally, carotenoids, anti-ophthalmic factor, and EFAs have been used for skin regenerating agents, skincare, and as antiaging cosmeceuticals (Concha et al. 2006).

Oils of *R. canina* are usually preferred to be utilized in the therapeutical administration because the antioxidant activity of oils is a fundamental factor to sustain the long-term stability (Grajzer et al. 2015).

*R. canina* is prosperous in vitamin C, so it is obtainable as a dietary supplement in the drugstore (Larsen et al. 2003). Based on high vitamin C substance, especially Rose hips are utilized for efficacy in upper respiratory infections and body defense system. Decoction of fruits is utilized as urinative and against cauld (Fan et al. 2014).

Extracts of *R. canina* are utilized as antimicrobial and antioxidant ingredients due to total phenolics (Yilmaz and Ercisli 2011).

Extracts of *Rosa canina* fruits other than liquid extracts showed that COX-1 and -2 were strongly inhibited compared to other extracts (Jäger et al. 2007). This consequence showed that various composites could be responsible for the inhibitory activities of cyclooxygenase isoforms (Larsen et al. 2003).

Rose hips are utilized for the pharmaceutical preparations that are used in standardized fields in Langeland in respect of good agriculture practice. Using laser technique, rose hips production is made and temperature should not exceed 40 degrees (Rein et al. 2004). In this study, standardized *Rosa canina* pharmaceutical preparation is assumed to be of the equal standard and thereby includes the same amounts of minerals, vitamins, carotenoid, and another agent as utilized in other clinical experiments (Larsen et al. 2003). Another experiment showed that, for 4 weeks, 10.5 g pharmaceutical preparations about *Rosa canina* do not affect laboratory tests or clinical investigations indications in clinical results. On the contrary, previous investigations have reduced CRP concentration (Kirkeskov et al. 2011).

Using per day preparations of the *Rosa canina* in three different doses was dosed for one week. A week later, oral medication was demonstrated as an anxiolytic effective (Nemati et al. 2015).

## 33.9 Ethnomedicinal and Scientific/Clinical Evidences

*Rosa canina* is a considerable medicinal plant because of pharmaceutical industries, nutraceutical, and commercial importance. Because of con-

taining levels of high-value minerals and bioactives, nutrients were utilized as medicine, drink, and food traditionally (Sen and Gunes 1996). Conventionally, fruits of *R. canina* were used to cure flu, infection, and chronic tortion. Besides, rose hips are utilized for the cure of dermatoses and ulcer like symptoms (Guimarães et al. 2010).

Preclinical, clinical, and experimental studies demonstrated that *Rosa canina* has biological activities such as antioxidant (Daels-Rakotoarison et al. 2002), anti-inflammatory, and antinociceptive (Orhan et al. 2007), anticarcinogen (Trovato et al. 1996), hepatoprotective (Miraj 2016), anti-α-amylase activity (Asghari et al. 2015), anti-ulcer agents (Gürbüz et al. 2003), antimicrobial activities (Shiota et al. 2000), and debilitation of recognition memory, depression risks (Farajpour et al. 2017), and immunomodulatory effects (Sadigh-Eteghad et al. 2011).

When all the studies were examined, it was seen that the ethnomedical uses were compatible with preclinical, clinical, and experimental at certain doses.

## 33.10 Potential Drug Candidate

Clinical, preclinical, and experimental studies showed that the chemical composition and pharmacological activity of *Rosa canina* have been poorly investigated (Ercisli 2007). So, further studies on bioactive composition and the clinical efficiency of *Rosa canina* are essential in order to produce convenient drug and cosmetic productions and excipients standardization and rational analysis.

Although various pharmacological studies containing anti-inflammatory, antiobesity, and antioxidant effectiveness have been demonstrated for *Rosa canina* in experimental and preclinical studies, still more investigations are essential to fill existing gaps in the information of *Rosa canina's* pharmacological effects and bioactive agents.

Extract of *R. canina* antioxidant activity recommends that it can be utilized as an ingredient for the nutrients that are important in order to ensure protection against oxidative damage.

Resolvent combination for extraction of bioactive components can be the point of view in new design and formulation of the drug, cosmetic excipients, and food with advanced significance.

For topical use in the cure of dermatoses, present researches showed that it is required to explain the significance of the informed test results in clinical use and to characterize *R. canina* pharmaceutical preparation.

So, it is important to enlighten the different doses of the plant and to examine its biological activity in detail.

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# *Rosmarinus officinalis* L.

# 34

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**Abstract**

*Rosmarinus officinalis* L. (Rosemary) is a medicinal and aromatic herb belonging to the Lamiaceae family. The geographical distribution of the plant covers especially the Mediterranean Region and regions with a Mediterranean climate. In addition, it has been cultured in many countries around the world so far. The aerial components of the plant, particularly the leaves, are rich in both volatile and nonvolatile phytochemicals: terpenes, flavonoids, phenolic compounds, alcohols, and esters. Phenolic compounds such as carnosol, carnosic acid, and rosmarinic acid in its content have been associated with the plant's anticancer, anti-inflammatory, antihyperglycemic, antithrombotic, and antioxidant activities. The antimicrobial and antioxidant bioactivities of its essential oil have been utilized and accepted as a safe conservator in the food industry. While the bioactivity of the plant has been proven by in vivo and in vitro experiments, the results of clinical studies support the existence of these bioactivities. The potential of rosemary to be transformed into herbal medicine is considerable. In this chapter, we present an overview of the distribution, ethnobotany, bioactive and nutritional composition and available extraction techniques, scientific evidences, clinical and toxicological studies, available commercial formulations, and challenges and future recommendations as potential drug candidate of rosemary.

**Keywords**

Rosemary · Phenolic compounds · Rosmarinic acid · Biological activity · Toxicity

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## 34.1 Introduction

*Rosmarinus officinalis* L., also known as rosemary, is a medicinal and aromatic plant belonging to the Lamiaceae family. Nowadays, the plant has a wide cultural area, but it grows specifically in the Mediterranean countries (Allegra et al. 2020; Andrade et al. 2018). The synonym of the plant *R. officinalis is* reported as *Salvia rosmarinus* Schleid. and *Rosmarinus angustifolius* Mill. (Borges et al. 2019; Heinrich et al. 2006). According to the scientific classification, it is known in the literature as a member of the Magnoliopsida class, Asteridae subclass, and



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Lamiales order (Begum et al. 2013). *R. officinalis* is subdivided due to morphological differences such as the size of leaves, calyx, and corolla differences, and it is scientifically shown that there are a multitude of varieties (Zaouali et al. 2010) (Fig. 34.1).

Among all *Rosmarinus* species, only *R. officinalis* has an importance in terms of covering all these sectors in terms of medical, cosmetic, pharmaceutical, and industrial aspects, especially food industry (Zaouali et al. 2010; Hernández et al. 2016).

Rosemary is used in the food industry in several ways, one of which is as a flavoring agent (Hussain et al. 2010). Another way of usage is with rosemary extracts' anti-oxidation and antimicrobial properties for food preservation. As a preservative, rosemary extracts are reported to have technological advantages and benefits to consumers (Nieto et al. 2018). Rosemary oil is utilized in the food industry to preserve nearly all meat products, including pork, beef, lamb, poultry, and fish products (Hernández et al. 2016).


**Fig. 34.1** Rosemary (*Rosmarinus officinalis* L.) plant. (Source: Lešnik et al. 2021)

Rosemary has been utilized in traditional medicine for ages against various conditions (Satyal et al. 2017). The branches of the plant have been utilized as herbal tea in order to benefit from its abortive, stomachic, carminative, cholagogue, and antispasmodic effects (Soliman et al. 1994). Experimental studies have revealed that the herb has antibacterial, antifungal, antidepressant, antidiabetic, anticancer, antioxidant, anti-inflammatory, hepatoprotective, and neuroprotective effects (Ribeiro-Santos et al. 2015; Hamidpour 2017; Olfat 2012; Kensara et al. 2010).

Rosemary oil is not only used in therapeutic areas, but also has a widespread use in the cosmetic industry. Bath essences, cologne waters, shampoo, and hair toners are also cosmetic preparations in which rosemary essential oil is frequently used (Éva Stefanovits-Bányai et al. 2003).

## 34.2 Distribution and Status of Species

Rosemary is a medicinal and aromatic herb that has been benefited by people for centuries. In ancient Egypt, it is recorded that rosemary leaves were used at funerals to help the Pharaohs find peace after death (Borges et al. 2019).

The plant has been used as a foliage plant in various countries of the world since ancient times. Although it is cultivated in many countries of the world, its origin is Mediterranean region (González-Minero et al. 2020).

Iberian Peninsula is a district where rosemary is widely grown, but this distribution has been reported to decrease towards the north and northwest regions. With the recognition of Spain as the region where the plant grows naturally, it has been determined that it can grow naturally on almost all kinds of land, especially in the sunshiny and arid regions of the forest areas in the

Mediterranean region (Fig. 34.2) (Salido et al. 2003).

In a study where the geographical coordinates and sample numbers of the wild rosemary populations are grown in San Remo, Italy, and collected and grown from the Tyrrhenian Sea environment in 2013, Southern Tuscany, Island of Capraia, Northern Corsica, and Central Sardinia have been reported as the places where the plant was collected (Li et al. 2016).

It has been recorded that there are four varieties of *R. officinalis* in Tunisia: var. *typicus* Batt., var. *laxiflorus* De Noé, var. *troglodytorum* Maire, and var. *lavandulaceum* Batt (Yosr et al. 2013).

Considering the distribution of the taxon in Turkey, it is reported to be located in the provinces of Adana, Çanakkale, Hatay, and Mersin (Tübives 2021).

## 34.3 Comparison of Traditional/Ethnomedicinal/Local Uses

In Turkey, the flowers, branches, and seeds of rosemary are consumed as a herbal tea with infusion and decoction methods. While its consumption in the form of herbal tea is widely used for ailments such as migraine, flu, cold, and headache, the oil of the plant is used for hair booster (Polat and Satil 2012).

It has been analyzed that rosemary is mostly utilized in the remedy of respiratory, circulatory, and digestive tract diseases (Everest and Ozturk 2005). It is utilized for carminative and digestive purposes among the people in the Espiye-Giresun region (Polat et al. 2015). The use of decoction prepared from the aerial parts of rosemary in the Alasehir region for wound healing shows that infusion and decoction methods are the most common preparation methods for rosemary (Ugulu 2011). It is shown that it is used in gastrointestinal diseases, atherosclerosis, rheumatism, diabetes, and hypercholesterolemia (Sargin et al. 2013).

When the results of an ethnobotanical study conducted in Bayramic-Çanakkale region were evaluated, it was concluded that the people of the region used the flowers and leaves of the plant by preparing tea by infusion and consuming before breakfast against abdominal pain, cold, heart diseases, and stomach ailments (Bulut and Tuzlacı 2015). In a study conducted in Kırıkhan (Hatay) between 2011 and 2013, some ethnobotanical features of frequently consumed plants were investigated by visiting herbalist in the area.


**Fig. 34.2** Geographic dissociation of *Rosmarinus officinalis*. (Source: González-Minero et al. 2020)

According to the results, it was found that the rosemary leaves were used by the people of the region to weaken and reduce cholesterol (Altay et al. 2015).

According to an ethnobotanical survey conducted between 2004 and 2006 in Kapıdağ Peninsula, rosemary leaves act as a blood pressure regulator (Uysal et al. 2010). According to the results of an ethnobotanical study carried out in a master's thesis, it has been reported that all parts of rosemary are used as mosquito repellents in Izmit region (Kızılarslan 2012).

In North Africa, it is recorded that rosemary is used to protect wounds from germs due to its antiseptic properties (Dafni et al. 2019).

In Iran, decoctions prepared from rosemary are used as cholagogue, diuretic, and antiseptic against rheumatism and wounds (Naghibi et al. 2005).

In an ethnobotanical investigation on medicinal and aromatic plants in the Arribes del Duero region of Spain, it was reported that the people of the region prepared maceration from the branches of the plant with ethanol and used it against varicose veins (González et al. 2010).

## 34.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques (Classification and Structures of Few Representatives)

Rosemary has a lot of strong biological activities such as anti-inflammatory, antioxidant, antihyperglycemic, antibacterial, and antithrombotic. When examined ethnobotanically, it has been determined that especially its leaves are used to cure many diseases. It is widely consumed as food, especially in the Mediterranean diet (Bourhia et al. 2019). Rosemary is available to be used fresh, dry, or in the form of its essential oil (Pintore et al. 2002).

Rosemary has a very high potential as a herbal medicine due to its high content of nonvolatile and volatile compounds. Many molecular groups responsible for bioactivity have been discovered in rosemary, including monoterpenes, di- and tripenoids, esters, flavonoids, sesquiterpenes, ketone, alcohol, hydrocinnamic derivatives, and other minor components (Ali et al. 2019).

When the structure of rosemary extracts prepared by different extraction techniques is investigated, they are fundamentally divided into five representative classes. These are monoterpenes, sesquiterpenes, diterpenes, waxes, and pentacyclic triterpenes (Bensebia et al. 2016).

### 34.4.1 Volatile Compounds

Secondary metabolites are special molecules synthesized by almost all medicinal and aromatic plants. Monoterpenes are compounds that are formed by the combination of isoprene main skeleton, constitute the fundamental substance of essential oils, and have quite valuable biological activities for plants and animals (Dehsheikh et al. 2020).

When the volatile compounds in rosemary were examined, it was found that the most effective compounds in terms of both medical and aroma were terpenoids (Boix et al. 2010). Rosemary essential oil (95–98%) consists of monoterpene and monoterpenic compounds, and the rest consisted of sesquiterpene compounds (Szumny et al. 2010).

In a study in which volatile compounds of rosemary essential oil and hydrosols were detected by gas chromatography (GC/MS), it was found that two fractions contained 67 volatile molecules (Tomi et al. 2016).

Comparison of different oils is as follows: Rosemary (Spain): 1,8-cineole (12.1–14.4%), camphor (17.2–34.7%), α-pinene (10.2–21.6), α -terpineol (1.2–2.5%), borneol (3.2–7.7%), camphene (5.2–8.6%), *p*-cymene, limonene, myrcene, borneol, bornyl acetate, and β-caryopliyllene. Rosemary (Tunisia, Beja): 1,8-cineole (33.08%), camphor (18.13%), α-pinene (9.23%), α-terpinole (8.17%), borneol (5.48%), camphene (5.07%), and *p*-cymene (2.42%), limonene, bornyl acetate (Salido et al. 2003; Hcini et al. 2013).

It has been recorded that 1,8-cineole is used against respiratory tract infections such as colds, influenza, rhinitis, and sinusitis. Manifold experimental studies have been published, including animal experiments proving that eucalyptol has anti-inflammatory, analgesic, antimicrobial, antioxidant, and spasmolytic activities (Seol and Kim 2016).

Eucalyptol has been evaluated as an agent that can be used against SARS-CoV-2 due to its extremely low binding energy. However, the number of in vivo and in vitro experiments that will support these studies should be increased and the level of contribution to drug discovery should be investigated in further detail (Sharma and Kaur 2020).

Rosemary essential oil can be acquired by distillation types from traditional essential oil extraction methods. Analysis of the essential oil obtained can be done by both GC and GC-MS chromatography methods. In experimental studies, the compounds in the content of the essential oil were detected by comparing the mass spectrometry and retention times of reference standards (Boutekedjiret et al. 2003).

### 34.4.2 Nonvolatile Compounds

Most of the bioactivities of the plant have been associated with its phenolic compounds. While the phenolic diterpenes carried by the plant are listed as carnosol and carnosic acid, the major compound as phenolic acid is rosmarinic acid. Flavonoids such as genkwanin and cirsimaritin are also important phenolic compounds that increase the antioxidant activity of the plant (Borras Linares et al. 2011).

In a study where the chromatographic analysis of the ethanolic extract of rosemary was carried out, it was revealed that it is a very rich plant in terms of flavonoids and phenolic substances. The most common molecules in the leaves of the plant as carnosic acid, rosmarinic acid, and carnosol have been associated with the plant's anti-inflammatory, antioxidant, and antitumor effects (Bai et al. 2010). Although Rosmarinic acid is thought to be the most important antioxidant molecule found in rosemary, there are numerous scientific studies proving that these three molecules are very important in terms of the plant's bioactivity (Bulduk and Gökce 2017). Experimental studies revealed that Rosmarinic acid also has antiangiogenic and antiproliferative effects (Martins-Gomes et al. 2019).

It has been proven that rosemary extracts contain six triterpenic molecules: micromeric acid, benthamic acid, oleanolic acid, augustic acid, betulinic acid, and ursolic acid (Martínez et al. 2012; Fernández-Ochoa et al. 2017.). There are experimental studies that show that ursolic acid obtained from Rosemary inhibits tumor initiation (Liu 1995).

It has been proven that α, β-amyrin molecules in pentacyclic triterpene structure have manifold biological activities. Hepatoprotective, antimicrobial, and anti-inflammatory activities are biological effects that have been defined until today (Bensebia et al. 2016).

The analysis of the phenolic diterpene molecules in the composition of rosemary, which provides antioxidant effects, was carried out in an experimental study. According to the study, these compounds were obtained by solvent, supercritical fluid extraction (SFE), and Soxhlet extraction by reversed-phase HPLC method that was used for the detection of the compounds (Bicchi et al. 2000).

Detailed information about the process of obtaining and characterizing bioactive compounds from the *R. officinalis* plant is schematized in Fig. 34.3 (Lešnik et al. 2021).

## 34.5 Scientific Evidences: Pharmacological Activities

### 34.5.1 Antitumor Activity

Animal experiments and in vivo studies on the anticancer activity of rosemary have been reported frequently. Anticancer activity was associated with the antioxidant effect of rosemary, and the main compounds rosmarinic acid, carnosic acid, ursolic acid, and carnosol, were also blamed for anticancer activity (González-Vallinas et al. 2015).

