The Genus *Ferulago*: A Review on Ethnopharmacology, Phytochemistry, and Pharmacology

Yahya Rahimpour\(^a\), Abbas Delazar\(^b\), Solmaz Asnaashari\(^d\) and Parina Asgharian\(^e\)*

\(^a\) Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran. \(^b\) Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. \(^c\) Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. \(^d\) Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. \(^e\) Department of Pharmacognosy, School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

Abstract

The Ferulago genus appertains to the Umbelliferae family comprises 49 species which are mainly distributed in Asia, Europe, and Africa. This paper aims to review the morphological properties of *Ferulago* species, herbal components, and their pharmacological properties.

The information of this review paper has been collected from journals available in databases including Science Direct, Web of Science, Scopus, PubMed, EBSCO, Google Scholar, and Hindawi up to March 2020. In traditional medicine, the genus of *Ferulago* has been used to treat intestinal worms, snake bites, wound skin infections, diseases of the spleen and gastrointestinal tract, and headaches. It not only has been used traditionally as a preservative agent to dairy, oil ghee, and meat but also has given them a pleasant taste. The main components of *Ferulago* spp. are monoterpenes, sesquiterpenes, coumarin, furanocoumarin, flavonoids, and terpenoids have been the reason for the antimicrobial, antioxidant, anticoagulant, antidiabetic, Alzheimer, and larvicidal properties of this plant. This review confirms that many traditional uses of some *Ferulago* species have now been validated by modern pharmacology research. Rigorous investigations of all the species of *Ferulago* concerning phytochemical and pharmacological properties, mainly their mechanism of action, efficacy, and safety might offer a context for researchers to prosper plant-derived medications like anti-diabetes, antibiotics, and sedatives treating drugs, and the key to directing clinical trials.

Keywords: *Ferulago*; Essential oil; Pharmacological activity; Herbal medicine; Phytotherapy.

Introduction

Herbal used in traditional and modern medicine presents a valuable source of secondary metabolites and different pharmacological and biological activities. Hence, they could be utilized as a lead compound to produce new drugs and treat numerous diseases (1). The Apioideae or Umbelliferae, commonly known as the parsley, carrot, or celery family, is one of the biggest plant families in the world usually characterized by aromatic plants with hollow stems (2). Several plants belonging to this family are well-known as vegetables, culinary, and medicinal plants, including *Apium graveolence*, *Foeniculum vulgare*, *Centella asiatica*, *Pimpinella anisum*, *Cuminum cyminum*, *Carum carvi*, *Ligusticum officinale*, *Coriandrum sativum*, *Anethum graveolens*, *Ammi visnaga*, *Anthriscus cerefolium*, *Ferulago*.
angulata, and Ferula assa-foetida (3). Plants of the Apiaceae family are commonly aromatic and pungent owing to the existence of essential oil or oleoresin in their diverse organs (4). Among several Umbelliferae families, the species belonging to the genus Ferulago W. Koch. are broadly employed in traditional medicine. The genus Ferulago W. Koch. (called Chavil or Chavir in Persian, Çaştır or Çağşır in Turkey) appertains to the Umbelliferae family consisting of 49 species which are mostly distributed in Asia, Europe, and Africa (5, 6). The occurrence of several bioactive secondary metabolites, including coumarin, coumarin esters, furanocoumarin, flavonoids, quinones, steroids, essential oils, steroids, and terpenoids are owing to their pharmacological activities (7). Extensive studies have been conducted to evaluate the ethnomedicinal uses of Ferulago species antibacterial, antioxidant, Alzheimer, anti-diabetics, anti-malaria, anti-coagulant, and aphrodisiac effects. The information of this review paper has been collected from journals available in databases including Science Direct, Web of Science, Scopus, PubMed, EBSCO, Google Scholar, and Hindawi up to March 2020. The keywords and search terms contained “Ferulago”, “Ferulago spp.” “essential oil of Ferulago”, “phytochemistry and Ferulago”, “coumarins and Ferulago”, “bioactive compounds and Ferulago”, “pharmacological activity and Ferulago”. Therefore, we conducted the present review article to provide a complete overview of a current state of knowledge on botany, ethnomedicinal uses, phytochemistry, and the most noticeable pharmacological effects of species belonging to the genus Ferulago.

The botany of Ferulago plants

The Ferulago genus appertains to the Umbelliferae family and comprises 49 species which are mainly distributed in Asia, Europe, and Africa (8). The genus Ferulago is distributed in Turkey with 34 species, out of which 18 are endemic (9). The 8 species exist in Iran, out of which three are endemic (10). According to The Plant List website, the genus Ferulago consists of 48 accepted species names and 13 unassessed species (11). Table 1 depicts the name of accepted species and their synonyms. Ferulago genus is 60-150 cm tall; annual or perennial plants grow at altitudes of 1900-3200 m above sea level with yellow fruits. They are characterized by persistent bracts and bracteoles and small flowers which are widely distributed in Turkey, Iraq, and west of Iran (from the flora of Iran, particularly in Kermanshah, Ilam, Lorestan, and Kurdistan) (8, 12, 13). Pictures of Ferulago bernardii and fruits of ferulago stellata are shown in Fig 1. The high distribution of Ferulago spp. in these areas suggests that the core center of the biodiversity of the genus Ferulago is in Anatolia. Based on taxonomy the species of this genus resemble Prangos and Ferula species. They are widely used in the Anatolia region for several purposes (7, 14). The most studied species is F. angulata which is divided based on ovaries, the flowering in fluorescence, and fibers (rather absence or presence of trichomes) into two subspecies: F. angulate subsp. angulata and F. angulate subsp. Carduchorum by Chamberlain in 1987 (15).

Traditional use of Ferulago spp.

Ferulago like Ferula and Prangos species have been traditionally utilized back in history in folk medicine for the medicament of hemorrhoids, and intestinal worms, peptic, sedative, carminative, digestive, aphrodisiac, snakebite, wound skin infections, headache, diseases of the gastrointestinal tract and spleen (5, 16). Due to the aromatic property of Ferulago, some of them have been applied in Iranian tradition as spices in different foods, such as dairy and meat products, for increasing the flavor and as an aroma. They have also been employed as natural preservatives for enhancing food expiration dates (8, 16 and 17). Bakhtiari nomads use F. angulata to make some foods and Nomads of Fars province utilize this plant to flavor yogurt. The F. angulata is also used as a sedative, food-digestive, tonic, antibacterial, and antiparasitic (18). In Turkish traditional medicine, the aerial parts of a few members of this genus are used as an immunostimulant, tonic, sedative, digestive, anti-bronchitis, flavor, vermicidal, anthelmintic, and anti-peptic (19, 20). Likewise, the root parts are used for the treatment of dermatological
Table 1. The accepted genus of Ferulago species based on The Plant List.

