The genus *Ferula*: ethnobotany, phytochemistry and bioactivities - a review

Majid Mohammadhosseini[1*], Alessandro Venditti[2], Satyajit D. Sarker[3], Lutfun Nahar[3], and Abolfazl Akbarzadeh[4]

[1]*Department of Chemistry, Shahrood Branch, Islamic Azad University, Shahrood, Iran*

[2]*Dipartimento di Chimica, Università di Roma "La Sapienza", Piazzale Aldo Moro 5, 00185 Rome, Italy*

[3]*Medicinal Chemistry and Natural Products Research Group, School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, United Kingdom*

[4]*Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*

*Corresponding author at: Department of Chemistry, Shahrood Branch, Islamic Azad University, Shahrood, Iran. Tel: +98-023-32394530; Fax: +98-023-32394537

E-mail addresses:

majidmohammadhosseini@yahoo.com; majidmohammadhosseini@gmail.com; m_mhosseini@iau-shahrood.ac.ir (M. Mohammadhosseini)

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Abstract

This study aims to provide a comprehensive overview of the medicinal, folkloric and traditional culinary uses of *Ferula* species, related products and extracts in different countries together with the description of recently isolated new components and the related bioactivities. The phytochemical composition of the essential oils (EOs), oleo-gum-resin (OGR) and the non-volatile fractions obtained from several endemic and indigenous *Ferula* species is also reported. A special emphasis is placed on their unusual components, i.e. sulfur-containing volatiles from the EOs and the new phytochemicals with mixed biogenetic origins. More than 180 chemical constituents (excluding common essential oils components), including sulfur-containing metabolites, terpenoids, coumarins, sesquiterpene coumarins, etc., as both aglycones and glycosides, are reported, along with their occurrence and biological activities when available. A large number of new secondary metabolites, belonging to different classes of natural products possessing interesting biological activities, from the antiproliferative to the anti-inflammatory to the neuroprotective ones, among the others, have been recently found in the *Ferula* genus. Several of these phytochemicals are exclusive to this genus; therefore may be considered chemotaxonomic markers. All these aspects are extensively discussed in this review.

Keywords: Ferula spp.; Apiaceae; Ethnomedicine; Secondary metabolites; Traditional uses; Essential oil; Non-volatile components

1. Introduction

The genus *Ferula*, the third largest genus of the Apiaceae (*alt.* Umbelliferae) family, is composed of ca. 180 species (Yaqoob and Nawchoo, 2016), 15 of which are endemic to Iran (Mozaffarian, 1996), nine species to Turkey, seven to China (Yaqoob and Nawchoo, 2016) and one species to Italy (Conti et al, 2005), and the rest are indigenous entities of several other countries.

The majority of the *Ferula* plants have a pungent odor and can be used for different purposes. The endemic and indigenous species of the *Ferula* in the flora of some countries, of which the data are available, are listed in Table 1.

In the literature, numerous reports have described various biological and medicinal activities for different essential oils (EOs) and extracts of the *Ferula* plants. These include anticancer (Paydar et al., 2013; Perveen et al., 2017; Upadhyay et al., 2017), anthelmintic (Kakar et al., 2013; Upadhyay et al., 2017), anti-epileptic (Sayyah et al., 2001; Kiasalari et al., 2013), aphicidal (Stepanycheva et al., 2012), antioxidant (Kavoosi et al., 2013; Paydar et al., 2013; Amiri, 2014; Znati et al., 2014; Lahazi et al., 2015; Moosavi et al., 2015; Yusufoglu et al., 2015c; Zhang et al., 2015; Nguir et al., 2016), antimicrobial (Yang et al., 2007; Kavoosi et al., 2013; Liu et al., 2013; Paydar et al., 2013; Bashir et al., 2014b; Pavlovic et al., 2015), antihypertensive (Ghanbari et al., 2012), antifungal (Rani et al., 2009; Al-Ja'Fari et al., 2013; Bashir et al., 2014b; Upadhyay et al., 2017), antidepressant (Mohammadhosseini, 2016), phytotoxic (Bashir et al., 2014b), (Kavoosi et al., 2013; Paydar et al., 2013; Pavlovic et al., 2015), antiproliferative (Poli et al., 2005; Moradzadeh et al., 2017), acetylcholinesterase inhibitory (Adhami et al., 2014) and muscarinic receptors inhibitory (Khazdair et al., 2015), antiprotozoal activity (El Deeb et al., 2012; Bafghi et al., 2014; Barati et al., 2014), antihemolytic (Nabavi et al., 2011), antimycobacterial (Mossa et al., 2004; Fallah et al., 2015), anti-ulcer (Alqasoumi et al., 2011), antitumor (Zhang et al., 2015; Bagheri et al., 2017), anticoagulant (Lamnaouer, 1999; Fraigui et al., 2002), antifertility (Keshri et al.,

1999), antispasmodic (Fatehi et al., 2004; Upadhyay et al., 2017), anticonvulsant (Sayyah and Mandgary, 2003; Bagheri et al., 2014b), relaxant (Sadraei et al., 2001), antinociceptive (Mandegary et al., 2004; Bagheri et al., 2014a), hypnotic (Abbasnia and Aeinfar, 2016), hypotensive (Upadhyay et al., 2017), muscle relaxant (Upadhyay et al., 2017), memory enhancing (Upadhyay et al., 2017), enhancing digestive enzyme (Upadhyay et al., 2017), antiviral (Lee et al., 2009; Ghannadi et al., 2014; Upadhyay et al., 2017), anxiolytics (Upadhyay et al., 2017), antihyperlipidemic (Yusufoglu et al., 2015a; Yusufoglu et al., 2015b), antigenotoxic (Hu et al., 2009; Abbasnia and Aeinfar, 2016), anti-inflammatory (Mandegary et al., 2004; Paydar et al., 2013; Bagheri et al., 2015; Moosavi et al., 2015), cytotoxic (Elouzi et al., 2008; Valiahdi et al., 2013; Gudarzi et al., 2015; Mohd Shafri et al., 2015; Hosseini et al., 2017), antihyperglycemic (Yusufoglu et al., 2015a; Yusufoglu et al., 2015b; Yusufoglu et al., 2015c), acaricidal (Fatemikia et al., 2017), antidiabetic (Yarizade et al., 2017), hepatoprotective (Upadhyay et al., 2017) and antibiotic modulation (Paydar et al., 2013) activities.

In this review paper, we aim to cover the ethnobotany, phytochemistry and pharmacological activities along with chemical composition of the essential oils (EOs), volatiles, oleo-gum-resins (OGRs) and extracts of different species of the genus *Ferula* described in recent decades.

2. Research methodology

To prepare a comprehensive phytochemical and ethnobotanical review on the plants of the genus *Ferula*, the corresponding data were integrated in this report. To organize this review paper, ISI-WOS, PubMed, Scopus (date of access: 18 September 2017 and revisited on 10 March 2018) and Google scholar databases, papers published in recent decades by publishers such as Elsevier, Springer, Taylor and Francis and John Wiley, and English and non-English

reference books dealing with useful properties of the *Ferula* plants have been systematically reviewed.

3. Ethnobotany and traditional usage of the *Ferula* species

Medicinal plants have been of prime importance in the folkloric traditional medicine systems for centuries (Mohammadhosseini, 2017). The remedial properties of these plants are remarkable (Mohammadhosseini et al., 2017a; Mohammadhosseini et al., 2017b). Due to the unpleasant side effects and ineffectivness of many conventional drugs, the search for new drugs from natural origin has gained momentum in recent years.

In this regard, different species of the genus *Ferula* have always been in the focus, specifically in the Middle East and Asian countries including Iran, Pakistan, Iraq, India and others. According to the flora of Iran, different *Ferula* species are widespread in eastern and central parts of the country. Most *Ferula* species have a bitter taste and pungent odor. The genus *Ferula* has a Latin root meaning “vehicle” or “carrier”. In Persian, “asa” means resin. It is also noteworthy that the word “foetida” originates from the Latin word “foetidus” meaning “smell” accounting for its pungent sulfur-based odor. In the folk medicine of Iran, China, Germany, Italy, France and India, Asafoetida is often called "Anghouzeh", "A Wei", "Teufellsdreck or Stinkasant", "Assafoetida", and "ase-fetide", respectively (Iranshahy and Iranshahi, 2011). An oleo-gum-resin (OGR), as a milky and bitter substance, is exudated from the stem of some *Ferula* plants, e.g. *F. assa-foetida* and *F. gummosa* Boiss. and coagulates when exposed to the air.