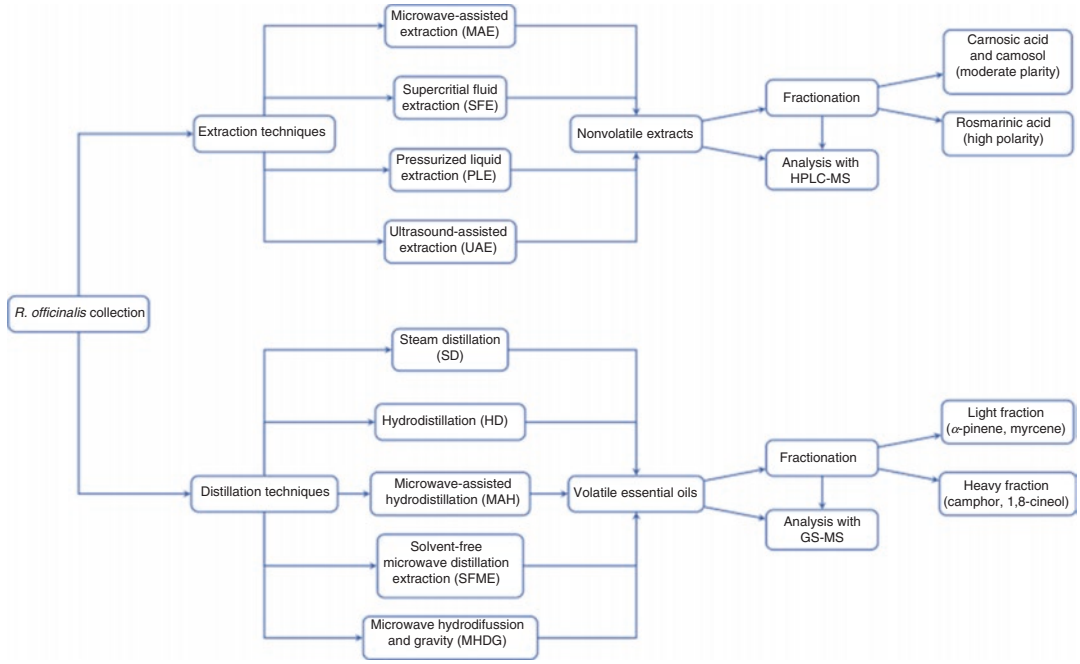


**Fig. 34.3** Process of isolating the ingredients of *R. officinalis* plant. (Source: Lešnik et al. 2021)

The 7,12-dimethylbenz [a] anthracene (DMBA) molecule has been found to be associated with breast tumors (Lai and Singh 2006). Rosemary extract and carnosol intraperitoneally (i.p.) were injected into female rats and inhibited the DMBA-induced rat memory tumor formation. It was concluded that this injection dose of rosemary and carnosol provided a notable reduction in the number of DMBA-mediated adenocarinomas in each rat compared to the control group. When the same experiments were repeated with ursolic acid, no positive results were obtained. According to this experimental study, rosemary and carnosol were evaluated as having high potential in terms of protective effect against breast cancer (Singletary et al. 1996).

An in vitro experiment was carried out with rosemary extracts on colon cancer cells known as CaCo-2 (Colorectal adenocarcinoma). It was determined that CaCo-2 colon cancer cells were exposed to rosemary extract at a dose of 30 μg/mL for 24 h, which significantly reduced colony formation. Antitumor activity was associated with the antioxidant capacity of the extract and its mechanism was explained as the DNA chain breaks induced by $H_2O_2$ and its reduction in oxidative damage (Moore et al. 2016).

In distinctive survey on the antitumor effect of rosemary, it has been discovered that components isolated from diverse rosemary extracts show anticancer activity in liver, bladder, cervix, breast, pancreas, leukemia, ovarian, lung, colon, and prostate tumors in in vitro experiments (González-Vallinas et al. 2015).

### 34.5.2 Anti-inflammatory Activity

For the purpose of examining the anti-inflammatory effect of rosmarinic acid, inflammation was induced in two methods using rats. In the first rat modeling, locally carrageenan-induced paw edema was created. In other modeling, a systemic inflammation was obtained in rats with models of thermal injury and ischemia reperfusion in the liver. In the first rat modeling with local edema, it was found that rosmarinic acid applied at 25 mg/kg effectively decreased paw edema at 6 h, performing a dose-response impact of over 60%. In the second rat modeling, the same amount of ros-

marinic acid was applied, and as a result, it was defined that it could also decrease multi-organ dysfunction markers by modulating NF-kB (nuclear factor kB) and metalloproteinase-9 (Sánchez-Camargo and Herrero 2017).

The formation of nitrogen species and reactive oxygen is stimulated by pro-inflammatory cytokines. Due to this pathway, it has been concluded that the procurement of such reactive species in macrophages is likely to be inhibited when the formation of pro-inflammatory cytokines is decreased. Dimethylsulfoxide is preferred in experimental studies due to its ability to mix with water and dissolve a wide variety of polar and nonpolar small molecules. In addition to protecting cells, tissues, and organs as an advantage of use, it is also important to increase the absorption of pharmaceutical agent. The impact of rosemary extracts dissolved in DMSO on pro-inflammatory cytokine procurement by peritoneal macrophages and J774 cells was evaluated. It was concluded that rosemary extracts have a more remarkable ability to inhibit IL-1 and TNF-α in macrophages. Inhibition of cytokines by rosemary extract has been potentially evaluated as alternating approaches in the healer of inflammatory ailments (Justo et al. 2015).

### 34.5.3 Antihyperglicemic Activity

α-Glucosidase enzyme breaks down oligosaccharides and disaccharides found in brushy edge cells in the small intestine into monosaccharides. Acarbose is an oral antidiabetic agent that reversibly binds to the α-glucosidase enzyme (Turan and Kulaksızoğlu 2015). A cell-free model resulted in an in vitro study where application of rosemary extract (5.5 mg/mL–55 mg/mL) found notable 60% reduction in α-glucosidase activity (Naimi et al. 2017).

Carnosol is one of the fundamental components of rosemary extract and has been analyzed in vitro to show remarkable α-glucosidase inhibitory effect. In an in vivo study, an oral sucrose tolerance test (OSTT) was enforced in normal mice to evaluate the hypoglycemic effect of carnosol. It was recorded that carnosol applied at a dose of 10 mg/kg caused a notable degree in the postprandial blood glucose level ($p < 0.05$) 30 min after sucrose loading. The data were evaluated to prove that carnosol exhibits strong hypoglycemic effects in in vivo, consistent with in vitro α-glucosidase inhibitory effect (Ma et al. 2020).

Skeletal muscle is one of the substantial target tissues of insulin and plays a vital role in glucose balance. Deteriorating effect of insulin on skeletal muscles emerges from increasing insulin resistance and advanced stages of type 2 diabetes mellitus (T2DM). As a result of activating the AMP-activated kinase (AMPK), also known as the energy sensor, it has been recorded that the muscles increase glucose uptake. The use of AMPK activators is considered an effective way to combat insulin resistance. The effect of carnosol, a significant ingredient in rosemary extract, on L6 rat muscle cells was investigated in an in vitro experimental study. In the study, it was recorded that use of carnosol enhanced glucose uptake, similar to insulin and metformin, in L6 muscle cells, and this effect was associated with an AMPK-dependent mechanism (Vlavcheski and Tsiani 2018).

### 34.5.4 Antithrombotic Activity

In a study investigating the antithrombotic effects of various plants both in vivo and in vitro, it was concluded that rosemary is an important plant in terms of antithrombotic activity. After the rosemary was crushed, centrifugation was applied and the filtrate was separated. The effect of rosemary permeate on platelet-rich thrombus formation was evaluated by hemostatometry, a share-induced in vitro platelet function test. The supernatants of plants display notable antithrombotic effect and were also evaluated using a laser-induced in vivo thrombosis test in mice. Rosemary was also examined in this in vivo study, and as a result, it was found that thyme and rosemary have significant antithrombotic effects because of their intrinsic inhibitory effect on platelets (Yamamoto et al. 2005).

In order to examine the impact of rosemary and thyme herbs on experimental thrombosis, thrombosis was induced on a group of male mice with injury to their carotid arteries by He-Ne laser. According to the experiment, the control group mice were given a diet mixture of pure nutrients rich in fat. On the other hand, the mice in the experimental group were fed a diet containing herbal ingredients by powdering both rosemary and thyme plants, adding 0.5% and 5% (w/w) concentration to the aforementioned pure diet mixture. Hemorrhage time evaluation and endothelium-dependent flow-mediated vasodilation tests (FMV) were performed in groups of mice with 12 weeks of diet feeding. In conclusion, it was revealed that long-term dietary intake containing 5% or 0.5% rosemary or 5% thyme remarkable suppressed the rate of thrombus formation in vivo, but the bleeding time did not prolong. The mechanism of the antithrombotic activity has been described as pressing of platelet reactivity and excitation of the vascular endothelium (Naemura et al. 2008).

### 34.5.5 Antioxidant Activity

The carnosol molecule has been demonstrated to have strong antioxidant impact in in vitro cell culture, cell-free and, in vivo animal models in various experimental studies conducted up to date (O'Neill et al. 2020).

In a study in which essential oil was obtained to determine the antioxidant impact of rosemary, antioxidant impact was evaluated by DPPH (1,1-diphenyl-2-picrylhydrazyl) radical method. The amount of phenolic substance contained in the essential oil of rosemary obtained with a yield of 0.40 mL/100 g was determined and the findings were evaluated in accordance with the normal value ranges in the literature. It has been proven that the powerful antioxidant impact in rosemary leaves is due to the carnosol, rosmarinic acid, and carnosic acid contained in the plant. Within the scope of the research, antioxidant capacity values of essential oils were made by DPPH radical scavenging activity analysis and $IC_{50}$ values were calculated and the results were given in μg/mL extract. The $IC_{50}$ value of rosemary essential oil was found as 2.75 μg extract/mL. Rosemary essential oil has been contrived to include high amounts of total phenolic substances and show antioxidant activity. Based on this discovery, it has been reported that its antioxidant effect is evaluated as a potential agent for the food and pharmaceutical industry (Özbek Yazıcı et al. 2020).

The nematode *Caenorhabditis elegans*, a free-living nematode abundant in earth ecosystems, can be used as an experimental model (Wu et al. 2012). In a study using *C. elegans* as a model, the antioxidant and antiaging potential of carnosol was investigated. Reactive oxygen species (ROS) are formed as a by-product of cellular metabolism. ROS formed in excessive amounts in the cell cause many diseases from cancer to aging by damaging lipids, proteins, and DNA. It was found that *C. elegans* treated with various concentrations of carnosol evinced a remarkable decline in ROS levels compared to those of control *C. elegans*. In particular, the amount of reactive oxygen species in the group exposed to 180 μM carnosole demonstrated a decrease of up to 76%, a decrease compared to control group. Consequently, carnosol has been reported to significantly reduce ROS accumulation in *C. Elegans* (Lin et al. 2019).

## 34.6 Clinical Studies

In a double-blind randomized restricted search using university students, 68 students with age ranges of 22.9 ± 1.7 were randomly assigned to receive placebo and 500 mg rosemary two times per day for one month. Students were divided into two groups by block randomization, with 34 people receiving rosemary and 34 placebos. In the study, dried aerial parts of rosemary were put in capsules as 500 mg and given to 34 twice a day for a month. The other 34 in the control group were given starch in the capsule to create a placebo effect. According to the results, it was revealed that rosemary can be used by college students to strengthen prospective and retrospective memory, decrease dejectedness and anxiety,

and enhance slumber quality (Nematolahi et al. 2018).

A clinical search was performed on the activity of rosemary extract on acetylcholinesterase (AChE), total antioxidant capacity (TAC), effect on lipid peroxidation, and protein carbonylation. In a double-blind, randomized controlled study, 50 healthy participants aged 21–25 years were divided into two groups. While 25 people were given 500 mg of starch powder twice a day as a placebo, 25 people were given 500 mg of rosemary powder prepared from rosemary extract and this administration was carried out for a month. According to the results, it has been demonstrated that rosemary has a preventive impulse on both AChE impact and nonenzymatic antioxidant defense system (Fatemeh et al. 2021).

An experiment was conducted in 22 healthy volunteers to designate the impress of rosemary tea on plasma anxiety and depression biomarkers. In the study, volunteers between the ages of 20 and 50 were given tea prepared by pouring 100 mL boiled water over 5 g of dried rosemary per day for 10 days. Before and 10 days after the experiment started, brain derived neurotrophic factor (BDNF), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukine-6 (IL-6), interleukine-4 (IL4), and cortisol levels were evaluated with ELISA kits. According to the findings, in healthy volunteers participating in the trial, rosemary tea consumption was found to have promising anxiolytic and/or antidepressant effects. This effect was associated with the increase in BDNF level, which is considered to be the most important marker in the depression marker (Achour et al. 2021).

It was recorded that prehospital emergency technicians had a significant degree of occupational fatigue and also became depressed. A study was conducted to investigate the impacts of rosemary essential oil on the symptoms of occupational fatigue and depression experienced by prehospital emergency service technicians. The rosemary oil used in the study was diluted with odorless sweet almond oil to contain 25% pure rosemary oil. Linen badges were prepared and placed at a distance of 30 cm from the uniforms of the participants. Before each work shift, the participants sprayed a mixture of 25% pure rosemary essential oil on their rosettes with a total volume of 1 cc in two breaths each morning. The implementation continued for a month and the participants shift three days a week. Although all the procedures applied in the placebo group are the same, unlike the control group, the sprayed oil consists entirely of 100% sweet almond oil without fragrance. On the day of the last application, one hour after the application, DASS-42 (Depression subscale) and OFER-15 questionnaires were reapplied to the participants in both groups. According to the evaluations, it has been recorded that the mixture prepared with 25% rosemary essential oil does not reduce occupational fatigue, but may have affirmative effects in reducing depression in prehospital emergency service technicians (Hatami et al. 2021).

There are no human studies that provide convincing evidence of the activity of rosemary extracts on the human inflammation or immune system mechanism. Only in a randomized clinical study of 19 people, rosemary extract tablets were given for 21 days, and markers such as proinflammatory cytokine TNF-α, cellular adhesion mediating proteins ICAM-1 and VCAM-1, and high sensitivity C-reactive protein (hs-CRP) were measured and recorded. According to the results, no remarkable changes in biomarkers were observed and no considerable link was established between the consumption of rosemary extract and inflammation. More clinical research on the subject should be done (Ahmed and Babakir-Mina 2020).

## 34.7 Toxicological Studies

### 34.7.1 Dose and Safety Profile

Many studies have been carried out on the safety of rosemary. The rosemary herb has been qualified as "generally safe" or GRAS (CFR182.10; 182.20) by the FDA in America (Ghasemzadeh Rahbardar et al. 2020).

EFSA could not determine acceptable daily intake dose for rosemary due to insufficient toxicological data (Belsito et al. 2013). Depending

on the data supplied with the food industry, the Panel was organized by the EFSA and the exposure calculations of Rosemary extracts (E 392) were redefined. The highest mean was redescriptioned, with the exposure estimate (non-brand-related scenario) assessing 0.09 mg/kg body weight daily in kids (3–9 years) and 0.20 mg/kg body weight daily in the highest 95th percentile of exposure in children. The uncertainty factor was also taken into account in the Panel; these exposure estimates were interpreted and evaluated as exaggerating the actual exposing from the utilization of rosemary extracts (E 392) as food additives according to Annex II (EFSA 2012).

### 34.7.2 Single Dose (Acute) Toxicity

In an acute oral safety study of rosemary extract, Wistar rats were administered as a monadic per os gavage at a dose of 2 g/kg body weight. No side effects or deaths were ascertained during the two-week observation period, including changes in behavior, food and water consumption, or body weight. Hereby, rosemary extracts were evaluated to have low acute toxicity, and oral lethal doses ($LD_{50}$) of more than 2 g/kg body weight were declared for both male and female rats (Anadon et al. 2008).

In an experiment in which methanolic extracts of rosemary leaves were injected intraperitoneally into mice, the mean lethal dose (LD50) was limited to be 4.125 g/kg (Ghasemzadeh Rahbardar et al. 2020).

Rosemary extract did not cause death in rats up to 1.2 g/100 g BW by intragastric administration; therefore, it was considered to have very low lethality. The lethal dose 50 (LD50) of rosemary essential oil in intragastric administration in rats was found to be 5.5 kg BW (Ferreira 2010).

In addition, surveys have also been carried out to show that the use of camphor in rosemary causes serious side effects and deaths. Ingestion of 1 g of camphor in camphor oil to a 19-month-old child resulted in death. Although adults survived the intake of up to 43 g of camphor, the conclusion was reached by the American Academy of Pediatrics that intake of 2 g usually produces hazardous impacts. Intake of 0.7–1.0 g of camphor in children has proven to be lethal (Ferreira 2010).

### 34.7.3 Repeated Dose Toxicity

A 21-day clinical study was conducted with patients with seasonal allergic rhino conjunctivitis, and rosmarinic acid was administered at a dose of 50 mg/day to 9 patients. A placebo at a dose of 200 mg/day was given to a control group of 10 people. The symptoms of the patients were followed up daily. As a result, no significant abnormality was detected in blood values and side effects were not observed (Belsito et al. 2013).

Rosemary extracts prepared with acetone were administered to a group of rats at dietary concentrations of 0 (control), 2100, 3600 or 5000 mg/kg, respectively, 14 days before, during, and after mating (during pregnancy and up to Lactation Day 13 for females). In the study, general toxicity (food consumption, clinical signs, body weight) and reproductive/developmental outcomes (estrous cycles, thyroid hormones, thyroid histopathology, anogenital distance, fertility and mating performance, reproductive organ weights) were examined. At the highest dose administration (equivalent to the average daily intakes of 149 or 189 mg/kg bw/day carnosic acid and carnosol), the result was determined as the level with no adverse effects for general and reproductive toxicity (Phipps et al. 2021a, b).