| No. | Ferulago species                  | Synonyms                                                                                                                                 |
|-----|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| 1   | F. angulata (Schdlf.) Boiss.      | F. angulata Schdlf., F. linearis Boiss., F. trifida Boiss.                                                                             |
| 2   | F. angulata subsp. carduchorum (Boiss. & Hausskn.) J.D. | F. carduchorum Boiss. & Hausskn., F. abbreviata C. C. Towns., F. pauciradiata Boiss. & Heldr., Ferula armena DC., F. boreguai Boiss. |
| 3   | F. Chambr.                        | Ferula taurica (Schischk.) M. Hiroe, F. galbanifera var. brachyloba Boiss., F. taurica Schischk.                                           |
| 4   | F. antiochia Saya & Miski         | Ferula kochii M. Hiroe, F. sintentii Gand.                                                                                               |
| 5   | F. medit radiata Boiss.           | Ferula sulcata var. biambelata Pomel. Ferula lutea var. mosretii (Maire) Maire. Bund.                                                       |
| 6   | F. asparagifolia Boiss.           | Ferula brachyloba Boiss. & Reut., Nyman F. amani Post ex Boiss.                                                                          |
| 7   | F. bernardi Tonik. & Pimenov      | Ferula fieldiana (Rech.f.) M. Hiroe Ferula daghestanica (Schischk.) M. Hiroe, Ferula campestris Boiss. Ferula meoides L., Ferula galbanifera Mil. |
| 8   | F. biembrallata Pomel             | Ferula granatensis (Boiss.) Steud. Ferula granatensis (Boiss.) Steud. F. puntila Boiss.                                                 |
| 9   | F. blancheana Post ex Boiss.      | Elaeocelium manganotianum Emb., Ferula capillaris Link ex Spreng., Ferula capillosa Link., Ferula lutea (Poir.) Maire, Ferula lutea var. microcarpa (Maire) Maire, Ferula pumila (L.) Boiss. |
| 10  | F. brachyloba Boiss. & Hausskn    | F. brachyloba Boiss. & Reut., C. C. Towns. Ferula sulcata var. microcarpa Maire, Ferula sulcata var. parviolata (Pomel) Bund. |
| 11  | F. castia Boiss.                  | F. barbata Guss., F. capillaris (Link ex Spreng.) cout., F. capillosa (Link) Franco, Ferula communis Petter ex Nyman, F. crassicaulata Pomel, F. leptocephalum Pomel, F. nodiflora Koch, F. parviflora Pomel, F. sulcata (Desf.) Ledeb., Ligusticum tyreum Pers. |
| 12  | F. contracta Boiss. & Hausskn     | Ferula lophopera (Boiss.) Benth. & Hook. l., Ferula metepotamica, F. lophopera Boiss.                                                   |
| 13  | F. crassicosta Boiss.             | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadozica Borrn.                                                     |
| 14  | F. crassicosta Schischk.          | Ferula cretica (Spreng.) M. Hiroe, Ferula gencilatata Guss., Ferula nodosa (L.) Benth. & Hook. L., Ferula rigida Ten., Paecianathan nodosum L., F. gencilata Boiss. |
| 15  | F. crassicosta var. Parvifolia (Pomel) | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 16  | F. dodonaei Kandemir & Hedge      | Ferula algiersia M. Hiroe, Ferula sulcata var. scabra (Pomel) Bund.                                                                     |
| 17  | F. dodek. Rech.f.                 | Ferula puntila Boiss.                                                                                                                    |
| 18  | F. galbanifera (Mill.) W. D. J. Koch | Ferula lophopera (Boiss.) Benth. & Hook. l., Ferula metepotamica, F. lophopera Boiss.                                                   |
| 19  | F. gazanensis Boiss.              | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 20  | F. ideae Ozturay & Akalin         | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 21  | F. humilis Boiss.                 | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 22  | F. isaurica Peqmen                | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 23  | F. lutea (Poir.) Grande           | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 24  | F. macrocarpa (Fenzl) Boiss.      | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 25  | F. macedonica Miecz. & E. Mayer    | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 26  | F. macrocata Boiss. & Balansa     | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 27  | F. mugilae Peqmen                | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 28  | F. nodosa (L.) Boiss.             | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 29  | F. pachyloba (Fenzl) Boiss.       | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 30  | F. phalaenopis Rech. f. & Reedi   | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 31  | F. praehensia Peqmen & Quedel     | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 32  | F. praehensia Boiss. & Balanva    | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 33  | F. prunifolia K. Koch             | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 34  | F. stellata Boiss.                | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 35  | F. stellata Boiss.                | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 36  | F. stellata Boiss.                | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
| 37  | F. stellata Boiss.                | Ferula cappadocica (Borrn.) M. Hiroe, Ferula pachyloba Fenzl., F. cappadocica Borrn.                                                     |
\begin{table}
\centering
\begin{tabular}{ll}
38 & \textit{F. silaifolia} (Boiss.) Boiss. \\
39 & \textit{F. subvelutina} Rech. f. \\
40 & \textit{F. sylvatica} (Besser) Rchb. \\
41 & \textit{F. sylvatica} \textit{subsp. confusa} (Velen.) Hautv. \\
42 & \textit{F. syriaca} Boiss. \\
43 & \textit{F. ternatifolia} Solanas, M.B.Crespo & García-Martin \\
44 & \textit{F. thienan} Boiss. \\
45 & \textit{F. tchycarpa} Boiss. \\
46 & \textit{F. thyrsifolia} (Sm.) Koch \\
47 & \textit{F. trojana} Akahn & Pi \\
48 & \textit{F. vesceritensis} Cors. & Dunte ex Batt. \\
\end{tabular}
\end{table}

Continued Table 1. The accepted genus of \textit{Ferulago} species based on The Plant List.
disorders and cancers and as an aphrodisiac and are preferred as fodder to improve animal productivity (7). The seeds are applied for eye pains in the form of inhalation (8). It has been reported that dried or fresh leaves of Ferulago are used as foot deodorant by indigenous people of the north of Iraq (21).

Phytochemistry of essential oils from the genus Ferulago species

Essential oils or volatile oils are the phytochemical complexes of different aromatic components, mainly monoterpenoids and sesquiterpenoids, which are obtained from plant materials, for instance, leaves, fruits, seeds buds, flowers, roots, and bark. They are characterized by having a strong odor generally lower density than water, being volatile, rarely colored, liquid, lipophilic, and soluble in organic solvents (7). Despite the way that these volatile oils involve around 20–60 constituents, just a few of them exist at high amounts (20–70%) in correlation with different constituents existing in low sums (22). These phytochemicals assume a vital part in the protection of the herbs from herbivores, insects, bacteria, fungi, viruses, and also help to attract pollinators (23). These essential oils could be extracted with conventional methods (steam distillation, hydrodistillation (HD), organic solvent extraction) and innovative techniques (In situ microwave-generated hydrodistillation, supercritical carbon dioxide, microwave steam diffusion, microwave hydro diffusion and gravity, and microwave steam distillation). Among these methods, the hydrodistillation method is the most prevalent technique for obtaining essential oils (7, 24 and 25). The method of extraction, drying methods, genotypic variation, geographical origin of the plant, stage of the development, and part of the plant used may drastically affect the composition of essential oils of plants (26-28). Based on the literature, researches have revealed that the species of the Ferulago genus are appropriate for the extraction of essential oils and many of them have been evaluated for chemical compositions, including F. macedonica, F. angulata, F. carduchorum, F. phialocarpa, F. contracta, F. macrocarpa, F. blancheana, F. bernardii, F. pachyloba, F. longistylis, F. isaurica, F. syriaca, F. platycarpa, F. thrysiflora, F. sylvatica, F. nodosa, F. pauciradiata, F. asparagiﬂolia, F. aucheri, F. galbanifera, F. confusa, F. humilis, F. campestris, F. idaea, F. macrosciadia, F. mughlæ, F. sandrasica, F. silaifolia, F. trachycarpa, F. thirkeana, F. setifolia, F. subvelutina, F. stellata, F. capillaries F. trifida. Table 2 represents the
Table 2. Main constituents of the volatile oils of 35 Ferulago species studied before.