The gum of the most important species of the genus *Ferula*, namely *F. assa-foetida* L. has many therapeutic properties. Significant amounts of this gum are annually exported from Iran and Afghanistan to the East Asian countries like China and Japan, via Mongolia, as well as to European and North American countries. Many people believe that the sticky gum from *F.*

assa-foetida L. is a strong carminative agent that can remove the stomach worms. In children, it is used as an antiparasite remedy. It has been reported that the roots of two species of *Ferula*, namely *F. assa-foetida* L. (Fig. 1) and *F. gummosa* Boiss., are rich sources of valuable natural compounds (Mozaffarian, 2012). The general properties of *F. assa-foetida* L. in traditional medicine are reported to have potent antiseptic, antimucous, anti-epilepsy (specifically in the children), anticonvulsant, antitetanus and aphrodisiac (see Table 2) activities, and to be of value in the regulation of the menstruation, and as an antidote for insect and animal bites (Mohammadhosseini, 2016). In the latter case, certain amount of the gum is dissolved in olive oil and subsequently placed on the site of the bite. This can lower the pain and considerably improve inflamed and infected wounds. The suspension of *F. assa-foetida* L. can be used to repel wild animals.

The gum or decoctions of *F. assa-foetida* L. has been used to treat certain wounds, hemorrhoids and rheumatism, and as a useful remedy to refine the liver blood in trade markets. In addition, its pickling serves as an effective agent to remove some parasites from the human body and it appears to have strong antiviral activity against influenza.

In some ancient civilizations, a necklace of *F. assa-foetida* L. was placed around the neck of patients suffering from severe cold or hay fever. In traditional Persian medicine, people believed that *F. assa-foetida* L. was effective in the treatment of a broad range of diseases and disorders, and for this reason it was called “food of God”. Interestingly, among the different stories about *F. assa-foetida* L., it was suggested that the name originates from the idea of God’s semen fertilizing the earth.

This valuable species is widely used as an additive in foodstuffs. Some nomads of central Iran still use fried *F. assa-foetida* L. along with some condiments as a carminative food. The rural people and nomads of Semnan province (Abbas Abad Village, Shahrood, Iran) use the dried aerial parts of *F. assa-foetida* L. in the preparation of their delicious local food,

180 “Loghri”, which also contains barley, Nagorno Qrvt (Qareh Qurut), tomato or tomato
181 paste, beans and other vegetables (Fig. 2).
182 There are myths of a spiritual nature that *F. assa-foetida* L. can strengthen the human body,
183 and repulse negative energy, evils and demons (Mahendra and Bisht, 2012).
184 Apart from some biological and medicinal properties, the spice prepared from *F. assa-foetida*
185 L. is regarded as an effective remedy for *Angina pectoris* (Srinivasan, 2005).
186 In Afghan folk medicine, the dried gum of *F. assa-foetida* is immersed in hot water and the
187 extract is used as an herbal drug to treat ulcers, whooping cough and hysteria (Mahran et al.,
188 1973).
189 In Morocco, *F. assa-foetida* L. is reputed to be a magical anti-epileptic drug, and another
190 endemic species of *Ferula* (*F. communis* L.) has been regarded as an antispasmodic agent
191 with some degree of toxicity (Bellakhdar et al., 1991).
192 In Nepal, the resins of *F. assa-foetida* L. are extracted with water and the extract is used
193 orally as an anthelmintic agent (Bhattarai, 1992). In desert localities of Saudi Arabia, the
194 inhabitants utilize the gum of *F. assa-foetida* L. for treating asthma, bronchitis and cough
195 (Seabrook, 1927).
196 In Brazil, the hot water extract from the dried leaves and stems of *F. assa-foetida* L. are used
197 orally to treat erectile dysfunction, and as an aphrodisiac (Elisabetsky et al., 1992).
198 Moreover, the crushed powder obtained from an OGR of *F. assa-foetida* L. has been used as
199 a condiment in India for many years (Seetharam and Pasricha, 1987).
200 In USA, resin extracts of *F. assa-foetida* L. taken orally have been used as an antispasmodic,
201 expectorant, aphrodisiac and a stimulant for the human nervous system (Lilly, 1898). In
202 addition, the black American people reportedly use the gum of *F. assa-foetida* L. for many
203 purposes, e.g. cancer, menstruatal problems, asthma, convulsion, laryngitis, corns of the feet,
204 hand and foot callous and madness. In America, *F. assa-foetida* L. is prescribed as an

effective diuretic, stimulant and sedative phytoremedy. In addition to diverse medicinal uses, different organs of *F. assa-foetida* L., either in fresh or dried form are used for cooking, as even small parts of this plant can give a pungent smell to foodstuffs. It has also found many applications as a condiment and flavoring agent in chocolates, seasoning and soft drinks. Due to emmenagogue properties of *F. assa-foetida* L., it is not recommended in the breast-feeding period and its overuse may cause abortion. Antipain, antitumor, digestive, lactating, fungicide, mutagenic, uterus tonic are among the other properties attributed to this plant. It also prevents platelet adhesion of the blood and lowers the fever and blood pressure. To treat pneumonia, bronchitis, cough and cold, *F. assa-foetida* L. is often considered among the frequently options in the folk medicine of many Asian countries. It is reported to cure rheumatism, gout, hysteria, and sciatica.

The stem of *F. gummosa* Boiss. has numerous elliptical ducts dispersed in the phloem tissues. In the vegetative stage of this plant, the OGR in these ducts is exuded manually or naturally (Mortazaienezhad and Sadeghian, 2006). In fact, the gum of *F. gummosa* Boiss. is reported to have numerous medicinal properties. When it is mixed with honey, it is said to aid removal of large kidney and bladder stones. The diluted gum of this plant is used by the local midwifes to expel the dead fetus.

In Iranian folk medicine, it is said that if the gum of *F. gummosa* Boiss. is dissolved in water and drunk for three sequential days, it can treat hemorrhoids. Moreover, when this gum is dissolved in nettle decoction and mixed with olive oil and put on painful places as a poultice, it can decrease the severe pains of waist. In different European countries, the gum, called galbanum, exuded from *F. gummosa* Boiss. has also been used to treat epilepsy, stomachache and as an effective wound healing agent (Miyazawa et al., 2009). This material has also been used as an anthelmintic agent and to treat diarrhea, constipation, and abdominal pains. In Iranian folk medicine, the OGR (galbanum) from *F. gummosa* Boiss. has been widely

prescribed as an antispasmodic and stimulant to treat digestive disorders such as colic and flatulence. It is also reported as a uterine tonic and to have expectorant properties in the treatment of chronic bronchitis.

Another species of this genus, *F. narthex* Boiss, is found widespread in Pakistan, especially in Gilgit and Chitral. The Pakistani people highly use this herbal plant or its gum resin to treat hysteria, gastric malfunctions, cough, fever, the sting of scorpions, constipation and habitual abortion as well as a strong sedative agent in painful toothaches (Bashir et al., 2013).

F. communis L., having two subspecies, namely *F. communis* subsp. *communis* and *F. communis* subsp. *glauca* (Pesmen, 1972) has been used in Sardinian folk medicine on account of reported antiseptic features of decoctions of its roots (Sanna et al., 2006; Maggi et al., 2016; Rahali et al., 2016). It has been reported that in the ancient Rome, *assa-foetida* was stored in jars with pine nuts which were used to give pleasant and specific flavors and odors to certain foods, including vegetables, barbecued meats, meatballs, pickles and other cooked dishes (Mahendra and Bisht, 2012; Mohammadhosseini, 2016).

During investigation of the chemistry and biology of the Umbelliferae plants (now Apiaceae), French (1971) pointed out the reported antihysteric properties of *F. communis* L. and its potential to treat dysentery. In fact, this species is a source of several medicinal and pharmaceutical substances. According to the Greek mythology, *F. communis* L. (Narthex) was employed by Prometheus, of Greek legend, to set fire to the earth where this species grew (Gennadios, 1914). Despite the high toxicity of some chemotypes of this plant to humans and animals (Marchi et al., 2003), it has been used to treat skin infections, dysentery and fever (Al-Yahya et al., 1998). In a study of the hormonal impact of *Ferula* plants, *F. hermonis* Boiss. has been introduced as containing a phytoestrogen having a high affinity toward estrogen receptors and capable of having a positive impact on certain disorders (Ikeda et al., 2002).