### 34.7.4 Mutagenicity

In a toxicological study, the mutagenic and genotoxic potency of rosemary essential oil in gnawers was investigated using comet, micronucleus, and chromosome aberration tests. Three doses of rosemary oil were administered by gavage to experimental animals. These doses were administered as 0.3 g, 1 g, and 2 g/kg. For the micronucleus test (mutagenicity endpoint), peripheral blood and liver jail cells were gathered along

with bone marrow cells. As a result, it has been concluded that rosemary essential oil causes mutagenic and genotoxic activities when implemented per os (Maistro et al. 2010).

The Ames test was performed for the extract of rosemary prepared by supercritical carbon dioxide method and it was proved to be non-mutagenic as a result (Phipps et al. 2021a, b).

### 34.7.5 GRAS

It has been recorded (21CFR182.10) that *R. officinalis* is predominantly considered safe (GRAS) as a spice and other natural seasonings and flavorings (FDA 2021).

## 34.8 Available Commercial Formulations/Products, Uses, Administration Methods and Pharmacokinetic Studies

Since rosemary extract contains compounds proven to have antioxidative effects, it has been recognized as a food additive since 2008 by the EFSA (Q-2003-140) (González-Minero et al. 2020).

Drying and grinding of rosemary leaves are carried out to prepare trading accessible rosemary extracts. Extracts are obtained by using various diluents such as methanol, hexane, acetone, ethanol, and water or a solvent admixture as solvent. It has been recorded that rosemary extracts are commercially available in the form of fine powder products or liquid forms after rarefaction/normalization with appropriate food grade carriers that entrench dependable output quality (Senanayake 2018).

The formulations of rosemary extract are marketed in the European Union and the United States as the solely trading accessible formulations as an antioxidant. As the formulation, it is commercialized in fat soluble form, as a dry powder, and dispersed or dissolved in water forms (Klančnik et al. 2009).

In a research article, comparing the conventional Rosemary extract (without carrier systems) and the extract including the liposomal distribution system, its effect on skin permeability rate in vitro was investigated according to determined parameters. As a result, it has been clearly exemplified that the rosemary extract mixture in the liposomal carrier system at a volume ratio of 1:1 has an in vitro release rate of approximately 30%, respectively, compared to 100% in 40 min compared to the conventional formula (Aslan and Kurt 2021).

An experiment has been conducted with commercial rosemary essential oils to provide antimicrobial effect against vaginal infection in pregnant women. According to the results, commercial rosemary essential oils have been established to be a promising treatment method for vaginal infections. However, it has been concluded that more toxicity and safety studies should be conducted on the subject (Bogavac et al. 2017).

Rosemary's extracts and essential oil have been used in hundreds of cosmetic products. Rosemary essential oils are used for massage and aromatherapy. Rosemary has also been found to be included in formulations such as eye cream, shampoos, deodorant, aftershave lotion, rosemary water, anti-wrinkle cream, gels, and moisturizing face cream (González-Minero et al. 2020). It has been determined that rosemary extracts have a stronger germicide impact on bacteria and molds. Due to its strong antimicrobial activity, various extracts prepared from rosemary leaves were allowed to be included in many cosmetic preparations (Damianova et al. 2010).

Various surveys have proven that extracts of rosemary have positive affect for hair growth, especially leaf extracts. As a result, products containing rosemary extracts for hair growth have also found their way into the market as commercially accessible forms. C57BL/6-coded mice with testosterone-mediated alopecia were cured locally with hydroalcoholic rosemary extracts at a dose of 2 mg per daytime. After the 16th day of cure, a significant increase in hair growth was observed in the experimental group compared to that in the control group (de Macedo et al. 2020).

It has been reported that the pharmacological potential of rosmarinic acid is important and shows a low bioavailability. Some solid dosage forms such as cyclodextrin complexes and lipid nanotechnology-based delivery systems have been proposed as solutions to increase the bioavailability of rosmarinic acid and to facilitate its application (Veras et al. 2019).

It has been reported that rosmarinic acid extracts can be utilized intranasally, topically, pulmonary, and by intravenous infusion routes. Besides, oral administration has been evaluated as the main route of taking rosmarinic acid into the human body. Regarding the pathway of metabolism, it is predicted to be metabolized by the intestinal microflora by splitting into phenolic units in a simpler and easily absorbable way.

It has been determined that the rosmarinic acid molecule also undergoes conjugation reactions. The main route of elimination has been recorded as renal excretion (Hitl et al. 2021).

Various studies have proven that essential oils and their mono- and sesquiterpenoid components probably interact with more than one type of receptor, causing fast-acting neurotoxic effects in insects. EcoTrol™ and TetraCURB™ are insecticidal preparations produced by the United States, consisting of active ingredients including rosemary essential oil (Isman 2019).

## 34.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

It has been recorded that rosemary is a widely used medicinal and aromatic herb against migraine by various countries, especially in Iran.

Rosemary is widely used for analgesic, anti-inflammatory, and anti-neurodegenerative purposes. This efficiency of rosemary has been particularly harnessed for rosmarinic acid, one of the therapeutically rich components in it. To investigate whether the use of rosemary in folk medicine coincides with reality, a model of neuropathic pain due to sciatic nerve chronic constriction injury (CCI) was created on rats, and the potency anti-inflammatory bears on rosemary and rosmarinic acid were investigated. According to the data, the conventional use of rosemary as an efficient treat for pain allayment and inflammatory ailments has been supported. The fact that tea prepared from rosemary leaves, rosemary extracts, and rosemary have an important potential use in the cure of different neurological disarrays such as neuropathic pain and inflammation should not be overlooked and this potential should be evaluated (Jivad et al. 2016; Ghasemzadeh Rahbardar et al. 2017).

Considering the current data, it has been determined that rosemary essential oil has important effects to be considered in the remedy of acute inflamed circumstance, given its efficaciousness and high safeness of use. In addition, more chronic inflammation models should be examined to explain and clarify the subject more broadly. Clinical studies on the subject are insufficient and their number should be increased. When the studies are examined in general, the accuracy of the ethno-pharmacological use of rosemary essential oil against inflammation-related diseases is supported (Borges et al. 2019).

Numerous explorations have been handled concerning the antimicrobial effect of rosemary. It has been confirmed that Rosemary essential oils with the best antimicrobial impact contain the highest amounts of verbenone, camphor, and borneol compounds (Santoyo et al. 2005). Rosemary has been used in the folk medicine in many regions of the world against influenza, colds, and influenza from past to present and is considered as an antiseptic herb. In this context, the antimicrobial activity proven in experimental studies with the ethnobotanical use of rosemary is because its antimicrobial activity coincides.

Rosemary essential oil has the ability to prolong the shelf life of food stuffs and resume their property during warehousing. Due to this feature, it is seen in the markets that it is already used as a biopreservative in the food sector (Rašković et al. 2014).

Another traditional utilization of rosemary is its consumption due to its antidiabetic and antihyperglycemic effects, as can be seen in the ethnobotanical studies section. In a study

investigating the antidiabetic effect of rosemary, it was observed that it improved hyperglycism in rats as well as dyslipidemia in rats which developed alloxan-induced diabetes. According to the result of the same study, it was recorded that rosemary had a hepatoprotective effect (Kensera et al 2010). In a infirmary survey handled to probe the effect of rosemary on diabetic patients and healthy people, significant effects were observed on the improvement of HbA1c and Vitamin B12 levels in both diabetic patients and healthy individuals (Shawabkeh and Jamal 2017). These studies showed that the antihyperglycemic and antidiabetic activities of rosemary are compatible with traditional use.

## 34.10 Challenges and Future Recommendations as Potential Drug Candidate

The potential of carnosol and carnosic acid, which are polyphenolic diterpene molecules of rosemary, as protective agents against prostate cancer has been evaluated in accordance with epidemiologic investigations. Studies have been executed to elucidate the mechanism of carnosic acid and carnosol's anticancer activity. Based on the pathways elucidated, the potential use of rosemary for a chemopreventive agent against prostate malignant neoplastic disease is considered (Petiwala et al. 2013).

It has been proven in experimental applications that rosemary extracts show anticancer effects against many types of cancer. Although this activity was associated with the major compounds in its content, it was reported that the application of rosemary extract by itself created synergism. Rosemary extracts were evaluated by FDA and EFSA as being potent for human wellness and the application of the extract as a whole was supported. Clinical studies should be focused without ignoring the potency of using rosemary extract as a tumor type-specific agent (González-Vallinas et al. 2015).

In terms of a disease that may be arising from assorted factors such as Alzheimer's disease, especially diterpenic molecules of rosemary have been proposed as a viable solution against this disease (Habtemariam 2016).

While medicinal and aromatic plants are transformed into herbal medicine, various problems are encountered, which can be claimed as a limiting factor in obtaining herbal medicine from the rosemary plant.

There are many factors affecting the production phase of herbal medicine such as quality, processing and collection, standardization, processes related to quality control, pharmacovigilance, and regulations. The inadequate clinical studies and the unreasonable use of herbal products with the perception of "harmless" are also considered as one of the factors that restrict studies on drugs (Sen and Chakraborty 2017).

In summary, the promising effect of the scientifically proven bioactivity of rosemary has shown to be a potential herbal medicine in the future. However, further clinical studies are needed.

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# *Silybum marianum* L. Gaertn.

# 35

Tuğsen Doğru and Nuraniye Eruygur

**Abstract**

*Silybum marianum*, commonly known as Milk Thistle and one of the important members of the Asteraceae family, is the focus of research due to both its wide range of medicinal effects and its use as vegetables. Having a history of over 2000 years, *S. marianum* has been used by different civilizations and cultures against various diseases. Traditionally, it comes to the fore with its use to treat liver diseases of different etiologies. Although there are some negative results for its efficacy against liver diseases, it is commercially sold under names such as Legalon®, Livergol®, Silipide®, and Siliphos® due to its hepatoprotective effect. Although several studies of the plant on various types of cancer and diabetes continue, its antioxidant, anti-inflammatory, immunomodulatory, and antidot against Amanita poising effects have been revealed by studies. Most of the biological effects of *S. marianum* are attributed to silymarin, which is a flavonolignan mixture such as silybinin A, isosilybinin A and B, silychristin, and silydianin in its structure. In clinical studies, no serious side effects were observed except for gastrointestinal disorders, diarrhea, vomiting, and allergic reactions, and it was revealed that the plant is safe and tolerable. since *S. marianum* has traditionally a wide range of uses, clinical studies can be performed on the plant other than its widely known uses.

**Keywords**

*Silybum marianum* · Milk Thistle · Hepatoprotective · Biological effects · Clinical trials

## 35.1 Introduction

*Silybum marianum* L. Gaertn belongs to the Asteraceae family and is known as milk thistle, Marian thistle, Mary thistle, Saint Mary's thistle, Blessed milk thistle, Mary's thistle, Mediterranean milk thistle, variegated thistle, and *Cardus marianus* L., Scotch thistle, and Lady's Thistle. The medicinal herb is traditionally used as a galactagogue, so this effect is thought to be the origin of its name (Bahmani et al. 2015; Ross 2008). This herb has been used since the time of earliest. It is estimated that it was first described as Pternix by Theophrastus (fourth century B.C.), a plant biologist. Later, Dioscorides was mentioned in Materia Medica (first century A.D.). Plinius called it "sillybum" and mentioned that this plant with honey was desirable for "carrying off bile" (first century A.D.) (Karkanis et al. 2011; Křen

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**Fig. 35.1** *Silybum marianum* (Barnes et al. 2007)

and Walterová 2005; Qavami et al. 2013). Since ancient times, *S. marianum* fruit and seeds have been used for hepatoprotection and the treatment of biliary disorders (Bahmani et al. 2015; Postwhite et al. 2007). Before the tenth century AD, the use of S. marianum in cardiovascular diseases was recorded in China's largest official medical text, Taiping Shenghui Fang (Abdelfattah et al. 2020; Zhao et al. 2019).

*S. marianum* is an annual or biennial plant with reddish-purple flowers that bloom in July–August. The stem is 20–150 cm tall, green, and glabrous or slightly arachnoid-pubescent; basal leaves (25–50 cm long, 12–25 cm wide), cauline, pinnatifid, leaves alternate, thick, glossy green, white-veined or variegated, and glabrous with strongly spiny margins. Wide inflorescence of red-purple tubular hermaphrodite florets gathered into a capitulum (2.5–4.0 cm in diameter) tucked into an involucre with thorny external bracts. 6–7 mm long fruits with a white, silky pappus (15–20 mm in diameter) at the apex, made up of 6–8 hard-skinned achenes (WHO 1999) (Fig. 35.1).

In the present study, the distribution of *S. marianum,* its history, biochemical characterization, extraction techniques, ethno-pharmacological, in vitro, in vivo and clinical studies, available formulations/products, uses, pharmacokinetic and toxicological studies, and adverse reactions in patients are generally evaluated.

## 35.2 Distribution and Status of Species

*Silybum marianum* is distributed in Southern Russia, Southern Europe, Northern Africa, and Asia Minor North and South America, South Australia, and New Zealand (Abouzid et al. 2016; Bijak 2017; Martinelli et al. 2021).

## 35.3 Comparison of Traditional/Ethnomedicinal/Local Uses in Turkey and Throughout the World (Asia and Europe)

*Silybum marianum* leaves, roots, seeds, and herbs have been used for a number of diseases in folk medicine, including cardiac disorders, kidney problems, liver disorders, heart failure, gastronomic disturbances, fever, mental disorders, rheumatism, and improving memory (Kumar et al. 2011; Marmouzi et al. 2021). The common uses and parts of *S. marianum* for diseases in different regions are given in Table 35.1.

## 35.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques

There are various extraction methods such as microwave-assisted method, sample pretreatment, soxhlet extraction, and reflux mercerization of silymarin, which is considered as a bioactive compound in *S. marianum* (Aziz et al. 2021). In a study, it was determined that ethanol at 60 °C recovered the greatest yield of silymarin and increasing the temperature increased the yield of silymarin in extractions with water (Wallace et al. 2015). Recently, new approaches have been developed for obtaining silymarin from plant tissue culture of *S. marianum* (Abdelfattah et al. 2020).

As a result of the quantitative and qualitative analysis studies, it was determined that seeds of *S. marianum* contain rutin, morin, and quercetin by HPLC-UV and fruits of *S. marianum* contain taxifolin, silydianin, silychristin, oxyderivative of silybin/isosilybin isomers, 2,3-dehydro derivatives of silybirdisosilybin isomers, silybin, and isosilybin by HPLC-MS (Farmaceutiche and Capponi 2001; Nazir et al. 2018). In another study, it was found that *S. marianum* contains various phytomolecules like kaempferol, β-carotene, naringenin, silandrin, apigenin, silymonin, tyramin, fumaric acid, histamine, $Ca^{+2}$, and oxalic acid (Guarrera and Savo 2016).

## 35.5 Scientific Evidences: Pharmacological Activities

Many in vitro and in vivo investigations have revealed the biological effects of silymarin for the treatment of different diseases such as viral infections, hepatic disorders, sepsis, burns, cancer, hypercholesterolemia, arthritis, diabetes, osteoporosis, Alzheimer's, and Parkinson's disease (Stolf et al. 2017).

The methanol extract of *S. marianum* showed acetylcholinesterase ($IC_{50}$: 110 μg/mL) and butrlycolinesterase ($IC_{50}$: 130 μg/mL) inhibitory activity and antioxidant activity against DPPH ($IC_{50}$: 280 μg/mL) and ABTS ($IC_{50}$: 220 μg/mL). At the same study, in mice with amnesia induced by scopolamine, *S. marianum* reversed spontaneous alternation performance in the Y-maze task (Nazir et al. 2018). Silymarin disrupted the proliferation of HSC-4 oral cancer cells and triggered caspase-dependent apoptosis in vitro and in vivo studies. Silymarin also inhibited tumor volume and growth. In addition, no hepatic or renal toxicity was observed in vivo (Won et al. 2018). Furthermore, animal models in vivo have been used to assess anti-skin cancer activity of silymarin due to its anti-inflammatory, antioxidant, and immunomodulatory properties (Katiyar 2005). Many studies have shown that silibin, the main component of silymarin, protects against UVB-induced DNA damage and phytocarcinogenesis in both topical (9 mg in 200 ml acetone) and oral (50 mg/kg body weight dose) applications by inducing gene/protein changes and triggering aberrant cellular signaling pathways (Raj et al. 2020).