| Plant name | Yield (%) | Methods | Part | Main components (%) | Class | Ref. |
|------------|-----------|---------|------|---------------------|-------|------|
| F. macdonaldiana | - | HD | Aerial parts | α-Pinene (31.7), 2,4,5-trimethyl benzaldehyde (20.7) | Monoterpene (62.5) | (42) |
| F. angulata | 2.8 | Aerial parts | α-Pinene (15.4), cis-Occimene (50) | Monoterpene (45.5) | (30) |
| F. campestris | 0.66 | Flowers | β-Phellandrene (16.5), α-Phellandrene (27), p-Cymene (10), α-Pinene (12) | Monoterpene (65.5) | (51) |
| F. pachyloba | 0.54 | HD | Stems | β-Phellandrene (16), α-Phellandrene (18), p-Cymene (17.7), α-Pinene (21) | Monoterpene (72.7) | (31) |
| F. carduchorum | 0.43 | Leaves | α-Pinene (16.8), α-Phellandrene (20.7), p-Cymene (14.5), β-Phellandrene (16) | Monoterpene (68) | (68) |
| F. angulata | 2.65 | HD | Fruits | Limonene (38), α-Pinene (18.1) | Monoterpene (56.1) | (32) |
| F. idaea | 6.5 | MAHD | Fruits | Bornyl acetate (49), 2,3,6-Trimethyl benzaldehyde (32) | Monoterpene (50.5) | (50) |
| F. campestris | 0.14 | Aerial parts | α-Pinene (41), α-Phellandrene (14.2), β-Phellandrene (9.5) | Monoterpene (64.7) | (55) |
| F. contracta | 0.08 | HD | Inflorescence | α-Pinene (43.8), cis-Chrysanthemyl acetate (6) | Monoterpene (43.8), Oxygenated monoterpene (6) | (36) |
| F. calophylla | 0.16 | Aerial parts | α-Pinene (15), E-β-Occimene (10) | Monoterpene (39.5), Oxygenated sesquiterpene (11) | (50) |
| F. bernardi | 0.54 | Leaves | β-Eudesmol (25.3), α-Phellandrene (25) | Oxygenated sesquiterpene (40.5), Monoterpene (12) | (37) |
| F. longijolia | 0.4 | Stems | β-Phellandrene (15.5), α-Phellandrene (11.5) | Monoterpene (27) | (38) |
| F. pachyloba | 0.16 | HD | Aerial parts | α-Pinene (16.4), β-Eudesmol (11) | Monoterpene (31.7) | (38) |
| F. longijolia | 6.4 | Fruits | α-Pinene (35), Bornyl acetate (11.6), α-Occimene (14.2) | Monoterpene (49.2), Oxygenated monoterpene (11) | (43) |
| F. sylvatica | 12 | Fruits | α-Pinene (31.5), Limonene (24.2), Myrcene (17.0) | Oxygenated monoterpene (38.9), Oxygenated sesquiterpene (11.7) | (42) |
| F. sylvatica | 1.1 | HD | Roots | Bornyl acetate (69.4), Terpinolene (12.5) | Oxygenated monoterpene (69.4), Monoterpene (11.7) | (43) |
| F. platycarpa | 0.07 | HD | Aerial parts | 2,3,6-trimethylbenzaldehyde (20.7), cis-Chrysanthemyl acetate (24.2) | Oxygenated monoterpene (29.8), Monoterpene (24.2) | (43) |
| F.Smartya | 0.80 | HD | Aerial parts | Spathulenol (41) | Oxygenated monoterpene (41) | (43) |
| F. angulata | 0.10 | HD | Aerial parts | 2,3,6-trimethylbenzaldehyde (92.7) | Oxygenated sesquiterpene (92.7) | (45) |
| F. angulata | - | HD | Aerial parts | Germacrene D (32.5) | Oxygenated sesquiterpene (32.5) | (46) |
| F. sylvatica | - | HD | Inflorescence | Myrcene (29.2) | Monoterpene (29.2) | (47) |
| F. angulata | 3 | HD | Aerial parts | p-Cymene (42.8), 2,4-dimethyl-p-Cymene (40) | Monoterpene (31) | (48) |
| F. angulata | - | SDE | α-Pinene (131) | Monoterpene (31) | (49) |
| F. angulata | - | SFE | α-Pinene (10), E-β-Occimene (7) | Monoterpene (7.5) | (48) |
| F. angulata | - | Fruits | Bornyl acetate (30.5), α-Pinene (7), Germacrene D (8) | Oxygenated monoterpene (30.5), Monoterpene (7) | (49) |
| F. angulata | - | HD | Roots | 2,5-dimethyl-p-Cymene (70), α-Pinene (12.5) | Monoterpene (82.5) | (40) |
| F. angulata | - | HD | Aerial parts | 2,5-dimethyl-p-Cymene (35), Nonacosane (9), α-Pinene (9) | Monoterpene (42), Hydrocarbon (9) | (40) |
| F. angulata | - | M.D | Fruits | 2,3,6-trimethylbenzaldehyde (42), α-Pinene (11) | Oxygenated hydrocarbon (42), Monoterpene (11) | (47) |
| F. angulata | - | HD | Fruits | 2,3,6-trimethylbenzaldehyde (38.9), Myrcene (18.2) | Oxygenated hydrocarbon (38.9), Monoterpene (18.2) | (48) |
| F. angulata | - | M.D | Fruits | α-Pinene (36) | Monoterpene (38) | (47) |
| F. angulata | - | M.D | Fruits | p-Cymene (24.2), 2,4-dimethyl-p-Cymene (43.5) | Monoterpene (87.5) | (45) |
| F. angulata | - | M.D | Fruits | trans-Chrysanthemyl acetate (17.2), Limonene (10) | Monoterpene (17.2) | (49) |
| F. angulata | - | M.D | Fruits | α-Pinene (31.8), Limonene (18.5) | Monoterpene (54.6) | (51) |
| F. angulata | 3.9 | HD | Fruits | Limonene (17.5), 2,5-dimethyl-p-Cymene (32.5), α-Pinene (9) | Monoterpene (82.5) | (40) |
| F. angulata | 0.11 | HD | Flowers | Nonacosane (25.5), Hexadecanoic acid (14.8) | Oxygenated hydrocarbon (25.5), Fatty acid (14.8) | (43) |
| F. angulata | 0.13 | HD | Roots | 2,3,6-trimethylbenzaldehyde (20.7) | Oxygenated hydrocarbon (29.8), Monoterpene (24.2) | (43) |

**Note:** The table lists the main constituents of the volatile oils of 35 Ferulago species, including their yields, methods, parts, main components, classes, and references.
main compounds of these essential oils, part of the herb that was used, methods of extraction, percentage yield, class of components, and their references.