In Tunisian folk medicine, *F. communis* L., has been reported to treat foot cracks, joint pains, parasitic worms, rheumatism, dysentery, hysteria and skin diseases (Nguir et al., 2016). However, domestic animals fed with *F. communis* L. can develop haemorragic and ferulotic diseases (Lamnaouer et al., 1991; Lamnaouer et al., 1994; Tanji and Nassif, 1995).

In the traditional medicine of Syria and Lebanon, *F. hermonis* Boiss. is called "Shirsh-el-Zallouh," which means "having a hairy root" on account of its general morphology. This plant has been long used as an aphrodisiac agent (Table 2) in the treatment of impotence and frigidity (Auzi et al., 2008; Al-Ja'Fari et al., 2011).

4. Chemical profiles of the essential oils, extracts, resins and volatiles from different *Ferula* species

Essential oil (EOs) are mixtures of natural compounds released from the secretory glands of a wide array of plants. EOs are often used in a variety of the industrial disciplines. In addition, EOs have a great impact on perfumery and fragrance enterprises.

Classical hydrodistillation (HD) and steam distillation (SD) have been used to extract EOs since antiquity. However, within the last decades of the 20^{th} century, microwave methods have resulted in faster and more efficient separations of EOs. Accordingly, microwave-assisted hydrodistillation (MAHD) (Mohammadhosseini et al., 2013; Hashemi-Moghaddam et al., 2014; Hashemi-Moghaddam et al., 2015) along with solvent-free microwave extraction (SFME) (Mohammadhosseini, 2015a; Nekoei and Mohammadhosseini, 2017), are now considered to be effective and advanced approaches for the isolation of volatile EOs.

On the other hand, volatiles produced by different organs of plant materials can be released thermally and can be directed onto the surface of diverse organic fibers (Mohammadhosseini, 2015b; Mohammadhosseini et al., 2016). The volatile parts can also be introduced directly into the injection port of gas chromatographic-based devices (Mohammadhosseini et al., 2017a).

The main components in the chemical profiles of a vast number of EOs, extracts and volatiles of the *Ferula* plants from 1989 to March 2018 are listed in Table 3. A careful perusal of Table 3 reveals that the most abundant non-terpenoid hydrocarbons found in the reported chemical profiles were sulfur-containing compounds involving (*E*)-1-propenyl-*sec*-butyl disulfide, dimethyl-trisulphide, *sec*-butyl-(*Z*)-propenyl-disulphide, *sec*-butyl-(*E*)-propenyl-disulphide, di-*sec*-butyl-disulphide, phenol 2-methyl-5-(1-methylethyl), trimethylthiophene, 2,5-diethylthiophene, 1-methylpropyl-(1*E*)-prop-1-en-1-yl-disulfide, 1-methylpropyl-(1*Z*)-prop-1-en-1-yl-disulfide and bis-[(1-methylthio)propyl]-disulfide (Khajeh et al., 2005; Iranshahi et al., 2006; Iranshahi et al., 2008; Dehpour et al., 2009; Sahebkar et al., 2010; Kanani et al., 2011; Li et al., 2011; Kavoosi et al., 2012; Mirzaei and Hasanloo, 2012; Kavoosi and Purfard, 2013; Kavoosi and Rowshan, 2013; Özek et al., 2017), along with 2-methyl octane (Kanani et al., 2011), nonane (Baser et al., 2000; Kanani et al., 2011) and aromatic derivatives (benzene-1-3-dimethyl etc.) (Sadraei et al., 2001; Chibani et al., 2012). Furthermore, the most frequently occurring monoterpene hydrocarbons in the characterized profiles were found to be α-pinene, β-pinene, limonene, *p*-cymene, γ-terpinene, δ-3-carene and myrcene (Garg et al., 1989; Rustaiyan et al., 2001a; Sadraei et al., 2001; Sayyah and Mandgary, 2003; Akhgar et al., 2005; Ferrari et al., 2005; Kose et al., 2010; Al-Ja'Fari et al., 2011; Kanani et al., 2011; Amiri, 2014; Bouratoua et al., 2014; Alipour et al., 2015; Ben Salem et al., 2016; Schepetkin et al., 2016; Najafabadi et al., 2017; Znati et al., 2017). On the other hand, oxygenated sesquiterpenes like carvacrol, neryl acetate, verbenone, thymol, *cis*-chrysanthenol and camphor had the highest frequencies in the reported profiles (Ghannadi et al., 2002; Chibani et al., 2012; Alipour et al., 2015). Moreover, germacrene D, bicyclogermacrene, (*E*)-caryophyllene, α-gurjunene, δ-cadinene, γ-cadinene and γ-elemene (Habibi et al., 2006a; Maggi et al., 2009a; Maggi et al., 2009b; Kanani et al., 2011; Bahramia et al., 2013; Mohammadhosseini et al., 2015) were instead the dominant sesquiterpene

hydrocarbons. The major oxygenated sesquiterpenes contributing to the aforementioned chemical profiles in Table 3 were α-cadinol, guaiol, (*E*)-nerolidol, α-eudesmol, (*Z*)-ocimenone, (*E*)-ocimenone, viridiflorol, *epi*-α-muurolol, carotol, valerianol and hinesol (Rustaiyan et al., 2001b; Shatar, 2005; Habibi et al., 2006b; Benchabane et al., 2012; Ozkan et al., 2014; Labed-Zouad et al., 2015; Kasaian et al., 2016; Nguir et al., 2016).

In the search for compounds of chemotaxonomic relevance from species in the genus *Ferula*, EOs of 23 populations relating to 18 species were screened (Kanani et al., 2011). Fig. 3, shows the molecular structures of the most prevalent compounds recognized in that study.

The sulfur-containing compounds have the highest frequency and are responsible for the specific odors of different *Ferula* species. Furthermore, a cluster analysis (Ward dendrogram) of the most abundant components in the characterized profiles of the EOs of the *Ferula* species revealed the presence of four groups, namely i) monoterpene hydrocarbons (first cluster) consisting of α-pinene (52%-69%) as well as α-pinene (16-37%) and β-pinene (36-66%) for the first and second subgroups, respectively;

ii) oxygenated monoterpenes (second cluster) involving α-terpinyl acetate (73%) and sabinene (20%), verbenone (69%) and *ar*-curcumene (6%);

iii) organosulfur compounds (third cluster) including 2,3,4-trimethylthiophene (**2**) (49%), and 2,5-diethylthiophene (**6**) (28%);

iv) monoterpene + sesquiterpene + aliphatic hydrocarbons (fourth cluster) containing (*Z*)-β-ocimene (42%), myrcene (35%), sabinene (75%) and (*E*)-caryophyllene (16%).

Maggi and collaborators (2009b) reported chemical profiles of the EOs from different parts, e.g. flowers, fruits, roots and leaves of *F. glauca* L. growing wild in Marche (Central Italy). In their study, EOs were obtained using classical hydrodistillation and were sequentially analyzed using GC-FID and GC-MS techniques. A total of 74 constituents were characterized, representing 87-95% of the total leaves oil. The predominant constituents were

sesquiterpene hydrocarbons that included (*E*)-caryophyllene, α-humulene and germacrene D, respectively involving 16-25%, 10-18%, 7-9%, and 5-10% of the total chemical profile. Furthermore, 95 compounds, accounting for 90-97% of the flower oils were identified. Once again, sesquiterpene hydrocarbons dominated over the other groups, with (*E*)-caryophyllene and germacrene D accounting, respectively, for 6-14% and 14-21% of the oil composition.

On the other hand, the analysis of the oil from the fruits of *F. glauca* L. revealed the presence of a total of 55 components (69-90%). In contrast to the oils from the leaves and flowers of *F. glauca* L., monoterpene hydrocarbons contributed to the profiles as the major fractions with pinene derivatives (α: 24-45%; β: 15-20%) being the most abundant. Finally, in the essential oil separated from the roots of *F. glauca* L., 54 compounds were identified altogether accounting for 69-80% of the oil. Similar to the oil profile from the leaves and flowers of *F. glauca* L., the root oil was rich in sesquiterpene hydrocarbons with (*E*)-β-farnesene and α-zingiberene each accounting for 5-10% of the compounds.