It was reported in a study using a full-thickness scalp wound healing model in mice that the lignin compound dehydrodiconiferyl alcohol isolated from S. marianum could support wound healing by increasing epithelial cell proliferation

**Table 35.1** Ethnomedicinal uses of *S. marianum* in different countries

| Country | Local name | Parts | Uses | References |
|---|---|---|---|---|
| Iran | Khar maryam | Flowers | Hypertension, Kidney pain, Hepatoprotective agents | Baharvand-ahmadi and Asadi-samani (2017), Delfan et al. (2015), Ghanadi et al. (2019) |
| Iran | Khar Khangaloo | Seeds, flowers | Decrease blood pressure | Dolatkhahi et al. (2014) |
| Serbia | Mlečni čkalj | Seeds | Liver cleansing, digestive system disorders | Jana et al. (2019) |
| Pakistan | Aghzai | Leaves, stems | Diabetes mellitus type II | Zain-ul-abidin et al. (2018) |
| Pakistan | – | – | Hepatitis | Ali et al. (2017) |
| Pakistan | Kandali | Stems, leaves and seeds | Liver problems, Urinary system and gall bladder problems | Shahid and Asad Shabbir (2018) |
| Pakistan | Kandyara | Seeds | Antioxidant, Appetite | Ajaib et al. (2015) |
| Pakistan | Dhmaan/ Kandiara | Whole plant | Snakebite victim | State (2017) |
| Italy | Carduggiu, cardu Marianu, | Fresh or dried leaves inflorescence | Galactogogue | Geraci et al. (2018) |
| Italy | Cardone | | High fever, Sores | Fortini et al. (2016) |
| Italy | Cardo | Nettle, mixed in the oil | Neuralgias, depurative | Campania et al. (2016) |
| Italy | Cardo santo | Whole plant, root | rheumatism | Campania and Motti (2017) |
| Georgia | – | Seed | Liver diseases | Bussmann et al. (2020) |
| Fas | Chouk lahmar | – | Cardiovascular | Ben Akka et al. (2019) |
| Northern Ethiopia | Dander | Fresh root with honey and swallow | Impotence in male | Kidane et al. (2018) |
| Azerbaijan | Maryam tikani | Stylus, Seeds | Rheumatism, appetizer, diuretic | Alizadeh Salteh and Amani (n.d.) |
| Algeria | Elkhanfra | Flowers | Hypotension | Senouci et al. (2019) |
| Spain | – | Flowery plant | Brucellosis | Benítez et al. (2010) |
| Spain | Cardo mariano | Roots | Injuries | González et al. (2010) |
| Turkey | Kenger dikeni, deve dikeni, Akkız dikeni | Stems and Leaves | Liver problems | Polat and Satil (2012) |
| Turkey | Deve dikeni tohumu | Seeds | Appetizing, rheumatism, antipyretic | Akgül et al. (2016) |
| Turkey | Diken böree, diken böreğe | Stems | Kidney diseases, kidney regeneration | Sargin (2015) |
| Turkey | Deve dikeni | Flowering shoots | Kidney stones, urine problems, rheumatism | Palabas and Koca (2020) |
| Turkey | Sütlü kenger, deve dikeni | Seeds, stems | Diuretic, rheumatism, appetizing, anorexia, hepatotonic | Sargin et al. (2013) |

and collagen formation while reducing inflammatory cell infiltration (Hu et al. 2020). In a previous study, silibinin was found to inhibit interleukin-1-induced inflammation, phosphorylation of phosphatidylinositol 3 kinase/protein kinase B, and activation of nuclear factor-kappa B in human osteoarthritis chondrocytes. Furthermore, silibinin has been reported to protect cartilage from degradation in mice with osteoarthritis (Zheng et al. 2017).

The effects of silymarin against early stage liver fibrosis in $CCl_4$-treated rats were investigated. At the end of the study, it was reported that silymarin given at a dose of 50 mg/b.w decreased oxidative stress, hepato-cytolysis, activation of Kupffer cells, expression of a-smooth muscle actin, and markers of hepatic stellate cells activation like transforming growth factor b1 (Clichici et al. 2014).

Silymarin has antidotal effects against biological toxins such as snake venoms, mycotoxins, and bacterial toxins. Especially, in *Amanita phalloides* poisoning, to reduce the intracellular concentrations of amatoxins and their toxic effect, silymarin can inhibit the uptake of amatoxins into hepatocytes and cut enterohepatic circulation (Fanoudi et al. 2020; Ye and Liu 2018). In January 2007, six family members poisoned with amatoxin were treated with intravenous *S. marianum* in California (Tamayo and Diamond 2007). Also, it has protective effect against chemical toxic agents such as metals, hepatotoxic pesticides and neurotoxic, and cardiotoxic, nephrotoxic agents (Ye and Liu 2018).

## 35.6 Clinical Trials

A number of experimental and clinical studies of milk thistle and some of its components (flavonolignans such as silymarin and silibin) have been published for several disease in past times. Its toxicity and side effects were found to be less in clinical studies. Milk thistle extracts are well-known for their safety and tolerability. (Tamayo and Diamond 2007). Some clinical studies conducted on *S. marianum* are mentioned in Table 35.2.

## 35.7 Toxicological Studies

Animal and clinical studies conducted on silymarin have shown no toxic effects. Standardized preparation has been reported that high doses of mild laxatives may be effective (WHO 2004; Porwal et al. 2019). Non-serious allergic reactions like urticaria, skin rash, and pruritus have been observed. Anaphylactic shock was reported in a person consuming S. *marianum* tea (Edwards and Costa Rocha 2015). Adverse effects such as headache and gastrointestinal disorders have been reported after oral intake. In patients with hepatitis C, silymarin injections induced abdominal pain, vomiting, diarrhea, and a heat sensation over the course of two days (1400 mg/day) (Biermer et al. 2012; Soleimani et al. 2019). In Austria, intermittent sweating, nausea, colicky abdominal pain, fluid diarrhea, vomiting, weakness, and collapse were reported in a 57-year-old woman patient using Milk Thistle Vegicaps for headache and liver cleanser for two months (Committee 1999).

The quantity of silybin in standardized *S. marianum* herbs should not be less than 0.6 percent, according to the Chinese Pharmacopoeia. Fruits of *S. marianum* contain at least 1.5–2% silymarin, according to the European Pharmacopoeia and the United States National Formulary (Wang et al. 2020). The daily dosage is 12–15 g as crude drug and as a standardized silymarin extract containing 200–400 mg of silybin and it is known to be tolerated at doses as high as 700 mg three times a day for 24 weeks. At 100 μM concentrations, silydianin, silybin, and silychristin were not cytotoxic or genotoxic (WHO 2004; Edwards and Costa Rocha 2015; Soleimani et al. 2019).

## 35.8 Available Commercial Formulations/Products, Uses, Administration Methods and Pharmacokinetic Studies

The leaves, young stalks, and roots of the *S. marianum* are added to salads or cooked and consumed as vegetables. Its achene can be used as coffee or tea (Azoz et al. 2019). Many medicinally used formulations have been developed for the standardized extract of the herbal plant to enhance bioavailability, flow ability, and compressibility (Cianchino et al. 2020). In different dosage forms like Tablets (Carsil®), tincture, syrups (Alrin-B®) and capsule are available

**Table 35.2** Some clinical studies conducted on *S. marianum*

| Disease | Participants number | Dose of administration | Therapy (days) | Effects | References |
|---|---|---|---|---|---|
| Type 2 diabetes mellitus | 40 | 140 mg silymarin | 45 | Fasting blood sugar ↓<br>Serum insulin ↓<br>Serum triglyceride ↓<br>Total cholesterol ↓<br>Low-density lipoprotein cholesterol ↓<br>High-density triglyceride ↓<br>Lipoproteincholesterol ↓ | Ebrahimpour-koujan et al. (2018) |
| Chronic hepatitis C | 24 | 600 mg or 1200 mg *S. marianum* extract | 84 | There is no significant difference among *S. marianum* and placebo | Gordon et al. (2006) |
| Acute radiodermatitis | 40 | 1% gel silymarin | 60 | Severity of radiodermatitis ↓<br>Radiodermatitis development and progression ↓ | Karbasforooshan et al. (2019) |
| Menopausal symptoms | 8 | 400 mg *S. marianum* extract | 84 | Frequency and severity of hot flashes ↓ | Saberi et al. (2020) |
| In patients taking isotretinoin for acne vulgaris | 74 | 140 mg Livergol | 30 | Alanin aminotransferase ↓<br>Aspartate transaminase ↓ | Mirnezami et al. (2020) |
| B-thalassemia | 82 | 140 mg Silymarin | 84 | C-reactive protein ↓<br>Interleukin (IL)-6 ↓<br>IL-10 ↑ | Darvishi-Khezri et al. (2020) |
| Nonalcoholic steatohepatitis | 99 | 700 mg silymarin | 336 | Fibrosis-4 score ↓<br>Nonalcoholic fatty liver disease Fibrosis-4 score ↓<br>Aspartate aminotransferase ↓ | Wah Kheong et al. (2017) |
| Hepatotoxicity in childhood acute lymphoblastic leukemia | 50 | 80 mg, 160 mg, 240 mg, 320 mg by weight | 56 | Alanin aminotransferase ↓<br>Aspartate transaminase ↓ | Ladas et al. (2010) |

↓: decreases

approximately 75 silymarin brands (Tighe et al. 2020). It commonly is used as a food supplement under the names of Legalon®, Livergol®, Silipide®, and Siliphos®. The FDA has not approved any products related with silymarin or *S. marianum* for the treatment of any disease (Post-white et al. 2007; Shavandi et al. 2017).

In a pharmacokinetics study of standardized *S. marianum* extract (Legalon®), healthy participants after oral administration of Legalon and flavonolignans were absorbed and eliminated quickly. Exposure to unconjugated flavonolignan compounds was mostly observed as silibinin A, followed by silibinin B, isosilybin B, isosilybin A, silychristin, and silydianin (Izzo et al. 2018). Generally, it was found that 20–50% of silymarin is absorbed when administered orally. Eighty percent of the dose is excreted in the bile in both oral and intravenous applications. In healthy volunteers, a half-life of 6 h has been reported when administering silymarin corresponding to 240 mg of silybin (Barnes et al. 2007). Silymarin can lead to changes in the metabolism of antihistamines, oral contraceptives, benzodiazepines, protease inhibitors, and cholesterol-lowering agents by inducing cytochrome P450, isoform 3A4, and p-glycoprotein (Polyak et al. 2013).

## 35.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

Except hepatoprotective effect, there are studies on antimicrobial, anticancer, cardioprotective, neuroprotective, antidiabetic, and detoxification effects of *S. marianum* (Abenavoli et al. 2010; Wang et al. 2020). Clinical studies on different types of cancer and diabetes are continuing rapidly (Huseini et al. 2006; Sagar 2007). Its use in Type II diabetes in Pakistan region supports the positive effects seen in clinical studies (Zain-ul-abidin et al. 2018). Traditionally, it was observed that it was used for kidney disease in Iran and Turkey (Delfan et al. 2015; Sargin 2015).

## 35.10 Challenges and Future Recommendations as Potential Drug Candidate

Since ancients times, the whole part of the *S. marianum* plant is used in the prevention of various illnesses or as a nutrient by physicians and herbalists. Drugs obtained by purifying fruit of *S. marianum* have been on the market for about 50 years and are used for their hepatoprotective action, as well as for antioxidant, anti-inflammatory, and antifibrotic properties (Martinelli et al. 2021). These effects are due to 3 flavonolignan isomers (silybin, silydianin, and silychristin). Silybin is the component with the highest medicinal effect and makes up 50% to 70% of silymarin (Abenavoli et al. 2010).

It is widely used due to its hepatoprotective effect; some clinical studies have shown that it has no effect on different types of liver diseases. Since it has been traditionally used widely, clinical studies on this subject can be expanded.

As a conclusion, since *S. marianum* has a wide range of traditional uses, clinical studies can be performed on the plant other than its widely known uses.

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# *Urtica dioica* L.

# 36

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**Abstract**

*Urtica dioica* L., known as nettle, is a herbaceous, perennial plant, belonging to Urticaceae family. This chapter covers description and distribution of the plant. Additionally, its chemical composition and traditional use were presented in detail. The in vitro and in vivo activities of nettle extracts (root, leave, and seed) such as antimicrobial, antiviral, antioxidant, anti-inflammatory, antidiabetic, hepatoprotective, hypotensive, and anticancer have been highlighted via its rich phytochemical composition.

**Keywords**

*Urtica dioica* · Nettle plant · Phytochemical composition · Antioxidant

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## 36.1 Introduction

*Urtica dioica* L., popularly known as nettle, is used as a medicinal plant (Genc et al. 2011). *Urtica dioica* L. is a herbaceous, perennial plant with an extensive sympodial system of rhizomes and stolons, 1 to 2 m tall, rooting at the nodes (Taylor 2009; Vijaykumar 2018). The soft leaves are 3 to 15 cm long, arranged oppositely on a green stem. The leaves have a strongly serrated margin, a cordate base, and an acuminate tip with a terminal leaf tooth longer than adjacent laterals (Miraj 2016; Pashazadeh et al. 2013). The plant has many hollow stinging hairs called trichomes on its leaves and stems, which act like hypodermic needles, injecting histamine and other chemicals that produce a stinging sensation when contacted by humans and other animals. It has widely spreading rhizomes and stolons, which are bright yellow as are the roots. It bears small greenish or brownish numerous flowers in dense axillary inflorescences. The leaves and stems are very hairy with non-stinging hairs and also bear many stinging hairs (trichomes), whose tips come off when touched, transforming the hair into a needle that will inject several chemicals: acetylcholine, histamine, 5-HT (serotonin), moroidin, leukotrienes, and possibly formic acid (Miraj 2016; Pashazadeh et al. 2013).

The nettle family (Urticaceae) consists of 54 genera, while the genus *Urtica* L., including



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*Urtica dioica* L., consists of 100 species (Kim et al. 2015; Kavalali 2003). Taxonomy of *Urtica dioica* L. is as follow: Kingdom: Plantae (Plants); Subkingdom: Tracheobionta (Vascular plants); Superdivision: Spermatophyta (Seeded plants); Division: Magnoliophyta (Flowering plants); Class: Magnoliopsida (Dicotyledons); Subclass: Hamamelididae; Order: Urticales; Family: Urticaceae (Nettle family); Genus: *Urtica* L. (Nettle); Species: *Urtica dioica* L. (Stinging nettle) (Fig. 36.1).

## 36.2 Distribution of *Urtica dioica* L.

*Urtica dioica* L. grows in some regions of the world depending on altitude, terrain, climate, and other environmental conditions (Davis 1989). It is distributed in temperate regions of Asia, Europe, and America and some cool regions of Africa (Mahlangeni et al. 2016). *Urtica dioica* L. shows the distribution in many countries such as Afghanistan, Andorra, Argentina, Austria, Belgium, Bulgaria, Canada, China, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, India, Iran, Ireland, Latvia, Liechtenstein, Lithuania, Luxembourg, Mexico, Morocco, Nepal, Netherlands, Norway, Peru,

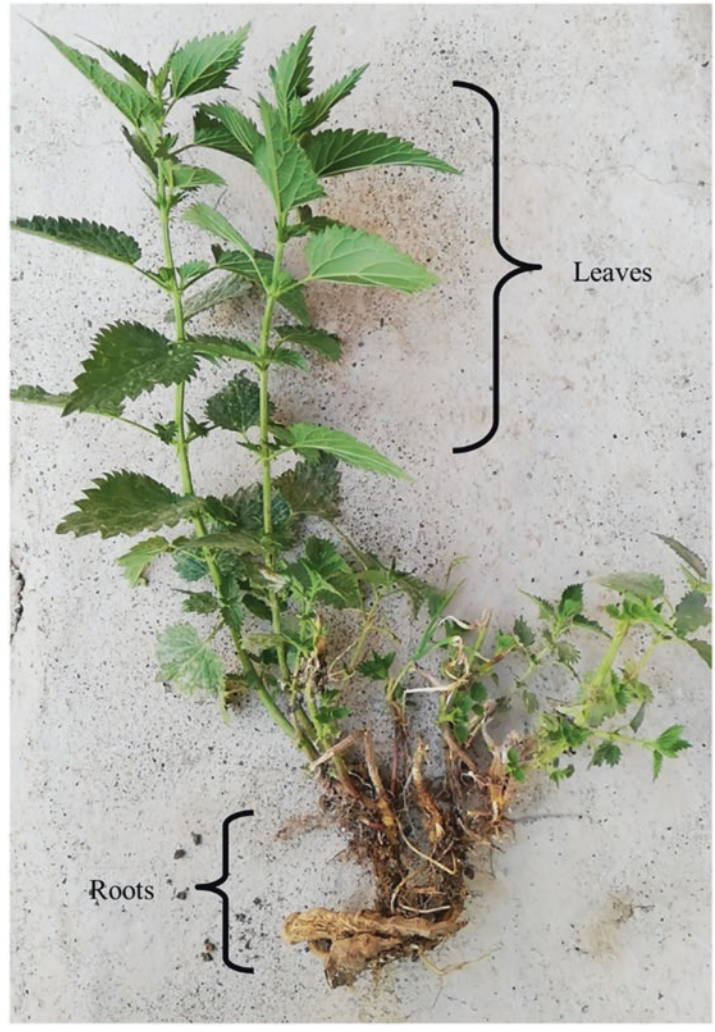


**Fig. 36.1** *Urtica dioica* plant

Poland, Romania, Slovakia, South Africa, Spain, Sweden, Switzerland, Tunisia, Turkey, United Kingdom, and United States.

## 36.3 Comparison of Traditional/Ethnomedicinal/ Local Uses

*Urtica dioica* is a plant that has traditionally both medicinal and non-medicinal uses. *Urtica dioica* can be made into tea, is edible, and can be used as a component in drinks and cocktails because of its nutritious nature (Kregiel et al. 2018). In addition, it has been used in many non-medical subjects such as fabric, thread, paper, dye, and fly repellent (Bodros and Baley 2008; Eser and Onal 2015; Đurić et al. 2019). In the medical use of *Urtica dioica*, parts of the plant such as whole plant, leaves, roots, and seeds are used. *Urtica dioica* L. has effects such as astringent, anti-inflammatory, diuretic, anticancer, antihypertensive, antioxidant, antihyperglycemic, antiproliferative and anti-dandruff, antibacterial, analgesic, antiviral, anti-colitis, and anti-Alzheimer (Erdogrul 2002; Asgarpanah and Mohajerani 2012; Dar et al. 2012). Additionally, it is used internally in the hemorrhoids, treatment of heavy menstrual bleeding, anemia, jaundice, stones in the urinary bladder, gout, preventing dizziness, hemorrhage, arthritis; used externally for the treatment of sciatica, hair problems, neuralgia, insect bites, nosebleed, and rheumatism (Erdogrul 2002; Jarić et al. 2014) (Fig. 36.2).

## 36.4 Bioactive/Nutraceutical and Nutritional Composition

*Urtica dioica* is a plant rich in ingredients that have been used for a long time (Dhouibi et al. 2020). Fresh plant shoot: It has been shown to contain (90%) moisture, total carbohydrate (7.1%), dietary fiber (6.4%), proteins (3.7%), ash (2.1%), and fat (0.6%). Besides, the plant (shoot) is rich in vitamin A, calcium, iron, and protein (Rutto et al. 2013). Phenolic, flavonoid, mineral, and vitamin contents in plant structure are given in Table 36.1.