According to data of the volatile oils extracted from various Ferulago spp., it is clear that every species and each part of the plant have a diversified set of main compounds. Therefore, it is hard to find the similarity among the species of this genus concerning the chemicals. Several compounds, like α-Pinene, p-Cymene 2,3,6-trimethyl benzaldehyde, cis-Chrysanthenyl acetate, α-Phellandrene, Sabinene, (Z)-β-Ocimene, Limonene, Myrcene, Terpinolene, Nonacosane, and δ-Cadinene, have been detected as main components of the volatile oils of many Ferulago species. To date, analysis has shown that the α-Pinene is a major compound of several Ferulago species; hence, this might be regarded as a perpetual constituent for the genus (7). There are certain other notable points to report; primarily, the compound of spathulenol was the major component from aerial parts of only two species namely, F. sylvestris and F. thysiflora (45). Second, the compound of ferulagone was found as the main compound of only F. thirkeana obtained from its fruits (59). Thirdly, carvacrol methyl ether obtained with MD from fruits of F. macroscadia and F. idaea was the major component of only these two species (47). Furthermore, Cecchini et al. compared the composition of the volatile oil from roots and fruits of F. campestris from two sites of collection and two periods of time. They found significant differences in the percentages of (2, 30 and 6)-trimethyl benzaldehyde (14.8–27.9% in the

| Plant name | Yield (%) | Methods | Part | Main components (%) | Class | Ref. |
|------------|-----------|---------|------|---------------------|-------|------|
| F. nodosa  | 0.26      | Aerial parts | Fruits | 2,4,5-Trimethyl benzaldehyde (77.8), 2,3,4-Trimethyl benzaldehyde (6.2) | Oxygenated hydrocarbon (84%) | (28) |
| F. pauciradiata | 0.13   | Aerial parts | Leaves | Ocimene (30.5), α-Pinene (17.8), β-3-Carene (27.4) | Monoterpene (75.7) | (56) |
| F. setifolia | 0.02     | Aerial parts | Limonene (29), α-Pinene (14), α-Pinene (15.6) | Monoterpene (58.8) | (57) |
| F. subvelutina | 0.62   | Aerial parts | δ-Carveol (12.7) | Monoterpene (68.2) | (60) |
| F. silasofia | 0.60     | Aerial parts | α-Pinene (5.5), α-Chrysanthemyl acetate (83.5) | Monoterpene (69) | (55) |
| F. trachycarpa | 7.3      | Aerial parts | α-Pinene (10) | Monoterpene (5.5) | (47) |
| F. thirkeana | 4.1      | Aerial parts | α-Pinene (35.8), α-Pinene (18.2) | Monoterpene (62) | (50) |
| F. sentifolia | 0.26     | Aerial parts | Limonene (27), α-Phellandrene (23.1), α-Pinene (13.3) | Monoterpene (65.4) | (60) |
| F. capitellaris | 0.60    | Aerial parts | α-Pinene (35.8), Loctinone (30.9) | Monoterpene (66.7) | (62) |
| F. carpenteri | 1.5      | Aerial parts | α-Phellandrene (23.1), α-Pinene (15.5) | Monoterpene (58.5) | (61) |
| F. trifida | 0.8       | Aerial parts | Limonene (33.5), α-Pinene (16.5), Borneol acetate (9.5) | Monoterpene (53.8), Oxygenated monoterpenes (9.5) | (66) |
| F. rufida | 1.6       | Aerial parts | α-Pinene (19.9) | Monoterpene (45.3), Oxygenated monoterpenes (8.5) | (64) |
| F. rufida | 1.4       | Aerial parts | α-Pinene (11) | Monoterpene (48.3), Oxygenated monoterpenes (11) | (54) |

**Table 2.** Main constituents of the volatile oils of 35 Ferulago species studied before.

| Plant name | Yield (%) | Methods | Part | Main components (%) | Class | Ref. |
|------------|-----------|---------|------|---------------------|-------|------|
| F. nodosa  | 0.26      | Aerial parts | Fruits | 2,4,5-Trimethyl benzaldehyde, 2,4,6-trimethyl benzaldehyde | Monoterpene (58.3–75) | (52) |
| F. pauciradiata | 0.13   | Aerial parts | Fruits | α-Pinene (58.3–75) | Monoterpene (56–62.7) | (53) |
| F. setifolia | 0.02     | Aerial parts | Fruits | α-Pinene (19.5), α-Pinene (27), α-3-Carveol (10) | Monoterpene (34.5), Oxygenated monoterpenes (13), Oxygenated hydrocarbon (14) | (47) |
| F. subvelutina | 0.62   | Aerial parts | Fruits | α-Pinene (25.4), Camphene (10.5) | Monoterpene (25.4), Oxygenated sesquiterpene (12.7) | (47) |
| F. silasofia | 0.60     | Aerial parts | Fruits | α-Pinene (37.5), Borneol (9.5) | Monoterpene (37.5), Oxygenated monoterpenes (9.5) | (54) |
| F. trachycarpa | 7.3      | Aerial parts | Fruits | α-Pinene (53.5), Myrcene (3.9), β-Phellandrene (11), Limonene (6) | Monoterpene (72.9) | (54) |
| F. thirkeana | 4.1      | Aerial parts | Fruits | α-Pinene (40.8), Germacrene D (8) | Monoterpene (40.8), Sesquiterpene (8) | (57) |
| F. sentifolia | 0.26     | Aerial parts | Fruits | α-Pinene (26.5), Camphene (5), Carophyllene oxide (26) | Monoterpene (31.5), Oxygenated sesquiterpene (6) | (55) |
| F. subvelutina | 0.02    | Aerial parts | Leaves | Ocimene (30.5), α-Pinene (17.8), β-3-Carveol (27.4) | Monoterpene (58.6) | (57) |
| F. silasofia | 0.60     | Aerial parts | Limonene (29), Terpinolene (14), α-Pinene (15.6) | Monoterpene (58.6) | (57) |
| F. trachycarpa | 7.3      | Aerial parts | Fruits | α-Pinene (37.5), Borneol (9.5) | Monoterpene (37.5), Oxygenated monoterpenes (9.5) | (54) |
| F. thirkeana | 4.1      | Aerial parts | Fruits | α-Pinene (53.5), Myrcene (3.9), β-Phellandrene (11), Limonene (6) | Monoterpene (72.9) | (54) |

MD: Hydrodistillation; SDE: SFE: Supercritical Fluid Extraction, MAHD: Microwave-assisted distillation.
roots gathered in the summer, 65.2% in roots gathered in the fall) and α-Pinene (58.3-75% in the roots gathered in the summer, 19.3% in the roots gathered collected in the fall) (23).

Phytochemistry of plant extracts from the genus Ferulago species

Phytochemical investigations on Ferulago species have shown the presence of various secondary metabolites including coumarins, coumarin esters, furanocoumarins, aromatic compounds, monoterpenes, sesquiterpenes, flavonoids, quinones, and stilbene. Table 3 depicts the main phytochemicals that have been isolated and characterized from Ferulago species. Up to now, several studies have been done to distinguish active compounds from different parts of the ferulago genus, from which about 73 (three simple coumarins, sixteen furanocoumarins, five dihydro-furanocoumarin, four sesquiterpene coumarin, twelve prenylated coumarins, six pyranocoumarin, nine flavonoids, and eighteen miscellaneous compounds) bioactive compounds were isolated. Based on the literature, coumarins and their derivatives are the most prevalent secondary metabolites on the Ferulago species and might be used as a chemotaxonomic marker in the genus Ferulago (65). The classification of different types of coumarins and various biological applications of each compound was reviewed by Venugopala et al. (66).

Pharmacological activities

In the last two decades, many ferulago species have been widely studied with advanced scientific methods and reported for several pharmacological properties such as antibacterial activity, antioxidant activity, antidiabetic activity, larvicidal activity, Alzheimer, and anticancer activity. These pharmacological activities of Ferulago are considered to be attributed mainly to its coumarins and furanocoumarins and essential oil (66). Table 4 depicts pharmacological activity and model of study of the genus Ferulago.