Recently, Moghaddam and Farhadi (2015), have studied chemical compositions of nine populations of *F. assa-foetida* L. growing wild in different localities of Kerman province, Iran. As shown in Table 3, a total of 30 constituents, accounting for 96-99% of the oil, were identified in the EOs of *F. assa-foetida* L. This study revealed the presence of some non-terpene sulfur-containing hydrocarbons, namely (*E*)-propenyl,*sec*-butyl disulfide (37-54%), (*Z*)-propenyl,*sec*-butyl disulfide (12-23%) and *n*-propyl,*sec*-butyl disulfide (0-5%) along with lower quantities of some monoterpene hydrocarbons such as α-pinene (4-7%), β-pinene (8-15%) and (*E*)-β-ocimene (3-6%). This study showed a great variation in the mean yields of the resins from *F. assa-foetida* L. Moreover, a statistical analysis displayed a positive correlation between the precipitation rates in the sampling area and the yield of the obtained resins. In addition, a remarkable increase in the yield of the obtained resins was noted when

the temperature increased. Accordingly, the highest contents of EOs were found in localities having the highest precipitation rates and altitude.

5. Phytochemistry of the *Ferula* species (2000 to March 2018)

In the literature, some reports occasionally discuss phytochemistry in addition to the biological and medicinal properties of some species of the genus *Ferula* (Iranshahy and Iranshahi, 2011; Sahebkar and Iranshahi, 2011; Zare et al., 2011; Kareparamban et al., 2012; Akaberi et al., 2015; Amalraj and Gopi, 2017; Sattar and Iranshahi, 2017a, b; Upadhyay et al., 2017; Zhou et al., 2017). However, the current review paper aims to give a deeper insight into the major ethnopharmaceutical properties, along with chemical compositions of the essential oils, organic extracts and volatiles from the different *Ferula* species growing wild worldwide. In addition, the phytochemistry of the different species of this genus is discussed over the period of 2000-to the present time (March 2018). It is also noteworthy that before the year 2000, many reports were published relating to natural bioactive sulfur compounds (Al-Said et al., 1996), triterpenes (Diaz et al., 1984; Díaz et al., 1984), sesquiterpene esters (Miski et al., 1983; Miski et al., 1984; Razdan et al., 1989; Appendino et al., 1990; González et al., 1993; Khalilova and Saidkhodzhaev, 1998a), sesquiterpene derivatives of the farnesyl-benzofuranone type (Kojima et al., 1999), esters (Saidkhodzhaev et al., 1985a; Saidkhodzhaev et al., 1985b; Golovina et al., 1987; Kerimov et al., 1987; Saidkhodzhaev et al., 1993b; Saidkhodzhaev et al., 1993d; Kobilov et al., 1995b, a; Nazhimutdinova et al., 1995), isocarotane esters (Garg et al., 1998), daucane esters (Miski and Mabry, 1985; Miski and Jakupovic, 1990; Appendino et al., 1997), sesquiterpene coumarins (Buddrus et al., 1985; Nassar et al., 1995; Ahmed, 1999), sesquiterpene lactones (Kir'yalov and Serkerov, 1966; Bagirov et al., 1979a, b; Bagirov et al., 1984; Sagitdinova et al., 1991; Serkerov et al., 1992; Kabilov et al., 1994), terpenoids (Nazhimitdinova and Saidkhodzhaev, 1993; Saidkhodzhaev

et al., 1993a; Saidkhodzhaev and Mamatkhanov, 1995; Khalilova and Saidkhodzhaev, 1998b), and terpene coumarins (Vandyshev et al., 1974; Savina et al., 1978; Sokolova et al., 1978; Veselovskaya et al., 1979; Kir'yanova et al., 1980; Kuliev et al., 1980; Veselovskaya et al., 1980; Sklyar et al., 1982; Veselovskaya et al., 1982; Nabiev and Malikov, 1983; Al-Hazimi, 1986; Serkerov and Mir-Babaev, 1987; Saidkhodzhaev et al., 1991; Saidkhozhaev et al., 1991; Saidkhodzhaev et al., 1993c).

In the recent decades, several natural products from different organs of a wide variety of the *Ferula* plants have been reported. The sulfur-containing compounds in these plants are often responsible for the pungent odors of the corresponding products. Furthermore, a large number of phytochemical reports have revealed the presence of novel natural compounds in the diverse species of the genus *Ferula*. In the following sub-sections, new identified metabolites are reviewed and subdivided in classes of natural compounds.

5.1. Coumarin derivatives

5.1.1. Hemiterpene coumarins

A variety of coumarin derivatives were identified in the methanol extract obtained from the dried roots of *F. sumbul* (Kauffm.) Hook.F. (Fig. 4), including two furanocoumarin esters: fesumtuorin A (**13**) and fesumtuorin B (**14**); one bicoumarin, fesumtuorin C (**15**); five spirobicoumarins, fesumtuorin D (**16**), fesumtuorin E (**17**), fesumtuorin F (**18**), fesumtuorin G (**19**) and fesumtuorin H (**20**), in addition to nineteen known coumarins (Zhou et al., 2000).

5.1.2. Monoterpene coumarins

In a different work, the group by El-Razek (El-Razek et al., 2001) was able to separate two monoterpene coumarins, namely ferulagol A (**21**) and ferulagol B (**22**) (Fig. 5) from a dichloromethane extract of *F. ferulago* L.

404 *5.1.3. Sesquiterpene coumarins*
405
406 Six sesquiterpenoids, named pallidones A-F (**23-28**) (Fig. 6), together with two known
407 sesquiterpenes (feselol and conferol) already found in several *Ferula* species, were isolated
408 from the ethyl acetate extract of the roots of *F. pallida* Korovin (Su et al., 2000). The possible
409 biogenetic pathway of the sesquiterpene coumarins, pallidones A (**23**) and B (**24**) was also
410 discussed: A common biosynthetic precursor for pallidones A-F and other sesquiterpene-
411 coumarins was hypothesized in 2-hydroxy-4-methoxycinnamic acid. This might be involved
412 in two different pathways: one proceed through cyclization to form the coumarin skeleton,
413 the other implies the addition of water to the double bond and the subsequent oxidation of
414 hydroxyl function to constitute the appropriate intermediate, then both pathways imply the
415 reaction of condensation with the appropriate sesquiterpene derivative.
416 Assafoetidnol A (**29**) and assafoetidnol B (**30**) (Fig. 7) were reported by Abd El-Razek et al.
417 (2001) in the organic extracts prepared of the roots of *F. assa-foetida* L. in addition to six
418 other compounds, gummosin, polyanthin, badrakemin, neveskone, samarcandin and galbanic
419 acid.
420 Motai et al (2004) purified six sesquiterpene coumarin derivatives, 2,3-dihydro-7-hydroxy-
421 2*R**,3*R**-dimethyl-2-[4,8-dimethyl-3(*E*),7-nonadien-6-onyl]furo[3,2-*c*]coumarin (**31**),
422 fukanefuromarin A (**32**), fukanefuromarin B (**33**), fukanefuromarin C (**34**), fukanefuromarin
423 D (**35**), and fukanemarin A (**36**) (Fig. 8), from the water-methanol extract of the roots of *F.*
424 *fukanensis* K.M.Shen.
425 Motai and Kitanaka (2004) identified four sesquiterpene coumarin derivatives from an 80%
426 aqueous methanol extract of the roots of *F. fukanensis* K.M.Shen: fukanemarin B (**37**),
427 fukanefuromarin E (**38**), fukanefuromarin F (**39**) and fukanefuromarin G (**40**) (Fig. 9).

Saradaferin ([decahydro-(3-α-hydroxy-4,4,10-trimethyl-8-methylene-9-naphthenyl)-α-hydroxymethyl] ether of umbelliferone), a sesquiterpene coumarin, (**41**) (Fig. 10) was separated from an OGR of *F. assa-foetida* L. (Bandyopadhyay et al., 2006).

Isofeterin (**42**), lehmannolol (**43**) and shinkianone (**44**) (Fig. 11) were identified from the 95% ethanol extract of the roots of *F. teterrima* Kar. & Kir. and *F. sinkiangensis* K. M. Shen (Yang et al., 2006).

Three sesquiterpene derivatives, together with ten other compounds, were isolated from the methanol extract from the roots of *F. gummosa* Boiss. Among those three compounds, gumosin (**45**) is a coumarin derivative, and gumosides A and B (**46** and **47**, Fig. 12) are coumarin glycosides (Iranshahi et al., 2010a).

The phytochemical characterization of the aqueous-ethanol (5:95, v/v) extract of the roots of *F. ferulaeoides* (Steud.) Korov led to the separation of three sesquiterpenoid coumarins, ferulin A-C (**48-50**) (Fig. 13) along with seven known sesquiterpenoid derivatives (Meng et al., 2013a).