## 36.5 Scientific Evidences

### 36.5.1 In Vitro Studies

#### Antioxidant

The antioxidant effect of *Urtica dioica* was determined by the DPPH method to neutralize free radicals from the environment. Studies have determined that various fractions of the nettle plant have a remarkable antioxidant effect when compared with antioxidant standards (Kataki et al. 2012; Chahardehi et al. 2009). Methanolic extract of nettle had the highest total antioxidant activity than infusion and decoction (Albayrak et al. 2012). It was reported that a protein fraction from aerial parts of *Urtica dioica* (called as $UDHL_{30}$) had anti-mutagenic and radical scavenger properties (Di Sotto et al. 2015). The hepatoprotective effect of *Urtica dioica* was demonstrated in vitro by 24-h exposure of HepG2 cells to various plant fractions. It has been shown that the ethyl acetate fraction has a hepatoprotective effect by increasing cell death and cell viability depending on the concentration (Joshi et al. 2015).

The antiproliferative effect was determined by measuring the effect of the plant in some cell lines at various concentrations. Studies have shown that *Urtica dioica* contributed to reduction of the proliferation (Fattahi et al. 2013; Güler 2011). Nettle tea obtained from leaves of plant prevented growth of acute leukemia cell lines (U-937 and KG-1) because of its phytochemical content (Hodroj et al. 2020). Methanolic extract of *U. dioica* effectively inhibited proliferation of colon cancer cell lines (HT 29 and HCT 116) without affecting normal *Vero* cells up to 250 μg/mL (Razak et al. 2020).

The anti-inflammatory effects include the plant's antagonist and negative agonist activity against the Histamine-1 (H1) receptor and the inhibition of mast cell tryptase, which prevents degranulation and release of a number of pro-inflammatory mediators. It also prevents prostaglandin formation by inhibiting Cyclooxygenase-1 (COX-1), Cyclooxygenase-2 (COX-2), and Hematopoietic Prostaglandin D2 synthase (HPGDS) in pro-inflammatory pathways (Roschek et al. 2009). The hypoglycemic

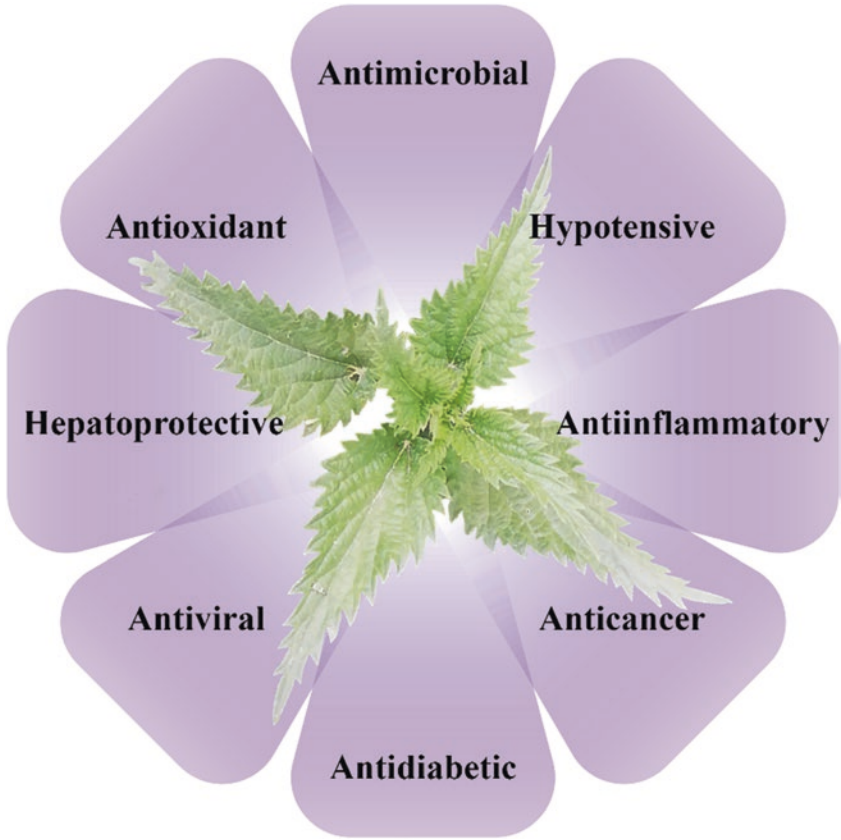


**Fig. 36.2** The effects of nettle (*Urtica dioica* L.) plant

effect was investigated by exposure of the cells to the plant. This effect is attributed to the mechanisms by which the plant mediates GLUT4 translocation and stimulates insulin (Kadan et al. 2013).

## Antimicrobial

*Urtica dioica* has a strong antibacterial effect on bacteria such as *Escherichia coli*, *Salmonella* spp., *Proteus* spp., *Bacillus subtilis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* by disrupting the stabilization, by facilitating the adhesion of bacteria to the surface, or by inactivating regions such as bacterial enzymes and receptors (Salih 2014). Pressured liquid extract of *Urtica dioica* L. showed antimicrobial activity against *Pseudomonas fragi*, *Campylobacter jejuni*, *Staphylococcus aureus,* and *Shewanella* strains (Elez Garofulić et al. 2021). Additionally, methanolic extract of *Urtica dioica* had an antibacterial potential against methicillin resistance *Staphylococcus aureus* (Salehzadeh et al. 2014). Moreover, the root, stem, and leaves of *Urtica dioica* plant possess in vitro antimicrobial potential to varying extent against various bacterial strains (Rajput et al. 2019). Furthermore, flavonoids and triterpenoids of nettle plant with crude purification exhibited antimicrobial activities against some bacteria because of dodemorph, phthalic anhydride, and their derivatives major compounds according to LC-MS analysis (Quan et al. 2021).

## Antiviral

Nettle plant has an antiviral potential against some influenza viruses (H1N1, H3N2), SARS-CoV virus, and HIV (Keyaerts et al. 2007; Gordts et al. 2015; Vanderlinden et al. 2020).

**Table 36.1** Phytochemical content of the *Urtica dioica* L. plant

| Groups | Compounds | References |
|---|---|---|
| Amino acids | Alanine, arginine, aspartic acid + asparagine, Glutamic acid + glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tyrosine, valine, γ-aminobutyrate | Rutto et al. (2013) Grauso et al. (2019) |
| Carbohydrates | β-Glucose, α-glucose, α-rhamnose, sucrose, Myo-inositol, inulin | Grauso et al. (2019) |
| Organic acids | Acetic acid, citric acid, formic acid, malic acid, malonic acid, quinic acid, succinic acid | Grauso et al. (2019) |
| Fatty acids | α-Linolenic acid, arachidic acid, arachidonic acid, behenic acid, cis-10-heptadecenoic acid, cis-11,14-eicosadenoic acid, cis-13,16-docosadienoic acid, cis-9,12-linoleic acid, cis-9-Oleic acid, heneicosanoic acid, heptadecanoic acid, lauric acid, lignoceric acid, myristic acid, myristoleic acid, nervonic acid, palmitic acid, palmitoleic acid, stearic acid, tricosanoic acid | Đurović et al. (2017) |
| Carotenoids | 13′-cis-lutein, 13-cis-lutein, 9′-cis-lutein, 9-cis-lutein, All-trans-lutein, all-trans-β-carotene, Lycopene, Neoxanthin, Violaxanthin, β-carotene-cis-isomers | Guil-Guerrero et al. (2003) |
| Phenolic compounds | (+)-Neo-olivil, 1,2-diguaiacyl-1,3-propanediol, 1-guaiacyl-1,2-propanediol, 1-hydroxy-1-(4-hydroxy-3-methoxy-phenyl) acetone, 1-hydroxy-1-(4-hydroxyphenyl)-2-propanone, 2,6-dimethoxy-hydroquinone, 4-acetyl-2-methylphenol, α-hydroxy-propiovanillone, caffeic acid, coniferol, esculetin, feroulic acid, ferulic acid, gallic acid, gentisic acid, guaiacyl-3-propanol, homovanillyl alcohol, homovanillyl alcohol-40-glycoside, isolariciresinol, m-hydroxy-acetophenone, neochlorogenic acid, p-coumaric acid, p-hydroxy-acetophenone, p-hydroxy-benzaldehyde, p-hydroxybenzoic acid, p-hydroxybenzyl alcohol, protocatechuic acid, quinic acid, salicylic alcohol, secoisolaicirisenol, sinapyl alcohol, skopoletin, syringic acid, tyrosol, vanillic acid | Proestos et al. (2006), Orčić et al. (2014), Kraus and Spiteller (1990) |
| Flavonoids | Amentoflavon, catechin, catechin hydrate, crysoeriol, epicatechin, isorhamnetin, isorhamnetin hexoside, isorhamnetin-3-O-rutinoside, kaempferol, kaempferol-3-O-glucoside, quercetin dihexoside, quercetin-3-O-glucoside, quercetin-3-O-rutinoside | Proestos et al. (2006), Orčić et al. (2014), Farag et al. (2013) |
| Volatile compounds | (E)- β-Ionone, (E)-anethol, (E)-geranyl acetone, 2-heptanone, 2-pentyl furan, benzyl salicylate, carvacrol, carvone, cumin aldehyde, dihydroatiniolide, ethyl palmitate, heptanal, hexahydrofarnesyl acetone, hexahydrofarnesyl acetone, hexanal, linalool, methyl palmitate, naphtalene, neophytadiene, nonanal, octanol, p-cymene, phytol, α-copaene, α-terpineol, β-bisabolene, β-bourbonene, β-carophyllene, γ-cadinene, γ-sitosterol, δ-cadinene | Gül et al. (2012), Iordache et al. (2009) |

The (*N-acetylglucosamine*)*n*-specific *Urtica dioica* agglutinin (UDA) caused strong inhibition of replication of the A/Fort Monmouth/1/47 and A/Netherlands/378/2005 viruses (Vanderlinden et al. 2020). It was reported that because of the presence of β-sitosterol, luteoxanthin, violaxanthin, and rutin, *U. dioica* might have antiviral activity against SARS-CoV 19 according to molecular docking results by interacting with active site of ACE-2 receptor (Upreti et al. 2021).

### 36.5.2 In Vivo Studies

#### Antioxidant

The antioxidant effect is the result of neutralization of reactive oxygen species in the environment. In various animal studies, it has been reported that the plant extract has an antioxidant effect by causing an increase in antioxidant enzyme levels such as decreased SOD, CAT, GR, and GST (Yener et al. 2009; Joshi et al. 2015). Nettle plant exhibited dose-dependent ameliorative effect against oxida-

tive stress induced by potassium boromate in rats (Dhouibi et al. 2021). Nettle leaf extract (methanolic) having antioxidant and anti-inflammatory effect exhibited positive effects on kidney damage induced by gentamicin in rats (Hajihashemi et al. 2020). The hepatoprotective effect of *Urtica dioica* was evaluated in vivo on CCl4-induced liver damage rats. The resulting liver damage was evaluated by liver-related biochemical parameters and histopathologically. The hepatoprotective effect of *Urtica dioica* was demonstrated by dose-dependent significant decrease in the levels of increased serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, alkaline phosphatase, and total bilirubin and decreased necrosis (Joshi et al. 2015). Nettle seed extract protected liver injury from radiation according to some serum biomarkers, liver antioxidant enzyme parameters, and histopathological findings (Yıldızhan et al. 2020). Moreover, in many preclinical studies, it has been reported that the seeds of the plant *Urtica dioica* suppress liver, kidney and testicular damage biomarkers, lipid peroxidation, and histopathological lesion formation against various toxic substances (Uyar et al. 2016, 2018, 2021).

## Antidiabetic

Diabetes is a metabolic disease characterized by hyperglycemia that occurs when there is insufficient secretion of insulin or resistance to secreted insulin, or in the case of both. It has been reported in various studies that *Urtica dioica* has an antidiabetic effect by lowering insulin level and insulin resistance in animal models (Gohari et al. 2018; Ahangarpour et al. 2012). Ethanolic extract of *U. dioica* has an antidiabetic potential by lowering fasting blood sugar level and glycolyzed hemoglobin (HbA1c %) and increasing plasma insulin level in diabetic mice (Pérez Gutiérrez et al. 2021). In the same study, nettle extract exhibited protective effects in diabetic mice according to results of liver damage biomarkers (AST, ALT, ALP, TBARS), antioxidant enzyme activities, and lipid profile parameters. Recently, it was reported that the use of nettle extract together with exercise training in STZ-induced diabetic rats resulted in reduction in negative effects of diabetes on cognitive functions (Rahmati et al. 2021). Additionally, 50 mg/kg/day ethanolic nettle extract together with moderate exercise might contribute to increase in improvement of central neural activities in diabetic rats induced by streptozotocin (Keshvari et al. 2020).

## Anticancer

Cancer is a group of diseases that occur as a result of the uncontrolled and abnormal growth of normal cells in any organ or tissue (Esposito et al. 2019). Anticancer activity of *Urtica dioica* and its effects on azoxymethane-induced colon cancer were investigated in rats. It has been shown that the extract causes an increase in cancer-related antioxidant parameters and that adenomas and adenocarcinomas significantly decrease both numerically and in size according to the histopathological results (Uyar et al. 2021).

## Hypotensive

The hypotensive effect of the herb was experimentally evaluated on rats. It has been reported that the leaf extract of *Urtica dioica* reduces systolic blood pressure and diastolic blood pressure in rats with hypertension (Vajic et al. 2018). Additionally, nettle root extract caused decrease in tension in rats by increasing nitric oxide and opening calcium channels (Testai et al. 2002). The presence of flavonoid compounds in *Urtica dioica* might have been one of the mechanisms for lowering hypertension (Basati et al. 2021).

## Others

Lutein, ethanolic leave extract of *Urtica dioica,* and their combination improved on in vitro production of embryo and oxidative status in polycystic ovary syndrome in a model of mice (Bandariyan et al. 2021). In another in vivo gynecologic study, methanol extract obtained from nettle aerial part exhibited ameliorative activity because of its flavonoids in the rat endometriosis model (Ilhan et al. 2019).

Ethyl acetate root extract of nettle plant having antioxidant potential has antiepileptic effect against pentylenetetrazole and maximal electroshock-induced seizure models (Loshali et al. 2021). Nettle extracts, particularly roots, have ameliorative effects against scopolamine-

induced neuroinflammatory and/or Alzheimer-like phenotype in rats (Almaaty et al. 2021).

It was reported that seed extract of *U. dioica* had a protective role against asthma induced by ovalbumin containing aluminum hydroxide in mice model (Irani et al. 2020).

*U. dioica* extract not only prevented kidney stone formation, but also treated stones in rats induced by ethylene glycol (Keleş et al. 2020).

Hyperlipidemia is a metabolic problem that is characterized by high plasma lipid levels and can cause various disorders if not corrected (Dong et al. 2021). The antihyperlipidemic effect of *Urtica dioica* is explained by the decrease in LDL, total cholesterol, and LDL/HDL levels in studies conducted on rats (Daher et al. 2006; Nassiri-Asl et al. 1986).

## 36.6 Clinical Studies

Leave, root, seed, and aerial part of *Urtica dioica* are used as folk medicine due to its many beneficial pharmacological and clinical effects in, for example, diabetes, inflammatory, prostate cancer, liver diseases, impotence, etc. (Yıldızhan et al. 2020; Fattahi et al. 2016; Türkdoğan et al. 2003). It was reported that supplementation of *U. dioica* might have been beneficial for controlling of fasting blood sugar level in type 2 diabetes patients (Ziaei et al. 2020). Preclinical and clinical studies have shown that *Urtica dioica* root extracts are effective in improving benign prostatic hyperplasia in terms of IPSS score and patient quality of life, and an increase in mean and maximum urine flow rates and a decrease in prostate volume and residual urine level were observed after treatment (Mahboubi 2020). *Urtica dioica* tablets have been determined to reduce sleep delay and increase sleep duration in hemodialysis patients (Alizadeh et al. 2021). *Urtica dioica* leaf aqueous extract has been reported to have an antiproliferative effect on the human breast cancer cell line (MCF-7) and may be a potential chemotherapeutic agent for breast cancer (Fattahi et al. 2013). Moreover, in the light of available information, it is clear that *Urtica dioica* has pharmacological functions including anti-inflammatory, analgesic, antiandrogenic, antihyperglycemia, antihyperlipidemia, antiviral, and anticancer activities (Asgarpanah and Mohajerani 2012). Ethanolic extract of *U. dioica* improved inflammatory markers (TNF-α and fecal calprotectin) in patient with inflammatory bowel disease (Nematgorgani et al. 2020).

## 36.7 Toxicological Studies

Toxicological studies with *Urtica dioica* revealed the $LD_{50}$ (median lethal dose) value of the plant. The $LD_{50}$ value of the hydroalcoholic leaf extract of the plant for oral administration to mice was found to be 5770 mg/g (Farahpour and Khoshgozaran 2015). The $LD_{50}$ value of the aqueous leaf extract for intraperitoneal administration to mice was calculated as 3500 mg/kg (Bnouham et al. 2003). In another study, the intraperitoneal $LD_{50}$ value of the aqueous leaf extract in mice was found to be 3625 mg/kg (Lasheras et al. 1986). The rat intraperitoneal $LD_{50}$ value of the hydroalcoholic root extract of the plant was found to be 600 mg/kg (Pourahmadiđ et al. 2014). In addition, the intravenous $LD_{50}$ values of root aqueous extract and infusion were shown as 1721 and 1929 mg/kg for rats, respectively. The oral $LD_{50}$ value of the plant infusion has been shown as >1310 mg/kg for rats (Baraibar et al. 1983). Finally, the $LD_{50}$ of plant seed fixed oils in mice was shown to be >12.8 mg/kg (Tekin et al. 2009). It was reported that methanolic extract of *U. diocia* did not show toxicity up to 3000 mg/kg body weight without any morbidity and mortality symptoms (Razak et al. 2020).

## 36.8 Available Commercial Formulations/Products, Uses, Administration Methods, and Pharmacokinetic Studies

Soft gel capsule, drop, oral spray, and tablet are commercially available forms of *U. dioica* plant (Table 36.2).