Antibacterial activity

The volatile oils of many herbs of genus Ferulago have been the focus on pharmacological activity, particularly from an anti-oxidant, antimicrobial and antifungal point of view (7, 20 and 29). In the literature, antimicrobial and antifungal properties of essential oil were screened versus Gram-positive (Staphylococcus aureus, S. epidermidis, and methicillin-resistant S. aureus), and Gram-negative (Escherichia coli, Salmonella typhiurium, Bacillus cereus, Proteus vulgaris, Enterobacter aerogenes, and Pseudomonas aeruginosa) bacteria, and the yeast (Candida albicans, C. parapsilosis, and C. tropicalis) via broth microdilution assay. Sucu et al., 2019, studied the antimicrobial effects of volatile oil from the roots and aerial parts of F. sandrasica and found that both essential oils were not active against C. tropicalis and C. parapsilosis compared to positive controls (55). The volatile oil of the aerial portions was found to be active against Salmonella typhiurium, Staphylococcus aureus, and Bacillus subtilis, however, inactive against E. coli; the root essential oil was active against B. subtilis and S. typhiurium compared with E. coli, but not active against S. aureus. Recently, Karakaya et al. assessed antimicrobial activity of n-butanol, ethyl acetate, dichloromethane, methanol extracts, and aqueous residue parts of methanol extracts from the aerial parts and roots of four Ferulago species (F. pachyloba, F. bracteata, F. trachycarpa, and F. blancheana) along with 14 isolated compounds via micro broth-dilution methods. Their result demonstrated that the best antimicrobial effect against B. subtilis, E. coli, S. aureus, P. aeruginosa, and C. albicans were obtained with methanol extract of the roots, n-butanol fractions, and methanol extract of the aerial parts from F. blancheana (62.5 µg/mL), dichloromethane fraction of the roots and aerial parts from F. pachyloba (62.5, 31.25 µg/mL), the n-butanol fraction of the aerial parts, dichloromethane fractions of the aerial parts, dichloromethane fractions of the aerial parts and roots, methanol extracts and ethyl acetate fraction of the roots from F. bracteata (62.5 µg/mL), dichloromethane
### Table 3. Chemical compounds isolated from the *Ferulago* genus.

| Compounds          | Class                  | Structure | Plants and References                                      |
|--------------------|------------------------|-----------|------------------------------------------------------------|
| Umbelliferone      | Simple coumarin        | ![Umbelliferone](image) | *F. asparagifolia* (67), *F. cassia* (8), *F. bernardii* (68) |
| 6-hydroxymethyl herniarin | Simple coumarin               | ![6-hydroxymethyl herniarin](image) | *F. trifida* (69) |
| Crenulatin         | Simple coumarin        | ![Crenulatin](image) | *F. trachycarpa* (14) |
| Imperatorin        | Furanocoumarin         | ![Imperatorin](image) | *F. trifida* (69) |
| Isoimperatorin     | Furanocoumarin         | ![Isoimperatorin](image) | *F. trifida* (69) |
| Isopimpinellin     | Furanocoumarin         | ![Isopimpinellin](image) | *F. carduchorum* (70) |
| Isooxypeucedanin   | Furanocoumarin         | ![Isooxypeucedanin](image) | *F. turcomanica* (71) |
| Oxypeucedanin      | Furanocoumarin         | ![Oxypeucedanin](image) | *F. bernardii* (68), *F. mesiades* (72), *F. capitaries*, *F. brachyloba* (65), *F. turcomanica* (71), *F. grandatensis* (73), *F. subvelutina* (74), *F. platycarpa* (75), *F. sylvatica* (76), *F. angulata* (77), *F. trifida* (69) |
Continued Table 3. Chemical compounds isolated from the *Ferulago* genus.

| Compounds                        | Class       | Structure | Plants and References                  |
|----------------------------------|-------------|-----------|----------------------------------------|
| Oxypeucedanin Hydrate (Pangol)   | Furanocoumarins | ![Structure](image) | *F. capillaries, F. brachyloba* (65), *F. meoides* (72), *F. syriaca* (70), *F. turcomanica, F. subelata* (74), *F. angulate* (77), *F. trifida* (69) |
| Oxypeucedanin methanolate        | Furanocoumarins | ![Structure](image) | *F. trifida* (69) |
| Oxypeucedanin hydrate senecioate | Furanocoumarins | ![Structure](image) | *F. capillaris* (65) |
| Psoralen                         | Furanocoumarins | ![Structure](image) | *F. turcomanica* (71), *F. bernardii* (68) |
| 8-methylpsoralen                 | Furanocoumarins | ![Structure](image) | *F. asparagifolia* (67) |
| Xanthotoxin                      | Furanocoumarins | ![Structure](image) | *F. syriaca* (19), *F. isaurica* (19), *F. bracteata, F. pachyloba, F. trachycarpa, F. blancheana* (78), *F. angulate* (77), *F. carduchorum* (70), *F. trifida* (69) |
| 8-(1,1 dimethylallyl) bergaptol  | Furanocoumarins | ![Structure](image) | *F. syriaca* (19), *F. capillaris* (65) |
| (-)-Pranferol                    | Furanocoumarins | ![Structure](image) | *F. capillaris* (65) |
### Continued Table 3. Chemical compounds isolated from the *Ferulago* genus.

| Compounds         | Class             | Structure | Plants and References            |
|-------------------|-------------------|-----------|----------------------------------|
| Bergamotin        | Furanocoumarin    | [Structure Image](#) | *F. capillaris* (65)            |
| Bergapten         | Furanocoumarin    | [Structure Image](#) | *F. syriaca* (19), *F. isaurica* (19), *F. pachyloba*, *F. blancheana*, *F. trachycarpa*, *F. bracteata* (78), *F. carduchorum* (70), *F. trifida* (69) |
| Alatol            | Furanocoumarin    | [Structure Image](#) | *F. capillaris* (65)            |
| Marmesin          | Dihydrofuranocoumarin | [Structure Image](#) | *F. blancheana* (78),          |
| (-)-Isovaleryl Marmesin | Dihydrofuranocoumarin | [Structure Image](#) | *F. grunatensis* (73), *F. capillaris* (85) |
| Felamidin (Benzoyl marmesin) | Dihydrofuranocoumarin | [Structure Image](#) | *F. pauciradiata* (20), *F. syriaca* (19), *F. isaurica* (19), *F. pachyloba*, *F. trachycarpa*, *F. bracteata*, *F. campestris* (79), *F. blancheana* (78) |
| Prantschigmin (2''-senecioyl marmesin) | Dihydrofuranocoumarin | [Structure Image](#) | *F. pauciradiata* (20), *F. syriaca* (19), *F. isaurica* (19), *F. aucheri* (80), *F. bernardii* (88), *F. pachyloba*, *F. trachycarpa*, *F. bracteata*, *F. blancheana* (78), *F. carduchorum* (70), *F. asparagifolia* (67), *F. trifida* (69) |
| Rutarin           | Dihydrofuranocoumarin | [Structure Image](#) | *F. asparagifolia* (81)         |
| Umbelliprenin     | Sesquiterpene coumarin | [Structure Image](#) | *F. cassia* (8), *F. campestris* (82-85) |
**Continued Table 3.** Chemical compounds isolated from the *Ferulago* genus.

| Compounds          | Class              | Structure                                                                 | Plants and References                     |
|--------------------|--------------------|---------------------------------------------------------------------------|-------------------------------------------|
| Samarcandin        | Sesquiterpene      | ![Structure](image1.png)                                                   | *F. campestris* (86)                     |
| Coladin            | Sesquiterpene      | ![Structure](image2.png)                                                   | *F. campestris* (82, 83)                  |
| Coladonin          | Sesquiterpene      | ![Structure](image3.png)                                                   | *F. campestris* (82, 83)                  |
| Osthole (Osthol)   | Prenylated coumarin| ![Structure](image4.png)                                                   | *F. aucheri* (80)                         |
| Ostheneol          | Prenylated coumarin| ![Structure](image5.png)                                                   | *F. aucheri* (80)                         |
| 7-Isopentyloxy coumarin | Prenylated coumarin | ![Structure](image6.png)                                                   | *F. campestris* (84)                     |
| Peucedano1-2’-benzoate | Prenylated coumarin | ![Structure](image7.png)                                                   | *F. bracteata* (78), *F. blancheana*      |
| Peucedano1         | Prenylated coumarin| ![Structure](image8.png)                                                   | *F. cassia* (8)                           |
Continued Table 3. Chemical compounds isolated from the Ferulago genus.