Recently, Bashir and colleagues (2014a) have identified two sesquiterpene coumarins, fnarthexone (**51**) and fnarthexol (**52**) (Fig. 14), as well as three known coumarin derivatives (umbelliferone, conferone and conferol) from the methanol extract of *F. narthex* Boiss. obtained by using a maceration method. It is interesting to note that from the stereochemical point of view, fnartexol (**52**) is the epimer at C-5′ of conferol, a natural compound also identified in *F. nartex* Boiss. during the reported study.

Liu and collaborators (2015) separated 28 sesquiterpenoids from the ethanol extract of the roots of *F. ferulioides* (Steud.) Korovin. Seven of these terpenoids were described for the first time from the genus *Ferula*. Of these, three compounds (**53-55**) resulted to be sesquiterpene coumarins (Fig. 15).

Dastan and co-workers (2012) separated two disesquiterpene coumarins from the *n*-hexane extract of *F. pseudalliacea* Rech.f. roots (**56-57**) (Fig. 16), in addition to four known sesquiterpene coumarins.

Li and colleagues (2015a) reported a sesquiterpene coumarin, namely sinkiangenorin D (**58**) (Fig. 17), along with ten known sesquiterpene coumarins from the seeds of *F. sinkiangensis* KM Shen. It is interesting to note that (**58**) is a sesquiterpenoid with a rare cycloheptene unit in its structure. This structural feature might be subsequent to several rearrangements since the common head-tail connenction between the isoprene units is no longer observable in its structure.

In a similar study, sinkiangenorin F (**59**) and 8-*O*-acetyl sinkiangenorin F (**60**) (Fig. 18) were characterized as the sesquiterpene coumarins in the ethanol extract of *F. sinkiangensis* KM Shen (Li et al., 2015b).

Among the sixteen identified compounds in the chloroform extract of *F. sinkiangensis* K. M. Shen, two compounds, (3′*S*, 8′*R*, 9′*S*, 10′*R*)-sinkianol A (**61**) and (3′*R*, 5′*R*, 10′*R*)-sinkianol B (**62**) (Fig. 19) were identified for the first time (Xing et al., 2017). In addition, eleven known compounds, including ferukrin, (3'*S*,5'*S*,8'*R*,9'*S*,10'*R*)-kellerin, (3'*S*,5'*S*,8'*R*,9'*S*,10'*R*)-deacetylkellerin, farnesiferol A, farnesiferone A, gummosin, polyanthinin, (3'*R*,5'*R*,10'*R*)-sinkianol B, galbanic acid, methyl galbanate and karatavicinol were reported for the first time for this species.

5.1.4. Coumarinyl esters

In a related study, coumarin esters, 7-*O*-(4,8,12,16-tetrahydroxy-4,8,12,16-tetramethyl-heptadecanoyl)-coumarin, ferulone A (**63**), and 7-*O*-(4-hydroxy-4,8,12-trimethyl-trideca-7,11-dienoyl)-coumarin, ferulone B (**64**), (Fig. 20) were isolated from the non-polar (*n*-hexane) fraction of extracts from the roots of *F. orientalis* L. (Razavi et al., 2016). These two coumarin esters were isolated by a combination of vacuum liquid chromatography (VLC) and

preparative thin-layer chromatographic (PTLC) and were characterized by means of spectroscopic methods.

Razavi and Janani (2015) isolated a coumarinyl ester, ferulone C [7-*O*-(4,8,12-trihydroxy-4,8,12-trimethyl-tridecanoyl)-chromen-2-one] (**65**) (Fig. 21) , from an *n*-hexane extract of the roots of *F. persica* Wild.

5.1.4.1. Dihydrofuranocoumarinyl esters

Analysis of the dichloromethane soluble fraction of a methanolic extract from the roots of *F. lutea* (Poir.) Maire afforded an inseparable mixture of two isomeric dihydrofuranocoumarin esters with senecioic and angelic acids, respectively, (−)-5-hydroxyprantschimgin (**66**) and (−)-5-hydroxydeltoin (**67**) (Fig. 22) (Ben Salem et al., 2013), together with eight other compounds, (−)-prantschimgin, (−)-deltoin, psoralen, xanthotoxin, umbelliferone, caffeic acid, β-sitosterol and stigmasterol.

5.2. Prenylated benzoic acid derivatives

Chen et al. (2000a) characterized the prenylated benzoic acid derivatives, kuhistanol A (**68**), kuhistanol B (**69**), kuhistanol C (**70**), and kuhistanol D (**71**) (Fig. 23), in *F. kuhistanica* Korovin, one of the most important medicinal plants of Uzbekistan.

Finally, this group introduced four further derivatives of farnesyl hydroxybenzoic acid, kuhistanol E (**72**), kuhistanol F (**73**), kuhistanol G (**74**) and kuhistanol H (**75**) (Fig. 24) from *F. kuhistanica* Korovin a medicinal plant growing wild in the Uzbekistan region (Chen et al., 2001).

5.3. Sesquiterpene chromones

In a complimentary work by Motai and Kitanaka (2005a), five sesquiterpene chromone derivatives, fukanefurochromones (A-E) (**76**-**80**) (Fig. 25) from a water-methanol (20:80, v/v) extract of *F. fukanensis* K.M.Shen roots were isolated.

Phytochemical analysis of the aqueous-ethanol (5:95, v/v) extract of the roots of *F. ferulaeoides* (Steud.) Korov led to the separation of two sesquiterpene chromone derivatives, ferulin D,E (**81**-**82**) (Fig. 26), along with seven known sesquiterpenoid derivatives (Meng et al., 2013a).

5.4. Sesquiterpenes

Chen and colleagues (2000b) isolated five daucane-type sesquiterpenes, kuhistanicaol A (**83**), kuhistanicaol B (**84**), kuhistanicaol C (**85**), kuhistanicaol D (**86**) and kuhistanicaol G (**87**) (Fig. 27) from the methanol extract of the air-dried of stems and roots of *F. kuhistanica* Korovin.

An eudesmanolide (**88**) and a carotene derivative (**89**) (Fig. 28) were isolated from a methanol-methylene chloride (1:1) extract from the leaves of *F. sinaica* Boiss. (Ahmed et al., 2001).

An oxygenated sesquiterpenoid, (1*S*,4*S*,5*R*,6*S*,7*S*,10*S*)-5,10,11-cadinanetriol (**90**) (Fig. 29), from a distinct Sardinian chemotype of *F. communis* L. was isolated from the acetone extract (Appendino et al., 2001).

Diab and co-workers (2001) isolated 2,3-α-epoxyjaeschkeanadiol 5-benzoate (**91**) (Fig. 30) from the methylene chloride extract of *F. hermonis* Boiss roots.

Two daucane esters, 14-(4'-hydroxybenzoyloxy)dauc-4,8-diene (**92**,) (Fig. 31) and 14-(4'-hydroxy-3'-methoxybenzoyloxy)dauc-4,8-diene (**93**) (Fig. 31), were obtained from the *n*-hexane fraction of *F. hermonis* Boiss (roots) (Galal et al., 2001) together with four other diterpenes.

Found in the ethyl acetate extracts of the dried fruits of *F. kuhistanica* Korovin., were three derivatives of daucane esters, namely kuhistanicaol H (**94**), kuhistanicaol I (**95**) and kuhistanicaol J (**96**) (Fig. 32) (Tamemoto et al., 2001), along with nine other compounds.

Shikishima and collaborators (2002) characterized 17 sesquiterpenes in the ethyl acetate extract from the dry roots of *F. penninervis* Regel and Schmalh. Fifteen of these were the guaiane type (ferupennins A-O: **97-111)** (Fig. 33), while the remaining two were of the eudesmane type (**112-113**) (Fig. 33): 1α-hydroxy-2-oxo-5α,7β-11βH-eudesm-3-en-6α,12-olide (**112**), and penninervin (**113**), respectively. Nine additional sesquiterpenes, already known, were also identified.

Three daucane sesquiterpenes [(1*R*,4*R*)-4-hydroxydauca-7-ene-6-one (**114**), (1*R*,4*R*)-4-hydroxydauca-7-ene-6,9-dione (**115**) and (1*R*,3*S*,8*S*)-3-ethoxy-8-angeloyloxydauca-4-en-9-one (**116**), (Fig. 34) were characterized from the hexane extract prepared from the air dried roots of *F. hermonis* Boiss (Lhuillier et al., 2005).

Sesquiterpene lactones **117**-**122** (Fig. 35) were isolated from the ethyl acetate-soluble fraction obtained from the MeOH extract of *F. varia* (Schrenk) Trautv. roots (Suzuki et al., 2007) together with five other sesquiterpenes, dehydrooopodin, oopodin, spathulenol, ferupennin L and 8α-angeloyloxy-10β-hydroxyslov-3-en-6,12-olide.