**Table 36.2** Products containing *Urtica dioica* (Rx MEDIA)

| Products | Preparation | Manufacturers | Formulation |
|---|---|---|---|
| Forprost | *Urtica dioica* | Orthogen | Soft gel capsule |
| İlacto | *Urtica dioica* | Orthogen | Drop |
| Ex.O | *Urtica dioica* | Karefarma | Oral spray |
| D-Manosyst Plus | *Urtica dioica* extract | Ulus İlaç | Tablet |
| Inprost | *Urtica dioica* extract | İntrafarma | Soft capsule |
| Prostakaps | *Urtica dioica* extract | Vefa İlaç | Soft capsule |
| İnfantum Cold | *Urtica dioica* extract | Cnr Kozmetik | Solution |
| Urinag | *Urtica dioica* extract | Agiç İlaç | Oral drop |
| Bioxcin | *Urtica dioica* extract | Biota | Tablet |
| Durinosin | *Urtica dioica* extract | Beka Pharma | Tablet |
| Kanefron | *Urtica dioica* extract | Ade Medikal | Tablet |
| Eiger | *Urtica dioica* leaf extract | Interpharm | Tablet |
| Zermat | *Urtica dioica* leaf extract | Interpharm | Tablet |
| Stinging Nettle | *Urtica dioica* powder | Arkopharma | Capsule |
| Nutraxin | *Urtica dioica* root extract | Biota | Capsule |
| Prostaforton | *Urtica dioica* root extract | İlsan-İltaş | Capsule |
| Profera | *Urtica dioica* seed extract | Dervital | Capsule |
| Profect Plus | *Urtica dioica* seed oil | Efekt Pharma | Soft gelatin capsule |

## 36.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

It is used especially for antidiabetic and antioxidant source in traditional medicine. Both of in vitro and in vivo scientific studies support ethnomedicinal use of nettle plant. The plant contains many chemical compounds such as flavonoids, phenolics, carotenoids, fatty acids, and volatile compounds which may play important role for its effects. Still, more studies are needed for scientific confirmation of their traditional use. However, stability of phytochemical content of nettle plant seems a problem because of geographical limitations. Problems related with stability of bioactive compounds may change due to environmental effects originated by global warming.

## 36.10 Challenges and Future Recommendations as Potential Drug Candidate

There are lots of studies conducted on the phytochemical composition and biological activities of *Urtica dioica* up to now. *Urtica dioica* has a therapeutic potential for different ailments and diseases according to in vitro, in vivo, and clinical studies. Crude extract has been used in most of the studies up to now. Isolation and characterization of the phytochemical from nettle and testing their biological activities should be considered as further studies. Additionally, use of biotechnological techniques such as plant tissue culture and genetic transformation should be a new approach to enrich phytochemical ingredients of nettle. Moreover, nanoparticle synthesis from *Urtica dioica* extracts has become popular, recently. Their therapeutic potential needs to be investigated by in vitro and in vivo studies.

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# *Valeriana officinalis* L.

37

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**Abstract**

*Valeriana officinalis* Linn (valerian), medicinal plant belonging to the Valerianaceae family, is widely distributed in temperate regions. As a traditional herbal medicine, the roots of V. *officinalis* have long been used for insomnia treatment, sedative, antiepileptic, and antispasmodic purposes. In addition, in the researches, it is recorded that the plant has, for example, anxiolytic, antidepressant, anticonvulsant, myorelaxant effects. Valerian is known to contain monoterpenes, sesquiterpenes, valepotriates, alkaloids, flavonoids, and lignans. The use of valerian in treatment with other antidepressants and alcohol is not recommended.

**Keywords**

*Valeriana officinalis* · Valerian · Medicinal usage · Phytochemical content

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## 37.1 Introduction

*Valeriana officinalis* is a member of the Valerianaceae family. Valerianaceae is a family of annual or perennial herbaceous plants that grow in temperate regions. *V. officinalis* grows naturally in various parts of Europe and Asia. It is also cultured in some European countries due to its medicinal value (Tanker et al. 2007). The underground part is used in the treatment (PDR for Herbal Medicines 2000). The roots of *V. officinalis* have been used in the treatment of insomnia both in America and Europe for very long years (GKGM 2018). There are studies showing that it has antidepressant, sedative, anxiolytic, spasmolytic, muscle relaxant, and antiulcerogenic effects (PDR for Herbal Medicines 2000). Valerian constituents include sesquiterpenes, monoterpenes, alkaloids, flavonoids, caffeic acid derivatives, valepotriates, lignans, and amino acids (National Toxicology Program 2009a, b). While fresh valerian root contains valepotriates, the aged root contains isovalerianic acid (Tanker et al. 2007). In this study, various information about *V. officinalis*, which has medical importance, was presented.



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## 37.2 Botanical properties

The plant is 50 to 100 cm tall. It is androgynous and has pink to white flowers. The calyx consists of 10 revolute tips. The flowers have 10 rotary-ended calyx, 5-chambered corolla, 3 stamens, and a 3-chambered inferior ovary. The fruit is achene type. Basal leaves are oblong-ovate, subacute, pinnatisect, and stem leaves ampexicaul; upper stem leaves vary from pinnatisect to pinnatifid (FFD 2011; PDR for Herbal Medicines 2000).

## 37.3 Habitat

The plant grows naturally in Europe, Asia, Northeast America, and Turkey. It is cultivated in England, Europe, Japan, and the USA (FFD 2011; PDR for Herbal Medicines 2000).

## 37.4 Medicinal Parts

Dried underground parts and roots (PDR for Herbal Medicines 2000).

## 37.5 Traditional Uses

Fresh or dried roots of *V. officinalis* are traditionally used as hypnotic, hypotensive, antispasmodic, carminative, stomachic, and sedative. It has been reported that it is used as tea and infusion in migraine, insomnia, hysteria, neurasthenia, fatigue, rheumatic pains, dysmenorrhea, vomiting, and nervous stomach cramps (Barnes et al. 2007; Khan and Abourashed 2010; GKGM 2018). In addition, it is recorded that in traditional medicine, it is used as decoction as a menstrual remedy, antiperspirant, antidote, diuretic, pain reliever in epilepsy, headache, urinary system disorders, vaginal fungal infections, and sore throat (WHO 1999; GKGM 2018)

## 37.6 Chemical Constituent

*V. officinalis* is known to contain alkaloids, terpenes, organic acids, and its derivatives, valepotriates and flavones (Pilerood and Prakash 2013). It also contains compounds such as iridoids, steroids, amino acids, polyphenolic compounds, tannins, gums, and resins (GKGM 2018). Its essential oil contains monoterpenes, sesquiterpenes, and sesquiterpene carboxylic acids (ESCOP 2003). The underground part of *V. officinalis* contains mainly sesquiterpenes and secondly valepotriates. Valerinic acid is known as major component (Nandhini et al. 2018). The second main group is valepotriates. It mainly contains valtrate isovaltrate, but also includes valepotriates such as dihydrovaltrate, isovaleroxyhydroxydihydrovaltrate, and 1-acevaltrate (WHO 1999). It also contains alkaloids such as actinidine, valerianine, and caffeic acid derivatives such as chlorogenic acid (PDR for Herbal Medicines 2000).

## 37.7 Pharmacological Activities

### 37.7.1 Anxiolytic and Antidepressant

Hattesohl et al. evaluated CNS-related effects of different valerian extracts using behavioral paradigms (mice and rats). The results showed that valerian had anxiolytic and antidepressant effects, contributing to sleep development (Hattesohl et al. 2008). *V. officinalis* root extract reduced anxiety in rats compared to ethanol control group in the elevated plus maze test (Murphy et al. 2010). Valle-Mojica et al. stated that valerian and valerenic acid had anxiolytic effects in the zebrafish. They also noted that valerian interacts selectively with metabotropic glutamate receptors (mGluR I and mGluR II) (Valle-Mojica and Ortíz 2012).

### 37.7.2 Anticonvulsant Effect

Rezvani et al. evaluated anticonvulsant effect of diffrent extracts of *V. officinalis* in amygdala-kindled male Sprague-Dawley rats.The results showed that aqueous extract of valerian had anticonvulsant effect (Rezvani et al. 2010). Torres-Hernández et al. determined the anticonvulsant effects of *V. officinalis* extracts and valerenic acid in adult zebra rats. They also stated that valerian extracts increase the effect of clonazepam and phenytoin (Torres-Hernández et al. 2015).

### 37.7.3 Myorelaxant Effects

The myorelaxant effects of *V. officinalis* extract were investigated in mice comparison with tetrazepam. It caused a significant decrease in skeletal muscle strength with no significant effect on endurance and neuromuscular tone (Caudal et al. 2018).

### 37.7.4 Tension-Type Headache

Azizi et al. evaluated the effectiveness of valerian on tension-type headache in a double-blind randomized placebocontrolled trial. They stated that the valerian capsule could reduce tension-type headache (Azizi et al. 2020).

### 37.7.5 Cardiovascular System Diseases

Ethanol and aqueous extracts of *V. officinalis* L. root exhibited anticoronerspastic, antihypertensive, and antibronchospastic effects in anaesthetized guinea-pigs (Circosta et al. 2007). There are some studies showing that valerian extract regulates blood lipid level (Chen et al. 2015).

### 37.7.6 Gastrointestinal Activity

It has been noted that valerenic acid, valtrate, and valeranone contained in valerian have spasmolytic effects on smooth muscle in guinea pig ileum (Wagner et al. 1972; Murti et al. 2011).

### 37.7.7 Insomnia Treatment

As a result of 16 studies conducted by Bent et al. covering 1093 patients, it is stated that *V. officinalis* improves sleep quality without side effects (Bent et al. 2006; GKGM 2018).

## 37.8 Toxicity

### 37.8.1 Acute Toxicity

The ethanol extract of valerian root administered intraperitoneally to mice showed low toxicity ($LD_{50}$ = 3.3 g/kg) (EMEA 2007; Rosecrans et al. 1961).

### 37.8.2 Chronic Toxicity

Ethanol extract of valerian root was administered to rats at doses of 300 and 600 mg/kg p.o for 30 days. The blood pressures, animals weights and organs weights, hematological parameters, and biochemical parameters were examined. It was observed that the body weights of the animals receiving high doses were higher than the control groups ((EMEA 2007; Fehri et al. 1991). In another study, the ethanolic extract of valerian root at doses of 400–600 mg/kg was given intraperitoneally to rats for 45 days. It did not cause any significant changes in body weight, blood count, or urine status (EMEA 2007; Rosecrans et al. 1961).

## 37.9 Adverse Reactions

It has been stated that chronic use of Radix Valerianae may cause minor side effects such as headache, excitability, uneasiness, and insomnia, and in very high doses, bradycardia, arrhythmia, and intestinal immobility (Willey et al. 1995; WHO 1999). Rarely, gastrointestinal complaints can be observed. In addition, in long-term administration, restlessness, sleeplessness, mydriasis, and cardiac function disorders can be seen (PDR for Herbal Medicines 2000).

## 37.10 Drug Interactions

Valerian is not suitable for use with other antidepressants, benzodiazepines, barbiturates, and alcohol (PDR for Herbal Medicines 2000).

## 37.11 Use in Pregnancy and Lactation

Use of valerian during pregnancy or in nursing mothers is not recommended (PDR for Herbal Medicines 2000).

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# *Viburnum opulus* L.

# 38

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**Abstract**

*Viburnum opulus* L. is a perennial and medicinal plant of the Adoxaceae family. It spreads naturally in Europe, North America, and Asia. The barks, leaves, and fruits are used for ethnomedical purposes for a long time. The most prominent feature among medicinal uses is the effects of the bark of the plant on the uterus, in Europe and America. The use of fruit in Turkey is noteworthy because of its antiurolithiatic effects. The plant contains iridoids, sesquiterpenes, triterpenoids, sterols, coumarins, and high amounts of phenolic compounds. The presence of secondary metabolites with different structures is reflected in its pharmacological activity and is propped by in vitro and in vivo studies. Its distinctive pharmacological activities include antioxidant, anti-inflammatory, antimicrobial, anti-obesity, antidiabetic, osteogenic, cardioprotective, and cytoprotective features. However, unfortunately, the number of clinical studies is quite insufficient to understand the effects of the *V. opulus* on humans. This chapter aims to examine the botanical properties, chemical compositions, and pharmacological properties of *V. opulus*.

**Keywords**

*V. opulus* · Adoxaceae · Gilaboru · European cranberrybush · Secondary metabolites · Pharmacological properties

## 38.1 Introduction

*Viburnum opulus*, belonging to the genus *Viburnum* L., is from the Adoxaceae family. *Viburnum opulus* is a shrub-shaped perennial plant with white flowers that can grow up to 2–4 meters, and deciduous in winter. During the flowering period, it is a white umbrella on the outside and has a diameter of 5–10 cm. There are greenish-white fertile flowers in the interior. The red bright color of the plant, which forms a cluster of 25–50 fruits, is oval, tasteless, odorless, and acidic (Kollmann and Grubb 2002). It spreads naturally in Europe, North America, North Africa, and some parts of North Asia (Kajszczak et al. 2020). *Viburnum opulus* is located in the forest edge in the North and Central Anatolia in Turkey and it is grown as an ornamental plant in gardens especially around Kayseri (Baytop 1999). It is identified as cranberry bush, cran-

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berry tree, European cranberry bush, and guelder rose (Sedat Velioglu et al. 2006). During the Seljuk and Ottoman period, the name of the plant was "gül ebru"; over the time, the name has changed to "gilaboru, girabolu, gilabba, giligili, gilabu, gildar, giraboğlu" (Yıldız and Ekici 2019).

The fact that *V. opulus* is an important plant is not only because it is an ornamental plant, but also because it is used as food and has medicinal properties. Due to the bitter-sour taste of the fruits, it finds use in the traditional cuisine of Russia, Ukraine, and many Siberian countries in marmalade, jam, liquor, and "Kalinnikov" pie. In Scandinavia, fruits find use when cooked in canned food, while in Canada it is used instead of cranberries (Polka et al. 2019). The pulp obtained by squeezing the fruit after waiting in the water for 3–4 months and then sweetened with sugar is drunk in the form of fruit juice in the region of Kayseri, Turkey.

*Viburnum opulus* fruits in Anatolia are utilized traditionally as an antidiabetic, diuretic, and in the treatment of biliary and liver diseases (Baytop 1999). Also, squeezed fruit juice is consumed due to its effect of lowering sand and stones in the kidney (Sezik et al. 2001). Especially the barks and fruits of *V. opulus* were used for medicinal aims in Europe and Asia. In folk medicine, fruits have been employed in the treatment of blood pressure regulation, heart ailments, tuberculosis, shortness of breath, stomach pain, digestive problems, duodenal ulcers and bleeding, urinary system diseases, cough, and cold (Kraujalytė et al. 2012). The barks of the plant are included in the British Herbal Pharmacopoeia and are used in the UK to prevent miscarriage (Romm 2017). It is used in dysmenorrhea due to the pain spreading to the thighs and its relaxing effect on the uterus (Lennard et al. 2011).

This chapter aims to shed light on the pharmacological activities of *V. opulus*, a traditional medicinal plant, with scientific and clinical evidence. Besides, information about its traditional usage and bioactive/nutraceutical and nutritional composition will be given.

## 38.2 Distribution and Status of Species

*Viburnum opulus* is a plant found in regions with low temperatures and shady habitats (Kollmann 1997). The distribution range of *V. opulus* is Eurasiatic and suboceanic. The plant is widely distributed in western, central, eastern, and northeastern Europe and may occur in eastern parts of Asia. Although it is not seen in the Mediterranean region, it is rarely found in the subregions. It is also known to spread to the north of Western Asia and North America. Although common in Scandinavia, it has a limited distribution in the south-north region up to latitude 67° in Norway. It is rarely found north of Helsingland in Sweden and some individuals in Norrbotten. It is located on the northern border, probably 64° close to the polar circle in Finland and about 60° in northern Russia. The southern border in Russia comes across the northern edge of the steppes, where the species spreads in humid habitats such as gorges and the northern slopes of the Crimea. It is frequent in England, Wales, and Ireland and less common in Scotland (Kollmann and Grubb 2002). It grows wild in the various regions of Turkey (Ersoy et al. 2017).

## 38.3 Comparison of Traditional/Ethnomedicinal/Local Uses in Turkey and Throughout the World (Asia and Europe)

The medicinal uses of this herb date back to the Native Americans and the bark have been reported to be used as a diuretic. In Medical Flora (1828–1830), it was stated that the barks from *Viburnum* were utilized by the natives of North America for diuretic purposes, usually by boiling it, and that some western tribes burned the bark for use like tobacco. It is also stated that *Viburnum* leaves were prepared as a tea by the Indians and the first settlers. The United States Homeopathic

Pharmacopoeia recognized the fresh bark of *V. opulus* and also the root bark, officially, in the third edition. The bark has also been used to prevent any type of cramps and hysterics caused by dysmenorrhea or pregnancy and miscarriage (Youngken 1932).

In Europe, *V. opulus* has been used for its spasmolytic and sedative properties. It has also been used for uterine dysfunction and menopausal bleeding (Pharmacopoeia 1983, Zengion and Yarnell 2011). Especially, its flowers and barks are used as antidiarrheal, diuretic, and sedative (Baytop 1999).

In Russia, cranberry barks and fruits are generally used in the therapy of uterine, stomach, and hemorrhoidal bleeding by decoctions or preparing alcohol extracts. Furthermore, their preparations exhibit hypotensive, cardiotonic, sedative, spasmolytic, and anti-inflammatory properties (Andreeva et al. 2004).

In Turkey, it is used because of its laxative and sedative effects. Juice of fruits is used in middle Anatolia against bile and liver diseases. The pickled juice obtained by squeezing fresh fruits around Kayseri or keeping the fruits in water for a month is used against stomach pain. Gilaboru juice has been used as a traditional drink in central Anatolia for years (Baytop 1999). Towards the end of autumn, fruits are picked with a knife with their stems, washed with tap water, then kept in a bowl of water for about 3 months. At the end of the period, the fruits ripen and taste that can be eaten. Then the fruits are crushed, the resulting juice is thinned with water and sweetened with sugar. Gilaburu juice is used because of its properties of dissolving sand and stones in the kidney (Soylak and Divrikli 2002).