| Compounds        | Class               | Structure                                      | Plants and References                           |
|------------------|---------------------|------------------------------------------------|------------------------------------------------|
| Suberosin        | Prenylated coumarin | ![Structure](image)                             | F. trachycarpa, F. bracteata (78), F. carduchorum (70), F. trifida (69), F. trachycarpa (14), F. cassia (8) |
| Suberosin epoxide| Prenylated coumarin | ![Structure](image)                             | F. angulata (87)                                |
| Suberenol        | Prenylated coumarin | ![Structure](image)                             | F. carduchorum (70), F. trifida (69)            |
| Grandivitinol    | Prenylated coumarin | ![Structure](image)                             | F. pachyloba, F. trachycarpa, F. bracteata, F. Hanchonia (78), F. cassia (8) |
| Grandivitinin    | Prenylated coumarin | ![Structure](image)                             | F. campestris (79), F. asparagifolia (67), F. trifida (69) |
| Ulopterol        | Prenylated coumarin | ![Structure](image)                             | F. trachycarpa (14, 78), F. trifida (69)        |
| Auraptene        | Prenylated coumarin | ![Structure](image)                             | F. brachyloba (65), F. campestris (84)          |
| Agasyllin        | Pyranocoumarin      | ![Structure](image)                             | F. campestris (79), F. asparagifolia (67)       |
| Benzoyl aegelinol| Pyranocoumarin      | ![Structure](image)                             | F. campestris (79)                              |
| Aegelinol        | Pyranocoumarin      | ![Structure](image)                             | F. asparagifolia (67)                           |
Continued Table 3. Chemical compounds isolated from the *Ferulago* genus.

| Compounds                      | Class         | Structure | Plants and References |
|--------------------------------|---------------|-----------|-----------------------|
| Asparagifolin                  | Pyranocoumarin| ![Structure](structure1.png) F. asparagifolia (67)|                       |
| Decursin                       | Pyranocoumarin| ![Structure](structure2.png) F. campestris (86) |                       |
| 4''-hydroxy Grandivitin        | Pyranocoumarin| ![Structure](structure3.png) F. macrocarpa (88) |                       |
| Isoquercetin                   | Flavonoid     | ![Structure](structure4.png) F. sylvatica (86) |                       |
| Isoquercetin-3-O-glucoside     | Flavonoid     | ![Structure](structure5.png) F. aucheri (80), F. asparagifolia (67) |       |
| Rutin                          | Flavonoid     | ![Structure](structure6.png) F. asparagifolia (67) |                       |
| Hesperetin                     | Flavonoid     | ![Structure](structure7.png) F. carduchorum (70) |                       |
| 6-hydroxy apigenin 6-methyl ether | Flavonoid | ![Structure](structure8.png) F. aucheri (80) |                       |
Continued Table 3. Chemical compounds isolated from the *Ferulago* genus.

| Compounds                        | Class          | Structure                                      | Plants and References               |
|----------------------------------|----------------|-----------------------------------------------|-------------------------------------|
| Quercetin                        | Flavonoid      | ![Quercetin structure](image1)                | *F. sylvatica* (89), *F. angulata* (90) |
| Quercetin 3-O-glycoside          | Flavonoid      | ![Quercetin 3-O-glycoside structure](image2)  | *F. confuse* (91)                   |
| Rhamnetin                        | Flavonoid      | ![Rhamnetin structure](image3)                 | *F. asparagifolia* (67)             |
| (-)-angelocidenol-2-O-b-         | Other-compound | ![(-)-angelocidenol-2-O-b- structure](image4)  | *F. asparagifolia* (67)             |
| apiofuranosyl-(1/6)-b-           |                |                                               |                                     |
| glucopyranoside                  |                |                                               |                                     |
| Quinol monoacetate               | Other-compound | ![Quinol monoacetate structure](image5)        | *F. aucheri* (80)                   |
| Dillapiole                       | Other-compound | ![Dillapiole structure](image6)                | *F. thyrsiflora*, *F. nodosa*, *F. sylvatica* (45) |
| Lupanine                         | Other-compound | ![Lupanine structure](image7)                  | *F. thyrsiflora* (45)               |
| 3,5-di-(E,E)-caffeoylquinic acid | Other-compound | ![3,5-di-(E,E)-caffeoylquinic acid structure](image8) | *F. asparagifolia* (67)             |
Continued Table 3. Chemical compounds isolated from the *Ferulago* genus.

| Compounds             | Class         | Structure | Plants and References |
|-----------------------|---------------|-----------|-----------------------|
| Chlorogenic acid      | Other- compound | ![Structure](image) | *F. asparagifolia* (81) |
| Polycensoi din        | Other- compound | ![Structure](image) | *F. angulata* (92) |
| siol anisate          | Other- compound | ![Structure](image) | *F. campestris* (82, 83) |
| Fenutinin             | Other- compound | ![Structure](image) | *F. campestris* (82, 83) |
| Myristicin            | Other- compound | ![Structure](image) | *F. antiochia* (93) |
| 1-acetyl-5-angeloyl lapiferol | Other- compound | ![Structure](image) | *F. campestris* (82, 83) |
| 2-epilaserine         | Other- compound | ![Structure](image) | *F. campestris* (82, 83) |
| Ephelmannicine        | Other- compound | ![Structure](image) | *F. campestris* (82, 83) |
Continued Table 3. Chemical compounds isolated from the *Ferulago* genus.

| Compounds               | Class          | Structure | Plants and References                                      |
|-------------------------|----------------|-----------|------------------------------------------------------------|
| 9-epoxyfalcarindiol     | Other-compound |           | *F. campestris* (82, 83)                                  |
| Nonacosane              | Other-compound |           | *F. bernardii* (68)                                       |
| β-Sitosterol            | Other-compound |           | *F. pachyloba, F. trachycarpa, F. bracteata, F. blancheana* (78), *F. carduchorum* (70) |
| β-sitosterol linoleate  | Other-compound |           | *F. angulata* (77), *F. subvelutina* (74)                  |
| Stigmasterol            | Other-compound |           | *F. pachyloba, F. trachycarpa, F. bracteata, F. blancheana* (78), *F. angulata* (77), *F. macrocarpa* (41) |
fraction of roots, and methanol extracts of roots and aerial parts from *F. trachycarpa* (62.5 µg/mL) and prantschimgin (31.25 µg/mL) (78). According to them, the *E. coli* was less affected than the other microorganisms; the best activity against *C. albicans* (MIC = 31.25 μg/mL) was obtained by the CH₂Cl₂ fraction of aerial portions from *F. pachyloba* and isolated compound prantschimgin. Furthermore, Pinto et al. evaluated the antifungal effects of an essential oil, and two main compounds of it on germ tube formation, ergosterol biosynthesis, and mitochondrial function. Limonene presented a weaker activity (0.32 to 20 μL/mL) than the essential oil and α-pinene with low and similar to MIC and MFC values against the tested organisms (0.08 to 5.0 μL/mL). The essential oil of *F. capillaris* suppressed germ tube formation at sub-inhibitory dose on *Candida albicans*. The mechanism of antifungal activity of *F. capillaris* indicated no distribution on the ergosterol content and defect of mitochondrial role in a dose-dependent way in essential oil-treated *C. albicans* (62).