The sesquiterpene derivatives (Fig. 36), 10-hydroxylancerodiol-6-anisate (**123**), 2,10-diacetyl-8-hydroxyferutriol-6-anisate (**124**), 10-hydroxylancerodiol-6-benzoate (**125**), *epoxy*-vesceritenol (**126**) and vesceritenone (**127**), along with six other compounds, were reported among the components of the methylene chloride extract obtained from the aerial parts of *F. vesceritensis* Coss. & Dur (Oughlissi-Dehak et al., 2008).

Alkhatib and colleagues (2008) identified two sesquiterpene esters, namely 6-anthraniloyljaeschkeanadiol (elaeochytrin A) (**128**) and 4β-hydroxy-6α-(p-hydroxybenzoyloxy)dauc-9-ene (elaeochytrin B) (**129**) (Fig. 37), from the dichlorometane soluble fraction of the methanolic extract of the roots of *F. elaeochytris* Korovin. In the same work, eight other compounds were also identified. These included 6-angeloyljaeschkeanadiol, teferidin, ferutinin, 6-(*p*-hydroxybenzoyl)epoxyjaeschkeanadiol, 6-(*p*-

555 hydroxybenzoyl)lancerotriol, 5-caffeoylquinic acid, 1,5-dicaffeoylquinic acid and
556 sandrosaponin IX.
557 From the dichloromethane extract of roots of *F. badrakema* Koso-Pol., badrakemonin (**130**)
558 (Fig. 38) (Iranshahi et al., 2009), a sesquiterpene, was isolated together with six known
559 sesquiterpene coumarins: mogoltacin, feselol, badrakemin acetate, ferocaulidin, conferone
560 and conferol acetate.
561 Sesquiterpene lactones, diversolides A (**131**), D (**132**), F (**133**) and G (**134**) (Fig. 39) were
562 isolated from the roots of *F. diversivittata* Regel & Schmalh. by Iranshahi et al. (2010b).
563 A sesquiterpene ester, tunetanin A (**135**), along with a sesquiterpene coumarin,
564 tunetacoumarin A (**136**) (Fig. 40), were reported from the dichloromethane-soluble fraction
565 of the methanol extract of *F. tunetana* Pomel ex Batt. roots (Jabrane et al., 2010).
566 Dall'Acqua and colleagues (2011) isolated three daucane sesquiterpenes (**137**-**139**) (Fig. 41)
567 from the dichloromethane fraction of an ultrasound assisted methanol extract of the roots of
568 *F. communis* subsp. *Communis.* Among these, 2α-Acetoxy-6α-*p*-methoxybenzoyl-10α-
569 hydroxy-jaeschkeanadiol (**137**) and 2α-hydroxy-6α-*p*-methoxybenzoyl-10β-acetoxy-
570 jaeschkeanadiol (**138**) were found to be the epimers of two other daucane sesquiterpenes, 2α-
571 acetoxy-6α-p-methoxybenzoyl-10β-hydroxy-jaeschkeanadiol and 2α-acetoxy-6α-p-
572 methoxybenzoyl-10β-hydroxy-jaeschkeanadiol, respectively, which had already been
573 identified in *F. communis* subsp. *communis*. The third characterized compound (**139**) was the
574 8,9-dihydro-8,14-dehydro-9-hydroxyferutinin, which had been obtained previously by a
575 semisynthetic approach but had never been isolated from a natural source.
576 Three daucane esters, out of a total of seventeen, (Fig. 42), namely feruhermonins A (4β-
577 hydroxy-6α-benzoyl-dauc-7-en-9-one) (**140**), feruhermonins B (4β,8β-dihydroxy-6α-
578 benzoyl-dauc-9-ene) (**141**) and feruhermonins C (4β,9α-dihydroxy-6α-benzoyl-dauc-7-ene)
579 (**142**) were reported from the *n*-hexane-ethyl acetate (1:1) extract of the seeds of *F. hermonis*

Boiss (Auzi et al., 2008). The epimer at C-8 of feruhermonins B (**141**), reported in Fig. 33 as (**141a**), was isolated from the same species few years later by Ibraehim et al. (2012a).

From the water-soluble fraction of the methanol extract of *F. varia* (Schrenk) Trautv. roots, a species widely used in the traditional medicine of Uzbekistan, seven other sesquiterpene lactone glycosides with the eudesmane skeleton were isolated (**143-149**) (Fig. 43) (Kurimoto et al., 2012b). To establish their absolute configurations the authors applied a modification of Mosher's method.

The analysis of a water extract of *F. varia* (Schrenk) Trautv roots resulted in the characterization of eight natural compounds of which five (**150-154**), two (**155-156**) and one (**157**) (Fig. 44) are, respectively of the eudesmane, guaiane and germacrene lactone glucoside types (Kurimoto et al., 2012a).

Liu and collaborators (2015) separated 28 sesquiterpenoids from an ethanol extract of the roots of *F. ferulioides* (Steud.) Korovin, of which seven were described for the first time from the genus *Ferula* (Fig. 45). Four of these compounds (**158**-**161**) showed a structure in which a resacetophenone unit is linked to a linear (**158**, **159**) or rearranged sesquiterpene moiety to form a dihydrofurane structure (**160**, **161**).

5.5. Sulfur containing metabolites

From the chloroform extract of the aerial parts of *F. behboudiana* Rech. f. Esfand, four polysulphane related compounds, namely 1-*sec*-butyl-2-[(*E*)-3-(methylthio)prop-1-enyl]disulphane (**162**), 1-*sec*-butyl-2-[(*Z*)-3-(methylthio)prop-1-enyl] disulphane (**163**), 1-[(*E*)-3-(methylthio)prop-1-enyl)-2-(1-(methylthio)propyl] disulphane (**164**) and 1-[(*Z*)-3-(methylthio)prop-1-enyl)-2-(1-(methylthio)propyl] disulphane (**165**) (Fig. 46) were reported (Yousefi et al. (2010).

More recently, five novel sulfur-containing compounds, latisulfide A (**166**), latisulfide B (**167**), latisulfide C (**168**), latisulfide D (**169**) and latisulfide E (**170**) (Fig. 47), have been

606 isolated from the dichloromethane extract of *F. latisecta* Rech.f. & Aellen (Soltani et al.,
607 2018).
608 Sulfur-containing heterocylcic compounds, foetithiophene C (**171**), foetithiophene D (**172**),
609 foetithiophene E (**173**) and foetithiophene F (**174**) (Fig. 48), were also obtained from the
610 roots of *F. foetida* Regel (petroleum ether extract) (Chitsazian-Yazdi et al., 2015).
611 *5.6. Miscellaneous*
612
613 Abd El-Razek (2007) isolated a caffeic acid cinnamyl ester, (2*E*)-3,4-dimethoxycinnamyl-3-
614 (3,4-diacetoxyphenyl) acrylate (**175**), from the *n*-hexane soluble fraction obtained from
615 methanol extract of the OGR of *F. assa-foetida* L. (Fig. 49).
616 Meng and collaborators (2013b) isolated eight sesquiterpenoids, ferulaeone A-H (**176-183**)
617 (Fig. 50) from *F. ferulaeoides* (Steud.) Korov. The proposed structures assignment were
618 based not only on experimental spectroscopic data, but also on biosynthetic pathway, which
619 might imply the condensation between the appropriate Coenzyme-A activated C6–C3
620 derivative and farnesyl pyrophosphate.
621 Ibraheim and colleagues (2012b), isolated a saponin (sandrosaponin XI) (**184**) (Fig. 51) from
622 the *n*-butanol extract of the root of *F. hermonis* Boiss. Sandrosaponin XI has an oleanane
623 pentacyclic triterpene skeleton. The complete structure of the saponin (**184**) was shown to be
624 the methyl ester of 3β-*O*-β-D-glucopyranosyl-(1→2)-β-D-galactopyranosyl-(1→2)-β-D-
625 glucuronopyranosyl-oleanolic acid-28-*O*-β-D-glucopyranoside.
626 The steroidal esters, sinkiangenorin A (**185**) and sinkiangenorin B (**186**) and the organic acid
627 glycoside sinkiangenorin C (**187**) (Fig. 52) were isolated from the ethanol extract from the
628 seeds of *F. sinkiangensis* KM by Shen Li and co-workers (2014). Four known lignin-related
629 compounds were also identified during the same study.
630 Screening of a methanol-water (7:3) extract of the flowers of *F. lutea* (Poir.) Maire yielded
631 ferunide, (*E*)-5-ethylidenefuran-2(5*H*)-one-5-*O*-β-D-glucopyranoside (**188**), in addition to 4-

hydroxy-3-methylbut-2-enoic acid (**189**) (Fig. 53) (Znati et al., 2014). This extract also contained nine known compounds, which could be partitioned between ethyl acetate and *n*-butanol. Of these, six compounds, 5-*O*-caffeoylquinic acid, methyl caffeate, methyl 3,5-*O*-dicaffeoylquinate, 3,5-*O*-dicaffeoylquinic acid, isorhamnetin-3-*O*-α-L-rhamnopyranosyl(1→6)-β-D-glucopyranoside, narcissin, and (−)-marmesin, even if quite common plant metabolites, were identified for the first time in the *Ferula* genus.