When compared, the ethnomedicinal use of *V. opulus* in Europe, America, and Turkey, for sedative effect illustrate similarity. Common use in Europe and America is its effects on the uterus. Its kidney stone-dissolving properties are not reported among its local uses in Europe and America.

## 38.4 Bioactive/Nutraceutical and Nutritional Composition and Available Extraction Techniques (Classification and Structures of Few Representatives)

Macro elements of gilaburu fruit were found as: 0.52% nitrogen, 0.09% phosphorus, 0.93% potassium, 0.21% calcium, 0.05% magnesium, and 0.04% sodium. For microelements, the results are as follows: 12.81 mg/kg iron, 5.69 mg/kg copper, 6.45 mg/kg zinc, and 1.56 mg/kg manganese. In the protein content analysis, the content results for fruit, stems, and leaves were 0.52%, 0.51%, and 12.10%, respectively (Table 38.1) (Taşkın et al. 2019). Organic acids contained in *V. opulus* have been reported as malic acid, citric acid, quinic acid, shikimic acid, tartaric acid, fumaric acid, and succinic acid (Cam et al. 2007; Ersoy et al. 2017; Perova et al. 2014; Polka et al. 2019; Taşkın et al. 2019).

It has been reported that the plant contains iridoids, sesquiterpenes, triterpenoids, sterols, coumarins, and phenolic compounds (Altun et al. 2009; Kraujalytė et al. 2013). From the root bark of the *V. opulus*, coumarin and scopoletin were isolated (Jarboe et al. 1967). The iridoid glycoside esters called iridoids I-IV and arbutin were

**Table 38.1** The nutritional content of flowers, bark, and fruits of *V. opulus* (Polka et al. 2019)

| Content | Flowers g/100 g dried weight | Bark g/100 g dried weight | Fruits g/100 g dried weight |
|---|---|---|---|
| Protein | 9.72 ± 0.53 | 3.26 ± 0.10 | 5.40 ± 0.16 |
| Fat | 5.39 ± 0.26 | 10.06 ± 0.01 | 10.57 ± 0.54 |
| Total organic acid | 1.81 ± 0.02 | 1.84 ± 0.05 | 7.34 ± 0.06 |
| Total sugar | 11.92 ± 0.41 | 1.52 ± 0.10 | 32.27 ± 1.25 |
| Total fiber | 45.39 ± 2.07 | 59.34 ± 0.75 | 38.44 ± 0.41 |
| Total pectin | 8.58 ± 0.29 | 4.15 ± 0.06 | 6.23 ± 0.26 |

isolated from the leaves (Bock et al. 1978). It has been described that the *Viburnum* iridoids are symbolized by a group of iridoids (C-10) with structures analog to valerian iridoids, and these iridoids are called opulosides I, II, III, and IV (Perova et al. 2014). Sesquiterpene, viopudial was identified in the *V. opulus* bark (Nicholson et al. 1972). While α-amyrin and β-amyrin in triterpene structure, campesterol, stigmasterol, and β-sitosterol in sterol structure, were isolated from the leaves. Sitosterol and ursolic acid were identified in the flowers (Rychlinska 2008).

A high amount of polyphenolic components like hydroxybenzoic acids, hydroxycinnamic acids, and flavonoids was detected in *V. opulus* fruits. The major phenolic compound in fruits is chlorogenic acid in the form of hydroxycinnamic acid (İİ and AH 2017; Perova et al. 2014). Amentoflavone in biflavonoid structure was detected in the leaves and branches of the plant (Levent Altun et al. 2008; Lobstein et al. 1999). Salicin was detected in the leaves, branches, and fruits of the plant (Altun and Yilmaz 2007). According to the HPLC results, the amount in the fruit was slightly higher than the leaves and the branches. Also, caffeic acid, p-coumaric, and ferulic acid, gallic acid, protocatechuic acid, syringic acid, 3,4,5-trimethoxybenzoic acid, 3,4-dihydroxyphenylacetic acid, homogentisic acid, chlorogenic acid, and ellagic acid were determined in the barks of the plant (Turek and Cisowski 2007). The phenolic compounds of *V. opulus* fruit are detailed in Table 38.2.

**Table 38.2** The phenolic compounds of *V. opulus* fruit

| Structure | Phenolic compounds | References |
|---|---|---|
| Hydroxybenzoic acids | Gallic acid<br>Vanillic acid<br>Syringic acid | Özrenk et al. (2011) |
| Hydroxycinnamic acids | Chlorogenic acid<br>Caffeic acid<br>Coumaric acid<br>Ferulic acid<br>Protocatechuic acid | Özrenk et al. (2011), Sedat Velioglu et al. (2006), Perova et al. (2014) |
| Flavonoids | (+)-Catechin<br>(−)-Epicatechin<br>Procyanidin<br>Quercetin<br>Quercetin 3-vicianoside<br>Quercetin 3-rutinoside<br>Quercetin 3-rhamnoside<br>Quercetin 3-xyloside<br>Quercetin 3-arabinoside<br>Isorhamnetin 3-sambubioside<br>Isorhamnetin 3-rutinoside | Özrenk et al. (2011), Sedat Velioglu et al. (2006), Perova et al. (2014) |
| Anthocyanins | Cyanidin 3-sambubioside<br>Cyanidin 3-glucoside<br>Cyanidin 3-rutinoside<br>Cyanidin-3-vicianosid<br>Cyanidin-3-xylosyl-rutinoside<br>Cyanidin +2 hexose + pentose<br>Cyanidin +2 pentose + hexose<br>Cyanidin +2 hexose<br>Cyanidin +2 pentose + hexose<br>Cyanidin 3-arabinosyl-glucoside | Perova et al. (2014) |

## 38.5 Scientific Evidences: Pharmacological Activities (All Major Therapeutic Activity with In Vitro and In Vivo Studies, Mechanism of Action)

### 38.5.1 Antioxidant Activity

When the in vitro antioxidant studies related to the species are examined, it is seen that most fruit and fruit juice are studied. These activities generally consist of DPPH, ABTS, and DMPD radical scavenging activities, iron-reducing activity (FRAP), cupric-reducing antioxidant capacity (CUPRAC), oxygen radical absorbance capacity

(ORAC), nitric oxide scavenging activity, superoxide anion scavenging activity (SORS), hydroxyl radical scavenging activity (HORS), iron-chelating capacity, inhibition of lipid peroxidation, and total antioxidant capacity. Although the solvent used for extraction is different in these studies, it is seen that ethanol, methanol, acetone, water, and the same solvents together within different proportions of acetic acid and HCl. More rarely, ethyl acetate and phosphate buffer were used as extraction. In two different researches, it is seen that water and acetone (80%) + HCl (0.5%) extract of fruits has made similar DPPH radical scavenging activity with $IC_{50}$ ratio of 0.057 mg of extract/mL (Bujor et al. 2019; Levent Altun et al. 2008). The scavenging activity of the ABTS cation of fruit extracts differs in studies. According to the results, 50% ethanol extract exhibited 643 μmol Trolox equivalents/g of DW fruit activity, while 70% ethanol extract exhibited 265.7 μmol Trolox equivalents/g of DW fruit activity (Kraujalis et al. 2017; Polka et al. 2019). In three different studies, 70% acetone +0.5% acetic acid extracts prepared from fruit exhibited similar ferric-reducing activity with a value of 21.02–34.90; 23.41–32.70; 28.76–36.41 μmol Trolox equivalents/g of FW fruit (Ersoy et al. 2018; Ersoy et al. 2017; Ozkan et al. 2020). The cupric-reducing effects of the fruit were 208.87 mg ascorbic acid equivalents/$g_{extract}$ for the methanol extract and 156.49 mg ascorbic acid equivalents/$g_{extract}$ for the water extract (Barak et al. 2019). In the ORAC experiment, 70% methanol extract of the fruit showed 109.3 μmol Trolox equivalents/$g_{fruit}$ activity, while in another study, the result was 1277 μmol Trolox equivalents/$g_{fruit}$ for 50% methanol extract (Kraujalis et al. 2017; Polka et al. 2019). Results for superoxide anion and hydroxyl radical scavenging activity for 70% methanol extract of fruit are reported as follows, 897.7 and 100.5 μmol Trolox equivalents/$g_{fruit}$, respectively (Polka et al. 2019). In the research of Polka et al. (2019), flower and bark extracts were also studied. According to the outcomes of the research, bark extract was affirmed to be more effective than flower and fruit extract in ABTS, ORAC, HORS, and SORS. DMPD scavenging activity was reported as 52.55 and 50.00 mg Trolox equivalents/g of extract for 96% methanol and water fruit extract. Barak et al. (2019) also evaluated the total antioxidant capacity and he demonstrated that with 56.89 mg ascorbic acid equivalents/$g_{extract}$ value, methanol extract was active than water extract. Ethyl acetate extract of fruit was declared to be more powerful than water and methanol extract with a value of 60.5% in iron-chelating activity (Erdogan-Orhan et al. 2011). Rop et al. (2010) reported the lipid peroxidation inhibitory activity of phosphate buffer extract of fruit as 11.20–13.90% of prevention for 25% fruit extract (Rop et al. 2010). In the research of Altun et al. (2008), the leaf and the branches of *V. opulus* also studied for their superoxide anion radical and DPPH radical scavenging capacities, and the branch extract was found to be active than fruit extract in SORS. However, no significant activity was observed for leaf extract. In a study comparing the antioxidant capacity of methanol extracts of dried fruit and fresh fruit, dried fruit extract swept DPPH ($IC_{50}$ value:0.104 mg/mL) stronger while fresh fruit swept ABTS stronger. Both extracts have been reported to exhibit similar activity in inhibiting β-carotene bleaching effect (Koşar et al. 2011).

In cell culture studies, different cell lines were utilized to measure the antioxidant activity of *V. opulus.* Phenolic extracts of *V. opulus* can act as cytoprotective agents that can reduce ınduced oxidative stress. *V. opulus* extracts were evaluated in the activity in MIN6 pancreatic β-cells and according to the results, it has been notified that the extract rich in terms of phenolic compounds reduces intracellular oxidative stress (Zakłos-Szyda et al. 2020a). In mouse adipose tissue cell line (3T3-L1 cells), crude and semi-purified phenolic extract of *V. opulus* fruit reduced the intracellular reactive oxygen species. The authors stated that the appeared cytoprotective antioxidant mechanism may be linked with the induction of intracellular antioxidant enzymes (Podsędek et al. 2020). The same effect was shown for fruit juice and purified fruit juice of *V. opulus* in 3T3-L1 cells with the decrease of ROS by 10–15% (Zakłos-Szyda et al. 2020c). Fresh juice and purified juice showed an effect of

10–20% on ROS levels in the osteosarcoma cell line (Saos-2 cell) (Zakłos-Szyda et al. 2020b). In a different study, ethanol extract, decoction, and fruit juice of *V. opulus* showed a preventive activity towards oxidative damage caused by hydrogen peroxide in human SH-SY5Y neuronal cells (Paşayeva et al. 2019).

Although in vivo studies on antioxidant activity are very few, the first of these have been carried out by Zayachkivska et al. (2006). To evaluate the protective effect of *V. opulus* in rats with gastroduodenal mucosal damage, the extract was given orally at doses of 25, 50, and 75 mg/kg body weight. In the group treated with *V. opulus*, SOD and CAT levels were increased and MDA levels decreased (Zayachkivska et al. 2006). In the study investigating the preventive effect of *V. opulus* fruit extract against oxidative stress induced by ischemia/reperfusion during lung transplantation, the extract was administered i.p at a dose of 200 mg/kg body weight to rats. In the group treated with *V. opulus* fruit extract, it resulted in an important decrease in MDA and protein carbonyl levels and an increase in the antioxidant enzymes SOD, GPx, and CAT (Zayachkivska et al. 2006).

### 38.5.2 Antimicrobial Activity

In current years, multiresistant strains of bacteria have appeared, and this problem is closely related to the overuse of antibiotics. For this reason, research has concentrated on finding new antibiotic compounds. Studies show that plant extracts are an excellent alternative to antibiotics and that the secondary metabolites of plants have a bacteriostatic force. These metabolites have been found effective against many kinds of bacteria. The antimicrobial effects of *V. opulus* compounds are also particularly interesting due to their secondary metabolites. Investigations have shown that plant compounds can influence human pathogenic bacteria and they act as antimicrobial agents (Česonienė et al. 2012).

Česonienė et al. analyzed the bacteriostatic effects of the fruit juice of six *V. opulus* L. cultivars using the agar well diffusion method. According to the results, the juice of *V. opulus* fruits greatly prevented the increase of an extensive variety of human pathogenic bacteria (*Salmonella typhimurium, S. agona, Staphylococcus aureus*, *Lysteria monocytogenes*, and *Enterococcus faecalis*). All cultivars were appraised for numerous yeasts and finally, the juices were not manifested in any inhibitory impact on the *D. hansenii* and *T. delbrueckii,* but slightly effective on *Trichosporon cutaneum, Kluyveromyces marxianus* var. *lactis, Saccharomyces cerevisiae, S. cerevisiae* 12R, and *Candida parapsilosis* (Česonienė et al. 2012). In a different study, juices and extracts of *V. opulus* L. genotypes were assessed. The juices displayed significant results against *Salmonella typhimurium, S. agona,* and *Listeria monocytogenes* with inhibition zones of 23.6, 20.7, and 19.1 mm, respectively. *Staphylococcus epidermidis* and *Micrococcus luteus* have been noted to show the most important resistance with minimal inhibition zones (14.2 and 15.0 mm respectively). Also, the growth of yeast cultures presented slight sensitivity to juices and extracts of *V. opulus*. The results of this study revealed that fruits can be considered as potential antibacterial agents (Česonienė et al. 2014).

*V. opulus, V. lantana,* and *V. orientale* essential oils have been studied with different bacteria (*E. coli*, *K. pneumonia, P. aeruginosa, E. faecalis, S. aureus, B. cereus*, and the fungus *C. tropicalis*) to evaluate their antimicrobial activity at 250, 500, and 1000 μg/mL concentrations, but *V. opulus* essential oil has been reported that it has no activity against all test microorganisms (Yilmaz et al. 2008).

The probiotic potentials of lactic acid bacteria (LAB) strains isolated from fermented gilaburu (*V. opulus*) juice were examined in the study of Sagdıç et al. Approximately 332 isolates from 12 different LAB species were characterized with genotypic methods. As a result of the study, some isolated strains were found to be indestructible to the three antibiotics; kanamycin, streptomycin, and vancomycin. The selected LAB strains were evaluated for their antibiotic effects. *Listeria monocytogenes* and *Bacillus cereus* were found to be the most susceptible bacteria against LAB

strains, while *Escherichia coli* and *Staphylococcus aureus* were recorded as resistant bacteria (Sagdic et al. 2014).

Aqueous and ethanolic extracts of *V. opulus* L., *V. orientale* Pallas, *V. tinus* L., and *V. lantana* L. were examined against *S. aureus, S. aureus, Bacillus subtilis*, *E. coli*, *P. aeruginosa, Klebsiella pneumonia*, and *Candida albicans*. In this study, disk diffusion and tube dilution methods were utilized to screen the antimicrobial activities of *Viburnum* extracts. It has been remarked that ethanolic extracts of the chosen *Viburnum* species exhibit more notable antimicrobial activity than aqueous extracts (Eryilmaz et al. 2013).

In recent years, the antimicrobial properties of plants are used to make the fabrics used in textiles more functional. In a study conducted for this purpose, considering the antimicrobial properties of *V. opulus,* woolen fabrics were dyed with *V. opulus* juice. Compared to the undyed wool fabric, dyed fabrics were found to inhibit the growth of *E. coli* 3.19%, *P. aeruginosa* 0.77%, and *C. albicans* 2.05%. On the other hand, it was also noted that the extract prepared with the branches of *V. opulus* did not affect these pathogens. However, as an important detail, the dyeing process takes place at 100 °C, which causes the phenolic compounds to deteriorate. The authors reported that the antibacterial features of *V. opulus* juice may be linked to its high content of metal ions, mainly copper and zinc (Şapcı et al. 2017; Yılmaz et al. 2020).

In recent studies, plant extracts have been used to create nanomaterials to increase the efficiency of plant-based products, and this method has provided very promising results for effective biosensors and biomedicine applications. Extract-based $Cu^{2+}$ hybrid nanostructures named "Snowball" from *V. opulus* were prepared and found effective on *E. coli, Salmonella typhi*, *Enterococcus faecium, Enterococcus faecalis, B. cereus,* and *S. aureus*. However, the same effect could not be detected in *P. aeruginosa* and *Haemophilus influenza*. Interestingly, while free *V. opulus* extracts did not demonstrate effective antimicrobial properties at concentrations ranging from 2000 to 125 μg/mL, the extracts were found to be effective in nanoparticle form (Ildiz et al. 2017).

### 38.5.3 Anti-inflammatory Activity

Inflammation is an immune response that protects the body from cellular distress signals and stresses, as well as various pathogens (Hwang et al. 2019). Numerous diseases are closely related to inflammation, such as atherosclerosis, arthritis, asthma, cardiovascular disorders, and cancer (Moldovan et al. 2017). Regulation of inflammatory genes, production of inflammatory mediators, and activation of intracellular inflammatory protein complexes or inflammations are the main events that occur in the process of the inflammatory response (Hwang et al. 2019).

Studies were carried out to detect the anti-inflammatory effects of silver nanoparticles prepared from *V. opulus* fruit extracts in vitro (exposed to UVB radiation in the HaCaT cell line) and in vivo (acute inflammation). The results conclude that the synthesized silver nanoparticles have a strong anti-inflammatory effect and can be used as a therapeutic agent for inflammation (Moldovan et al. 2017).