**Anti-oxidant effect**

In recent decades, extensive studies have been conducted on the evaluation of the antioxidant function of medicinal plants as a source of natural compounds not only to combat several degenerative disorders, including cardiovascular disease and cancer, but also as a substitute compound to artificial additives, like butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) in food productions (94). Anti-oxidant constituents diminish the extent of oxidative damage via acting as free radical scavengers (95). There are numerous methods, such as radical scavenging power, reducing power, and inhibition of lipid peroxidation in a β-carotene–linoleate system for assessing the antioxidant activity of plant extracts or volatile oils (96). The DPPH radical-scavenging method is one of the easiest and rapid tests for evaluating the antioxidant activity of natural compounds(16). According to literature, an antioxidant activity study has been performed on *F. macrocarpa*, *F. carduchorum* (97), *F. bernardii* (16), *F. sandrasica*, *F. macedonica*, *F. trifida* (64), *F. subvelutina* (74), *F. cassia* (8), *F. angulata*, and *F. campestris* (79). The antioxidant activities of four fractions and crude extract of aerial portions of *F. carduchorum* at 2 vegetative periods (flower and fruit) were assessed using the DPPH method. The best activity belonged to flower crude extract (IC₅₀ = 0.44 mg/mL) (97). Shahbazi and Shavisi investigated the antioxidant activities of nonpolar and polar sub-fractions of methanolic extract, and the

### Table 4. Pharmacological activities and model of study of the genus *Ferulago*.

| Pharmacological activities | Plant                  | Model  | References |
|---------------------------|------------------------|--------|------------|
| Anti-microbial            | *F. sandrasica*        | In-vitro | (55)       |
|                           | *F. pachyloba*, *F. blancheana*, *F. trachycarpa*, *F. bracteata* | In-vitro | (78)       |
| Anti-fungal               | *F. capillaris*        | In-vitro | (62)       |
|                           | *F. carduchorum*       | In-vitro | (97)       |
|                           | *F. bernardii*         | In-vitro | (16)       |
|                           | *F. trifida*, *F. sandrasica*, *F. macedonica*, *F. cassia* | In-vitro | (64)       |
|                           | *F. angulata*, and *F. campestris* | In-vitro | (79)       |
|                           | *F. subvelutina*       | In-vitro | (74)       |
| Anti-oxidant              | *F. subvelutina*, *F. angulata* | In-vitro | (98)       |
|                           | *F. pauciradiata*      | In-vitro | (20)       |
|                           | *F. carduchorum*       | In-vitro | (34)       |
|                           | *F. isaurica* and *F. syriaca*. | In-vitro | (19)       |
|                           | *F. trifida*           | In-vitro | (64)       |
|                           | *F. angulata*          | In-vitro | (99)       |
|                           | *F. pauciradiata*      | In-vitro | (20)       |
| Alzheimer                 | *F. blancheana*, *F. pachyloba*, *F. trachycarpa* | In-vitro | (100)      |
| Anti-diabetic             | *F. carduchorum*       | In-vivo  | (17)       |
| Anti-coagulant            | *F. carduchorum*       | In-vitro | (101)      |
| Anti-malaria              | *F. carduchorum*       | In-vitro | (102)      |
| Aphrodisiac               | *F. syriaca*           | In-vitro | (103)      |
volatile oil of the aerial parts of *F. bernardii* and compared them to BHT via DPPH assay. The antioxidant activity with the mean of IC₅₀ were polar sub-fractions (5.66), non-polar sub-fractions (6.88), and essential oil (14.81), while they displayed lower radical scavenging activity compared with BHT(16). Tavakoli et al. found that due to lack of phenolic compounds in the conformation of the volatile oil of different parts of *F. trifida*, a feeble free radical scavenging effect was observed (IC₅₀: 95–120 μg mL⁻¹) compare to BHT (IC₅₀: 21.2 ± 2.6 μg mL⁻¹) (64). Moderate antioxidant activities were attained with DPPH test from isolated coumarin of the roots of *F. subvelutina* compare to BHT (IC₅₀ = 27 μg/mL) >oxypeucedanin hydrate (IC₅₀ = 160 μg/mL) >meranzin hydrate (IC₅₀ = 180 μg/mL) >osthole (IC₅₀ = 27 μg/mL) >oxypeucedanin (IC₅₀ = 217 μg/mL) >isoolimperatorin (IC₅₀ = 245 μg/mL) >xanthotoxin (IC₅₀ = 270 μg/mL) (74). In another study, the antioxidant activity of isolated compound, and the extracts and fractions of the aerial parts, fruits, flower, and roots of *F. cassia* were investigated via TBA assay. The highest antioxidant potential was obtained based on following order: Peucedanol (IC₅₀ = 18.1 μg/mL) > Suberosin (IC₅₀ = 23.5 μg/mL) > roots CH₂Cl₂ fractions (IC₅₀ = 43.1 μg/mL) > fruit CH₂Cl₂ fractions (IC₅₀ = 54.4 μg/mL) > Grandivitinol (IC₅₀ = 61.1 μg/mL) > Umbelliferone (IC₅₀ = 79.5 μg/mL) (8).

**Alzheimer’s disease (AD)**

Alzheimer’s is one of the neurological disorders with decreasing acetylcholine followed by the deterioration of short-term memory, which occurs in elderly people mostly based on genetic inheritance. One promising strategy for combating AD is using anticholinesterases or acetylcholinesterase inhibitors (AChEIs) to inhibit the hydrolysis of acetylcholine and raise its level in the synaptic cleft (82). Hajimehdipoor and co-worker studied the acetylcholinesterase inhibitory property of the total extracts and fractions of the aerial portions of *F. subvelutina* and the whole plant of *F. angulata* employing the Ellman method. Their result implied that a total extract of both *Ferulago* genes can inhibit the acetylcholinesterase enzyme with 19.7% and 15.8% respectively for *F. subvelutina* and *F. angulata*. The dichloromethane fraction displayed the highest AChEI activity among all the fractions (98). Golfakhrabadi et al. found that all the coumarins obtained from the aerial parts of *F. carduchorum* have AChE enzyme inhibition, among which xanthotoxin revealed the highest inhibitory (IC₅₀ = 39.64 μM) (70). The essential oil of *F. carduchorum* has been also found to be of AChE inhibitory activity (IC₅₀ = 23.6 μL mL⁻¹) (34). In another study on AChE inhibitors via bioassay-guided isolation, the dichloromethane extract from the root of *F. campestris* was investigated. Three daucane ester derivatives (1-acetyl-5-angeloyl lapiferol, ferutinin, and siol anisate), two phenol derivatives (epielmanticine and 2-epilaserine), one polyacetylene (9-epoxyfalcarindiol), and three coumarin derivatives (coladin, coladonin, umbelliprenin) were isolated. All the obtained constituents could inhibit the AChE, but at higher doses (IC₅₀ 1.2–0.1 mM) than the standard galantamine (6.7 μM) and the most active compounds were the epielmanticine and the siol anisate with IC₅₀ of 0.172 and 0.175 μM, respectively (82). In addition, Karakaya and co-workers studied the anticholinesterase effects of the fractions and extracts from the aerial parts and roots of *F. isaurica* and *F. syriaca*. Strong inhibitory activities against butyrylcholinesterase (BuChE) (88.56 ± 2.34%) and AChE (46.99%) at 20 µg/mL were observed in the CHCl₃ part of the root of *F. Isaurica*. Felamidin (77.11%); prantschimgin (74.82%), two obtained constituents from the chloroform part of roots, presented a strong inhibitory effect against BuChE (19). In another study, AChE inhibitory activities of the volatile oils of the fruits, roots, and flowers of *F. trifida* were investigated. The result revealed significant AChE inhibitory activity (78.7, 74.3, and 72.1% inhibition of Ach Enzyme, respectively) (64). Hriteu and co-worker found the volatile oil extracted from the aerial part of *F. angulata* has an anti-amnesic activity in scopolamine-induced memory deterioration in rats and diminish AChE activity in hippocampal (99). In another study the volatile oil from fruits of *Pauerciradiata* revealed strong inhibitory properties against BuChE and AChE (IC₅₀ = 0.567, 7.987 L/mL, respectively) (20).
Anti-diabetic effects