The phytochemical patterns recognized in *Ferula* species are varied. These include different classes of natural products, i.e. coumarins, sesquiterpenes, phenylpropanoids, saponins, chromones, sulfur-containing compounds and steroids. Among these phytoconstituents, the coumarins, and in particular the furanocoumarins (linear and/or angular), very often esterified with short chain organic acids such as acetic, angelic and/or senecioic acids, are characteristic constituents of several species of the Apiaceae family, for instance, *Coristospermum cuneifolium* (Guss.) Bertol. (Venditti et al., 2016), *Ligusticum pyrenaicum* W.D.J.Koch (Bohlmann and Grenz, 1969), *Ferulopsis hystrix* (Bunge ex Ledeb.) M. Pimen. (Shulʹts et al., 2012) and *Ferulago angulata* (Schltdl.) Boiss (Razavi et al., 2015), among the others. In this context, the peculiar spirobicoumarins are noteworthy to the best of our knowledge, since they have been recognized so far only in the Apiaceae family, i.e. in *Pleurospermum rivulorum* (Diels) M. Hiroe (Taniguchi et al., 1998). The sesquiterpenoids are also considered as chemotaxonomic markers in the Apiaceae, and the genus *Ferula* showed a widespread presence of compounds of several families of sesquiterpene lactones, including derivatives containing the cadinane, daucane, guaiane, eudesmane and carotane backbones. All these compounds are useful taxonomic markers within the genus, but they also provide evidence of the systematic proximity among various genera in the Apiaceae family itself. The main metabolic feature, which may be observed by considering the wide list of compounds and chemical structures reported in this review, is the presence of a huge number of metabolites

of mixed biosynthetic origin, such as hemi- mono- and sesquiterpene coumarins, sesquiterpene chromones, sesquiterpene polyketides, furochromones and prenylated benzoic acid derivatives. Concerning the sesquiterpene coumarins and the sesquiterpene chromones, the species of the *Ferula* genus resulted to be very efficient producer of these rare phytoconstituents. The occurrence of these secondary metabolites seems to be restricted to a few species within the Apiaceae, the Asteraceae and the Rutaceae families (Gliszczyńska and Brodelius, 2012). Last but not the least, the sulfur-containing secondary metabolites, present as different derivatives such as thiophenes, disulfanes and trisulfanes, found in both the volatile fraction and organic solvents extracts, are an additional distinctive chemical trait of the *Ferula* species which confer the characteristic smell to several species of the genus.

The presence of a wide variety of secondary metabolites of mixed biogenetic origin (i.e. hemiterpene-coumarins (Fig. 4), monoterpene-coumarins (Fig. 5), sesquiterpene-coumarins (Figs. 6-19), sesquiterpene polyketides (Fig. 45) and sesquiterpene-chromones (Figs. 25-26) have a relevance also from the medicinal chemistry standpoint. In fact, in recent years, the approach consisting in the fusion (by the use of a suitable linking group or exploiting directly the functionalizations already present on the structures to be connected) of two biologically active structural moieties has been largely explored for different purposes. For instance, with the scope of specific organ/tissue delivery or to enhance a specific bioactivity taking advantage from the synergistic properties of molecules with different structures or with different cellular targets which are involved in the development of a specific pathology. Currently, it is unknown why most of the species belonging to this genus showed this metabolic behavior. There could be many valid hypotheses, even different one from the other. One might be, obviously, the fusion of two molecules with different biological activity in one derivative so to have a compound effective toward different biological targets. Another might have its rationale in the physiological field i.e. the fusion of two molecules in one will reduce

682 the osmotic pressure by reducing the number of particles present in the cellular environment.
683 In any case, it remains an argument that deserves further investigation with dedicated studies.
684 However, it is a case that clearly represents how much Nature has already used some of the
685 chemical-pharmaceutical approaches that we believe to be innovative and, therefore,
686 emphasizes the importance of phytochemical studies that contribute to revealing chemical
687 aspects and physiological/ecological functions of secondary (specialized) metabolites and can
688 offer interesting approaches for use in medicinal and pharmaceutical chemistry.
689 To date, there are only a limited number of *Ferula* species already subjected to the systematic
690 phytochemical analysis. Therefore, it is obvious that in the future, several other new
691 compounds might be recognized as phytoconstituents of the *Ferula* genus and new biological
692 activities may be explored. This is particularly probable for the endemic entities since it has
693 been largely confirmed that the endemism is a condition which may promote the metabolic
694 diversity (Bianco et al., 2016) in respect to species with a more wide area of distribution.
695 Considering the chemical structures of the majority of the *Ferula* secondary metabolites and
696 the proposed biogenesis (Su et al., 2000; Meng et al., 2013b), it is evident that the biogenetic
697 pathways involving terpenoids and phenylpropanoids are particularly active. These are also
698 interacting among them to synthesize compounds with mixed biogenetic origin, thus it is
699 most probable that new metabolites possibly isolated in future studies might exhibit these
700 structural features.

701 ## 7. The bioactivities of diverse characterized compounds from the genus
702 ## *Ferula*

703 There have been numerous papers dealing with the biological and medicinal properties of
704 some species of the genus *Ferula*. These important characteristics are discussed in the
705 following subsections.

706 *7.1. Anti-HIV activity*
707
708 Some of the known compounds isolated form *Ferula* spp., namely oxypeucedanin hydrate,
709 heraclenol, oxypeucedanin, heraclenin, pranferol, pabulenol, osthol and xanthotoxin, were
710 tested for their anti-HIV activity by Zhou and collaborators (2000). These compounds
711 resulted effective with IC_{50} ranging from 11.7 to > 100 μg/mL and EC_{50} ranging from < 0.10
712 to 33.3 μg/mL, in comparison to AZT as positive control (IC_{50} and EC_{50}, 500 and 0.032
713 μg/mL, respectively). Several of these components, namely heraclenol, oxypeucedanin,
714 heraclenin and osthol, showed a Therapeutic Index (TI) > 5, thus denoting significant
715 activity. Interestingly, pabulenol showed a TI > 1000. Therapeutic indices > 1000 are
716 characteristic values of most of the drugs currently used in therapy. Based on this data,
717 pabulenol could be an excellent drug candidate having a little intrinsic toxicity.
718 Unfortunately, in this case, it is not possible to estimate the real quantity of these constituents
719 in the plant materials since in the experimental section are reported unlikely quantities of
720 plant material (500 g) compared to the volume of extraction solvent (50 l x 3) and the amount
721 of isolated components, some of which in gram scale. Therefore, the extracted plant material
722 was likely much greater than the reported value.

723 *7.2. Inhibitory activity on cytokine production*
724
725 Chen et al. (2000a) evaluated the inhibitory activity on cytokine production LPS-activated
726 human peripheral mononuclear cells. In this study, kuhistanol D (**71**) showed significant
727 immunosuppressive activity by inhibiting the production (%) of several cytokines at
728 concentrations of 3 μg/mL (IL-4; 70%, IL-2: 77%, IFN-γ: 62%), although the other
729 compounds showed no significant inhibitory effects even at higher concentration (10 μg/mL).
730 This result may suggest that the presence of the bicyclic chromane moiety in compound (**71**)
731 is necessary to exert the immunosuppressive activity. A quantity of 113.5 mg of (**71**) was

obtained from 2.25 Kg of plant materials, thus accounting for the 0.005% w/w and so resulting to be a minor component.