Altun et al. investigated the antinociceptive and anti-inflammatory effects of *V. opulus* leaf. In the research, the extract prepared with distilled water was tested on mice and rats. However, it was noted that the extract did not display anti-inflammatory activity at 100 and 200 mg/kg doses (Altun et al. 2009).

Amentoflavone is a natural compound isolated and identified from *V. opulus*, and studies have shown that amentoflavone powerfully prohibits pilocarpine-induced epilepsy in a mouse fever model. It shows that amentoflavone represses nuclear factor-B (NF-κB) activation and hinders the extra discharge of hippocampal neurons, resulting in a decrease in epileptic seizures. There have been reports that the compound reduces the duration of the attack and decreases the loss and apoptosis of hippocampal neurons. Consequently, amentoflavone inhibits inducible nitric oxide synthase through NF-κB, which produces nitric oxide (NO). Therefore, by blocking the inflam-

matory response caused by NO, it also prevented a gradual effect and several side effects of NO with tissue damage and apoptosis (Zhang et al. 2015).

Ovodova et al. conducted a study to show that water-soluble polysaccharide fractions of *V. opulus* fruit increase macrophage ability. Polysaccharides isolated from *V. opulus* have been discovered to have an immunostimulating effect and have been observed to increase phagocytosis, especially the phagocytic index and the secretion of lysosomal enzymes by peritoneal macrophages. Also, it was emphasized that calcium ions are necessary for the stimulative effect of acidic polysaccharides described in *V. opulus* (Ovodova et al. 2000).

Using tumor necrosis factor α (TNFα) and prostaglandin E2 (PGE2) tests, 105 herbs used in traditional Russian medicine were evaluated for the effect on the release of TNFα and PGE2 in lipopolysaccharide (LPS)-induced differentiated human acute monocytic leukemia THP1 cells. It has been noted that the barks of the *V. opulus* plant evaluated within the scope of the study inhibit TNFα production and reduce PGE2 release in cells, especially depending on the concentration (Kalinkevich et al. 2014).

### 38.5.4 Cytotoxic Effects

Plants contain important phytochemicals that have antiproliferative activities. For this purpose, research describing the cytotoxic effects of plants continues to discover new and efficient compounds.

Cytotoxic effects of *V. opulus* juice were tried to be determined on various cell lines by using the MTT method. One study showed that *V. opulus* juice could inhibit the growth of Caco-2 and HeLa cancer cell lines but could not effectively inhibit the A549 cancer cells. Besides, it was found to have only weak effects on MDCK and HUVEC cells. Cytotoxic effect was not observed in healthy cell lines (Koparal 2019).

In a study investigating the anticancer effects of *V. opulus*, the authors reported that VOP-E strongly inhibited the growth of HT29 cancer cells with an EC50 value of 0.39 ± 0.03 mg/mL. It was also noted that this effect is due to the plant extracts including high quantities of gambiriin, cinchonains, and anthocyanins (Dienaitė et al. 2020).

Investigating the effect of *V. opulus* methanolic extract at different concentrations (5–2000 μg/mL) on the colorectal cancer cell line (Lovo), the researchers showed that *V. opulus* methanolic extract exerted a prooxidant effect, causing DNA damage, apoptosis, and cytotoxicity in a dose-dependent manner in the range of 14.88–52.06% (Guler et al. 2020).

The effects of gilaburu (VO) juice on colon tumor formation have been investigated and it has been proven that VO reduces cell viability and cell number by exerting cytotoxic effects against EAC cells. According to the results of this study; it has been found that when anticancer agents are used to treat cancer cell lines (in vitro–in vivo), they have been found to exert very different effects like arresting the cell cycle, apoptosis, and necrosis (Ceylan et al. 2018).

In an in vivo study examining the chemopreventive impact of gilaburu juice on DMH-induced colorectal cancer, the mice were given gilaburu juice instead of water and then observed. According to the results, it was determined that the number of colon lesions induced by DMH in the colon decreased. It has been shown that gilaburu juice can prevent the progression of established tumors, not the chemical induction of colon tumors in mice. This result supports the view that polyphenolic compounds of *V. opulus* have properties related to inhibiting tumor cell migration and metastasis. Especially as the concentration of phenolic compounds increases, it has been determined that the migration time decreases (Ulger et al. 2013).

In a study investigating the effects of the extract prepared from *V. opulus* leaves on healthy epithelial cells CCD841CoN and two different colon cancer cell lines (HT29 and SW480), cell viability was tested using the MTT method. Two different extracts were prepared as leaf extract and phenol-rich leaf extract. When the results were evaluated, it was found that all the extracts had a moderate effect on the inhibition of HT29 cell growth. The phenol-rich leaf extract inhib-

ited the growth of HT29 and SW480 more than the leaf extract, and the growth of CCD841CoN cells was induced with the treatment of phenol-rich leaf extract (Chojnacka et al. 2019).

### 38.5.5 Effects on Lipid and Carbohydrate Metabolism

Diabetes mellitus (DM) is defined as the insufficiency of insulin secretion of the pancreatic gland, which is characterized by the impaired response of the related tissues known as hyperglycemia or insulin resistance. All types of diabetes can manifest themselves in different ways such as hyperglycemia, the relative or absolute absence of insulin, and selective insulin resistance of the pathway. Obesity is another important metabolic disorder affected by behavioral, genetic, and environmental factors. This disease is simply described as abnormal or excessive triglyceride accumulation in adipocytes due to adipocyte hypertrophy and hyperplasia.

The anti-obesity and anti-diabetic effects of *V. opulus* were investigated, either directly or indirectly, and various findings were obtained. In one study, the hypoglycemic activity of VO extract was tested in mice, but no effect of VO was noted in lowering the blood sugar. However, there is knowledge in the literature about the use of VO fruits as a hypoglycemic agent in Turkish traditional medicine. Therefore, the authors stated that more studies are needed to explain this incompatibility (Altun et al. 2010). In another study, α-amylase, α- glucosidase, and protein tyrosine phosphatase 1B enzyme activities were screened to test the antidiabetic effect of *V. opulus*. It has been emphasized that they are natural sources for active compounds with anti-diabetic properties (Zaklos-Szyda et al. 2015).

The effects of fresh juice and phenolic-enriched extract of *V. opulus* on mouse insulinoma MIN6 cells were studied. Extracts have been shown to affect the secretion of glucagon-like peptide-1 (GLP-1) and inhibit the in vitro activity of dipeptidyl peptidase-4 (DPP4) enzyme in the presence of a high glucose concentration. However, the decrease in cell membrane fluidity and the inhibition of glucose-induced insulin secretion, which increases the hyperpolarization effect, are also the data obtained as a result of this study. Also, enhanced free fatty acid uptake and collection of lipid droplets were seen (Zaklos-Szyda et al. 2020a).

Crude fruit extract and semi-purified phenolic-rich extract of *V. opulus* were tested on 3T3-L1 cells and their anti-obesity effect was investigated and various parameters were examined. As a result, it was discovered that the extracts had inhibitory activity against pancreatic lipase in the triolein emulsion, and it was noted that the extracts display the ability to inhibit the adipogenesis process depending on the dose. It was concluded that the extracts at a concentration of 75 μg/mL are not adequate to block lipid accumulation, but affect the size of the lipid droplets. The extracts also decreased the leptin level by 21–30%, and it was observed that the peroxisome proliferator-activated receptor-gamma and adiponectin did not affect the protein expression levels (Podsędek et al. 2020).

There was also a study investigating the potential of *V. opulus*, which has strong antioxidant activity, as a protective agent against chronic diet-related disorders such as obesity and type 2 diabetes. The phenolic-rich extract obtained from fruit juice was found to be the most effective product in reducing glucose, FFA uptake, and lipid droplet accumulation in Caco-2 cells (IC0 50 μg/mL) (Zakłos-Szyda et al. 2019).

### 38.5.6 Effects on Gynecological Disorder

Both the fruits and peels of *V. opulus*, traditionally used to treat many ailments, have also been frequently applied to treat gynecological diseases. Due to its uterine relaxant and antispasmodic properties, it is stated that it is used for premenstrual syndrome, pain correlated with uterine contractions, and to reduce the volume of menstrual fluid (Yilmaztekin and Sislioglu 2015).

Endometriosis is a gynecological problem discriminated against with the appearance of the uterine cavity. In one study, the impacts of fruit extract of *V. opulus*, known to be used traditionally in gynecological disorders, were assessed

using the surgically induced endometriosis in a rat model. As a result, it was determined that the EtOAc and MeOH extracts applied to rats decreased endometriotic volumes significantly. Also, significant reduction was achieved in TNF-α, VEGF, and IL-6 levels (Saltan et al. 2016).

### 38.5.7 Effects on Urinary System Disorders

In modern medicine, kidney stones and urinary system disorders are treated using various medical techniques. However, these methods are known to be quite expensive and have many side effects. For this reason, plant origin compounds and herbs are being investigated for use in urinary system disorders, as in many diseases.

The potential antiurolithiatic activity of *V. opulus* is closely related to its inhibitory effect on oxalate levels in urine and its diuretic effects. In the NaOx-induced urolithiasis model, there was no crystal aggregation in the rats given *V. opulus* fruit juice (100 mg/mL), while a high quantity of crystal aggregation was identified in NaOx group (Ilhan et al. 2014).

The nephrolithiasis effects of *V. opulus* extracts were investigated in the Spraque-Dawley rat model and it was determined that the extract elevated the urine volume and reduced the citrate grades in the urine due to its diuretic effects. It also reduced cystine and oxalate grades in urine. Thus, the crystal accumulation that causes damage to the kidney tissue is prevented (Erdem et al. 2016).

### 38.5.8 Effects on Osteoporosis

The potential benefits of *V. opulus* on bone metabolism were planned based on studies in which the positive effects of phenolic compounds on bone metabolism were determined. The effects of juice obtained from *V. opulus* and purified juice using with solid-phase extraction method on osteosarcoma Saos-2 cell lines and osteogenesis processes were evaluated. It appeared that purified juice of *V. opulus* exhibited the strongest effect as an inductive agent of osteogenic differentiation in the Saos-2 cell line. Primary osteogenic derivative markers such as ALP, collagen type 1, and osteonectin were found to increase at the level of transcription, suggesting that the increase in the RANKL/OPG ratio may have antiresorptive effects of *V. opulus* fruits. All these results may prove that fruit phenolics have the potential to reduce bone tissue demineralization (Zakłos-Szyda et al. 2020b).

### 38.5.9 Effects on Blood Vessels

Recent studies show that arginase is an important versatile enzyme in disease and health, especially it has been stated that increased arginase activity can cause dysfunction in the cardiovascular system and contribute to endothelial dysfunction (Caldwell et al. 2018). In a study, the possible vasodilator effects of *V. opulus* were studied and it was shown that arginase was significantly reduced by extract of *V. opulus* fruit, the most powerful effect observed in phenylephrine precontracted rat aortic rings in the research (Bujor et al. 2019).

Angiotensin I converting enzyme (ACE I) is an enzyme that is effective in the management of blood pressure. In a study conducted in Russia, angiotensin I converting enzyme (ACE I) inhibitory activities of 108 extracts provided from different plants were tested in vitro. As a result, it was determined that the ethanol extract of the *V. opulus* fruits had a weak inhibitory effect, and it was observed that the ethanol extract obtained from the bark didn't show any effect on the ACE I activity. It was noted that the enzyme activity decreased by 5.1% at 0.1 mg/mL (Ivanov et al. 2013).

### 38.5.10 Protective Effects

The cytoprotective effect of plant extracts may be due to their high phenolic content and with antioxidant properties. Therefore, the cytoprotective potential of *V. opulus* has been tried to be evaluated by testing it in various ways with cell-based experiments or animal models.

In a study, the chemopreventive properties of *V. opulus* on human epithelial Caco-2 cells were evaluated. Caco-2 cells were dosed with tert-butyl hydroperoxide (t-BOOH); furthermore, it was discovered that the polyphenols-rich fraction of *V. opulus* exhibited the strongest guarding effects on the metabolic activity of the cells and reduced the toxic effect of t-BOOH. Besides, the protective effect of the extracts facing DNA breakage in Caco-2 cells was investigated. Hydrogen peroxide and methylnitronitrosoguanidine that have mutagenic effects were applied to the cells and the DNA repair (%) effects of the extracts were compared. As a result, the polyphenol-rich fraction of the extracts eliminated DNA breaks in cells with the highest efficiency (93%). When methanol and acetone extracts were applied, the efficiency of DNA repair was calculated as 88% (Zakłos-Szyda et al. 2019).

To examine the protective effect of extract from *V. opulus* L. fruit on ischemia/reperfusion (I/R)-induced oxidative stress during lung transplantation, a study was planned on rats and lung damage due to transplantation was evaluated with many parameters. According to the results, a notable reduction in superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) enzyme activities was observed, glutathione and total antioxidant status (TAS) levels were significantly reduced, and malondialdehyde (MDA) in lung tissue examples in the I/R group indicated increased total oxidant status (TOS) and protein carbonyl compared to the control group. Besides, it was determined that *V. opulus* fruit extract decreased MDA and protein carbonyl levels and caused an increase in the antioxidant system. The radical scavenging and antioxidant activity of *V. opulus* fruit extract and its protective activity against I/R-induced oxidative stress during lung transplantation concluded that *V. opulus* fruit extract may be effective in preventing I/R-related lung toxicity (İİ and AH 2017).

Another study examined the impacts on the development of Alzheimer's disease through the degradation of acetylcholine to determine the neuroprotective activity of *V. opulus* leaf methanol extract. As a result, almost 88% inhibition of AChE was noted at the 100 μg/mL concentration (Erdogan-Orhan et al. 2011).

In a study examining the gastroduodenoprotective activity of *V. opulus,* the authors concluded that the active ingredients of *V. opulus* affect differences in the glycoconjugate substances of the rat's gastroduodenal mucosa. As a result, it has been determined that a rise in endogenous NO formation, prevention of lipid peroxidation, and mobilization of antioxidant efficiency are the main factors affecting this situation (Zayachkivska et al. 2006).

## 38.6 Clinical Studies

In a clinical study in which the action of *V. opulus* on distal ureteral stones was evaluated, 103 patients were randomly divided into two groups. The treatment group received 1000 mg *V. opulus* peroral 3 × 2. Comparison of stone-throwing rates and expulsion time between groups was used to evaluate the results. The stone removal rate was *significantly* higher in the V. *opulus* treatment group (82%), and the time to stone removal was found to be significantly shorter with 9 ± 1.8 days (Kızılay et al. 2019).

A clinical study with 30 female participants lasted more than 3 menstrual cycles over 3 months and was determined by the length of each participant's menstrual cycle. The purpose of the survey was to assess the effectiveness of *V. opulus* 3X in the treatment of primary dysmenorrhea. Each participant was given a 50 ml vial of homeopathic medicine or placebo and was asked to use 10 drops 3 times a day. However, information about the results was not uploaded to the clinical trials gov website for this study (https://clinicaltrials.gov/ct2/show/NCT02467543).

## 38.7 Toxicity

By continuous infusion in the isolated frog and canine heart, a digitalis-type cardiotonic effect of water extracts of the bark, flowers, leaves, and fruits of *V. opulus* has been stated. It has been reported that the bark extract has stronger activity and the glycoside concentrates obtained from the bark have a cardiotonic effect up to 1: 250,000 dilution and respond positively to all reagents of cardiotonic glycosides (Vlad et al. 1977).

The ethanol extract and n-hexane, ethyl acetate, butanol, and water fractions of leaves were exposed to the rats at the doses of 250, 500, 1000, and 1500 mg/kg body weight to evaluate the safety profile. Cellular or fibrotic damage was not observed in the liver tissues of rats in all treatment groups (Adebayo et al. 2017).

Altun et al. (2010), in their study, evaluated the lethality of the leaf water extract; the mice were administered the extract at a dose of 100 mg/kg body weight. The LD50 value of the extract is reported as 5.447 g/kg.

Acetone: water: acetic acid (80:19.5:0.5) fruit extract of *V. opulus* was evaluated in brine shrimp lethality assay. The concentrations of 5000, 2500, 1250, 625, and 312 µg/mL were applied to the *Artemia franciscana* and LC50 was found to be 3610 µg/mL (Bujor et al. 2019).

## 38.8 Available Commercial Formulations/Products, Uses, Administration Methods and Pharmacokinetic Studies (with Special Focus on Bioavailability and Metabolism of Active Constituents)

Gilaburine® is a 1000 mg tablet containing standardized extract of *V. opulus*. It is used internally and recommended to consume 2 tablets a day for 3 times with plenty of water with meals. Maximum 4 weeks' usage is recommended. There are no studies on pharmacokinetic studies, bioavailability, and metabolism of active compounds of this supplement.

## 38.9 Gap Between Ethnomedicinal and Scientific/Clinical Evidences

Unfortunately, despite its strong ethnomedical use, there are two clinical studies of gilaburu, and one of them is inconclusive. The effect on ureteral stone is one of the ethnomedical usages in Turkey which has proven in vivo recently in clinical studies. Although a clinical study has been initiated on dysmenorrhea, its traditional use in Europe, the data have not been shared. Therefore, this traditional use has not yet been proven.

## 38.10 Challenges and Future Recommendations as Potential Drug Candidate

Drug discovery from medicinal herbs involves a multidisciplinary approach that combines botany, ethnobotany, phytochemistry, and biology. The utilization of natural products in traditional medicine is very advantageous in terms of providing data on efficacy and safety. Despite these advantages and many natural products that have turned into successful drugs, some disadvantages have led pharmaceutical companies to limit their natural product-based drug discovery programs (Atanasov et al. 2021). Although the in vitro pharmacological activities of *V. opulus* have been extensively studied, in vitro and clinical studies are still needed. There are no case reports on the toxicity of *V. opulus*, and there are also insufficient data on its acute and chronic toxicity. Starting from the local use in Turkey, a promising food supplement Gilaburine® developed, but it needs more clinical data to complete the transformation phase to the drug.

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# Index





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