α-glucosidase, and α-amylase inhibitory activity of the extracts and some compounds from the roots of *F. blancheana*, *F. trachycarpa*, and *F. pachyloba* have been evaluated by in-vitro bioassay-guided isolation methods to determine the anti-diabetic properties of this plant. The obtained result demonstrated that the highest activities versus α-glucosidase with an IC50 value of 0.3, 2, 2 mg/mL belonged to CH2Cl2 extracts of the roots of *F. trachycarpa*, *F. pachyloba*, and *F. blancheana*, respectively. Suberosin and felamidin compounds possessed momentous α-glucosidase inhibitory activities with IC50 values of 0.9 and 0.4 mg/mL, respectively, while the IC50 for acarbose as standard was 4.9 mg/mL. The acarbose depicted a strong α-amylase inhibitory activity (82.3%) at a dose of 1 mg/mL whereas none of the other extracts displayed a significant α-amylase inhibitory effect (100).

Anti-coagulant activity

Golfakhrabadi *et al.* evaluated the toxicological profile of oral application of the *F. carduchorum* extract and the anticoagulant effects of two isolated coumarins (suberenol and suberosin) in male Wistar rats. The LD50 of the plant extract for acute toxicity was over 2000 mg/kg and there were no substantial variations (*p > 0.05*) among the control and the treated groups concerning the biochemical and hematological parameters. The prothrombin time (PT) of the treated group with a total extract from the aerial part of the plant has not shown a major impact relative to the control group (receiving tap water by gavage) (*p > 0.05*) at doses of 250 and 500 mg/kg. Meanwhile, suberosin expanded the PT at doses of 3 and 6 mg/kg (16.7 and 17.4 s, respectively) and suberenol at the same dose (16.5 and 17.1 s, respectively) (17).

Aphrodisiac activity

An in-vitro study was conducted by Ozturk et al. to investigate the aphrodisiac activity of the lyophilized water extract from the roots of *F. syriaca* on the human corpus cavernosum. For finding the mechanism involved in relaxation, the effect of the extract was investigated on the relaxing responses to selective guanilate cyclase inhibitor (oxadiazolo [4,3-α] quinoxalin-1-one (ODQ)), NO-synthesis inhibitor (NG-nitro-L-arginine methyl ester (L-NAME)), forskolin, Electrical field stimulation (EFS), sodium nitroprusside, and acetylcholine. The result displayed that the extract could have to relax in a dose-dependent way on corpus cavernosum strips, and the L-NAME (small dosages) and ODQ (in all dosages) were able to suppress the extract-induced relaxation in the human corpus cavernosum. The *F. syriaca* extract enhanced the relaxation response of strips with Ach incubation while the extract did not affect the and early 4th instar larvae of the malaria vector Anopheles stephensi. The LC90 of chloroform, ethyl acetate, the total extract, and methanol fractions were 0.455, 1.892, 1.509, and 10.886 ppm, respectively. Moreover, the LC50 of chloroform, ethyl acetate, the total extract, and methanol fractions were 0.236, 0.744, 0.480, and 3.702 ppm, respectively. The chloroform fraction indicated lower LC50 and LC90 values than the other extracts, which might be due to the presence of high content of phytosteroids and coumarins (101). In another study, the larvicidal activity of a few isolated coumarin, methanol, and chloroform extracts of the roots, leaves, and fruits of *F. trifida* were investigated on the third instar larvae of A. stephensi Listonas. Strong insecticidal properties were found for methanol extract of the fruit with LC90 and LC50 values of 18.12 and 2.94 ppm, respectively. Among pure compounds, oxypeucedanin presented moderate toxicity against A. stephensi with LC90 and LC50 values of 346.41 and 116.54 ppm, respectively. It could be concluded that the methanol extract from the fruit of *F. trifida* might be utilized as an effective bio-insecticide in green control programs of mosquitoes, particularly *A. stephensi* (102).

Anti-malaria

Khanavi *et al.* assessed the larvicidal activity of chloroform, methanol, ethyl acetate, and the total 80% methanol extract from the aerial part of *F. carduchorum* against late 3rd,
relaxation induced by EFS, forskolin sodium, and nitroprusside. The result suggested that the extract of *F. syriaca* could presumably act via stimulating the NO- cyclic guanosine monophosphate (cGMP) pathway (103).

**Toxicity profile of the genus Ferulago**

Nowadays, the usage of herbal remedies has increased around the world, and patients falsely feel that they are healthy because they are natural. While these products comprise several bioactive compounds and might cause adverse effects on consumers (104, 105). Therefore, it is essential to herbal medicines undergo current safety and efficacy tests. Based on the literature review, there is only one piece of scientific study about the safety of this herb. Golfakhrabadi *et al.* investigated oral acute, and sub-chronic toxicities of the total extract of the aerial parts of *F. carduchorum* in the rat (17). To study acute toxicity five rats were treated with one dose of the total extract (2000 mg/kg) orally and the control group was treated with tap water. For the sub- chronic study, the doses (250, 500, and 1000 mg/kg) of the total extract were applied to treated groups by gavage for thirty following days. During the acute toxicity study, the animals did not show any signs of side effects, mortality, and the LD$_{50}$ was over 2000 mg/kg in rats. The result of sub-chronic toxicity demonstrated that the total extract did not yield momentous changes in behavior, water, and food intake, breathing, body weight gain, blood metrics, and gastrointestinal properties in rats (17). This study indicated that *F. carduchorum* may be a healthy additive for conventional applications.

**Conclusion and future perspective**

To date, around 73 molecules, including coumarin, furanocoumarin, flavonoids, and stilbene have been isolated from the Ferulago species. Among the isolated constituents, mostly are phenolic compounds in which three simple coumarins, sixteen furanocoumarins, five dihydro-furanocoumarin, four sesquiterpene coumarin, twelve prenylated coumarins, six pyranocoumarin, nine flavonoids, and eighteen miscellaneous compounds. Coumarins and their derivatives are considered to be important taxonomic markers of the genus Ferulago. In the pharmacological effect part, we have discussed various studies to evaluate the ethnomedicinal uses and this has shown that the isolated constituents and different extracts from the Ferulago species possess several pharmacological effects including antibacterial, antioxidant, Alzheimer, anti-diabetics, anti-malaria, anti-coagulant, aphrodisiac effects. Accessible information regarding Ferulago spp. allows us to explore their potential benefits, highlight the gaps in our knowledge, and conduct future researches to develop new drugs. It can be concluded that the pharmacological study of Ferulago spp. is in agreement with the ethnomedicinal uses of the plants.

**Acknowledgments**

This work was a part of a Ph.D. project and financially supported by Tabriz University of Medical Sciences, Tabriz, Iran [Grant Number: 64064].

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