7.3. Inhibitory activity on NO production

The inhibitory activity on NO production of (**76**-**79**) was tested in a murine macrophage-like cell system induced by LPS/INF-γ (Motai and Kitanaka, 2005a). In this study, compound (**80**) was not isolated in a sufficient amount (1.5 mg) to be further tested. However, compounds (**76**-**79**) were effective in inhibiting NO production with IC_{50} values of 9.8 μg/mL (25 μM), 8.9 μg/mL (23 μM), 12 μg/mL (29 μM) and 9.5 μg/mL (24 μM), respectively, and showed no cytotoxicity at the tested concentrations. Among these sesquiterpene chromones, (**79**) showed a dose dependent inhibition of iNOS mRNA expression. Furthermore, the compound (**79**) showed a moderate inhibitory activity in LPS-induced NO production in a murine macrophage-like cells system (RAW264.7) with an IC_{50} value of 55 μM (Abd El-Razek, 2007). From 5.9 Kg of raw plant materials were recovered 23.8 mg of (**76**), 5.5 mg of (**77**), 19.6 mg of (**78**) and 7.9 mg of (**79**), accounting for 0.0004, 0.00009, 0.00033 and 0.00013 % (w/w), respectively, resulting so minor components.

7.4. The inhibitory on Epstein-Barr virus early antigen (EBV-EA) activation

The inhibitory potentialities on Epstein-Barr virus early antigen (EBV-EA) activation induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) were tested *in vivo* in a mouse model (Iranshahi et al., 2010b). All the new sesquiterpene lactones (**45**-**47**) resulted to be active (IC_{50} ranging from 8.7 and 10.7 nM) with inhibitor percentages comprised between 92.5 ± 0.6 and 89.2 ± 0.9 when applied at a concentration of 32 nM and between 63.6 ± 1.3 and 68.3 ± 1.6 when applied ad 16 nM, in respect to the positive control experiments. The compounds (**45**-**47**) accounted for the 0.0128, 0.051 and 0.042 % (w/w) in respect to the extracted plant materials, resulting therefore minor components.

7.5. Inhibitory against Plasmodium falciparum

It has been reported that sanandajin (**56**) and kamolonol acetate (**57**) showed moderate activity against *Plasmodium falciparum* strain K1, with IC_{50} values of 2.6 and 16 μM, respectively (Dastan et al., 2012). Compounds (**56**) and (**57**) are present in a percentage of 0.00134 and 0.00336 % (w/w), respectively, in the raw plant materials.

7.6. Antineuroinflammatory potential in LPS-activated BV-2 microglial cells

Xing and colleagues (2017), tested the isolated compound (**61**), together with several known metabolites, for the antineuroinflammatory potential in LPS-activated BV-2 microglial cells. Compound (**61**) showed a moderate inhibition of NO production (IC_{50} > 50 μM), whereas the most effective, and also the major constituent, resulted to be the known (3′*S*,5′*S*,8′*R*,9′*S*,10′*R*)-kellerin, which significantly inhibited the mRNA expression of several inflammatory factors (TNF-α, IL-6, IL-1β, COX-2) at concentration between 1 and 10 μM. Conversely, the other new sesquiterpene coumarin (**62**) was not subjected to the bioactivity test, even if isolated in sufficient amount (42.1 mg). The compounds (**61**), (**62**) and the known (3′*S*,5′*S*,8′*R*,9′*S*,10′*R*)-kellerin accounted for the 0.0036, 0.0087 and 1.5% (w/w), respectively, of the whole composition of the analyzed gum resin. Considering the relative abundance of (3′*S*,5′*S*,8′*R*,9′*S*,10′*R*)-kellerin and its pronounced activity at μmolar concentrations it is quite probable that the biological activity observable in the crude gum resin might be attributable to this single compound. In addition, due to the quite high amount of (3′*S*,5′*S*,8′*R*,9′*S*,10′*R*)-kellerin in the raw materials also the extractive approach to obtain the pure compound is applicable.

7.7. Cytotoxicity

The sesquiterpene lactones (**117**-**122**) from the ethyl acetate-soluble fraction obtained from a MeOH extract of *F. varia* (Schrenk) Trautv. roots, along with some known sesquiterpenes

785 (dehydrooopodin, oopodin, spathulenol, ferupennin L and 8α-angeloyloxy-10β-hydroxyslov-
786 3-en-6,12-olide), were tested for their cytotoxicity against multidrug-resistant cancer cells,
787 KB-C2 (colchicine-resistant KB) and K562/Adr (doxorubicin-resistant K562) (Suzuki et al.,
788 2007). This study revealed a significant selective cytotoxicity for the compound (**120**) (IC_{50}
789 value of 15.7 µg/mL) against KB-C2. Differently, compounds (**117**), (**119**) and (**121**) showed
790 enhanced cytotoxicity (IC_{50} values ranging from 25.4 to 67.8 µg/mL) in the presence of non-
791 toxic concentrations of colchicine (2.5 µM) against the same cell line showing so an
792 interesting synergistic activity which may suggest a possible use in combined therapy.
793 Unfortunately, these new compounds accounted for very low percentages of plant material
794 composition, 0.00014, 0.00078, 0.00078, 0.0018, 0.00028 and 0.00064% (w/w), respectively
795 for (**117**-**122**). Therefore, estractive procedure could be not adequate to obtain sufficient
796 amount of these compounds, instead a synthetic approach might be most useful and it could
797 likely be an interesting further challenge for synthetic chemistry.
798 In a different study, the new compounds (**135**) a sesquiterpene ester and **(136**), a
799 sesquiterpene coumarins, were tested for their cytotoxicity towards two human colon cancer
800 cell lines, HT-29 and HCT-116, but were found to be not effective (Jabrane et al., 2010)
801 against these cancer cell lines, showing IC_{50} > 100 µM. Conversely, the known coladin,
802 coladonin and 13-hydroxyfeselol, also isolated in the same study and tested toward the same
803 cell lines, showed weak activity with IC_{50} value of 3.7 ± 1.5, 15.1 ± 1.5, 34.1 ± 2.3 µM,
804 respectively, against HTC-116 and 5.4 ± 1.2, 13.3 ± 2.3, 35.4 ± 4.0 µM, respectively, against
805 HT-29 cell line. Paclitaxel was used as positive control. The most active compounds, coladin
806 and coladonin, are sesquiterpene coumarins with a structure related to those of (**136**). The
807 main structural difference of the active compounds is the presence of a double bond between
808 C-8 and C-12, while in (**136**) C-8 is a quaternary carbon functionalized with a methyl and
809 hydroxyl group in geminal configuration, and this may suggest that the unsaturation in this

position may enhance the cytotoxic activity. A second structural feature which, on the contrary, exert a lowering of the effectiveness is the presence of the ester function. In fact, coladonin, the less active, has an acetyloxy function in C-3 instead of the alcoholic function present in coladin at the same position. Moreover, the position and the nature of the acidic moiety of the ester functionalization might have a role in lowering the effectiveness of the sesquiterpene coumarins as observed in the derivative (**136**), bringing an angeloyloxy function in C-13, which showed no efficacy. The new compound (**135**) accounted for 0.00055% and compound (**136**) for 0.00066% (w/w) of raw plant materials, thus representing minor components. On the contrary the more active components, coladin and coladonin, accounted for 0.0741 and 0.0222% (w/w), respectively, of the whole raw materials composition. Considering the amount of coladin in the plant materials and its low value of IC_{50} this could be one of the few compounds of which the extraction from the natural source for medicinal purposes might be justifiable also from the economical standpoint.

In a similar study by Meng and colleagues (2013a), ferulins B and C (**49** and **50**), showed a moderate level of cytotoxicity against HepG2 (IC_{50} = 89 ± 2 and 76 ± 2 μM, respectively), and C6 (IC_{50} = 21 ± 1 and 36 ± 1 μM, respectively) cancer cell lines but resulted inactive against the MCF-7 cell line. Also in this case, these two compounds (**49** and **50**) resulted to be minor components of the raw plant materials, accounting for the 0.001055 and 0.000702% (w/w), respectively.

Similar results were obtained also for the new sesquiterpenoids ferulaeone F-H (**181, 182** and **183**) which exhibited a moderate cytotoxicity against HepG2 (IC_{50} of 86, 87 and 82 μM, respectively), MCF-7 (IC_{50} of 87, 92 and 82 μM, respectively), and C6 (IC_{50} of 65, 59 and 66 μM, respectively) cancer cell lines (Meng et al., 2013b). Among these terpenoids, the compound (**181**) resulted to have the higher percentage in the composition of raw materials with the 0.0244 % (while the other accounted for 0.001 and 0.0007% (w/w)). It should be

also underlined that the relative high value of IC_{50} recorded in the bioactivity test does not allow classifying it as a compound with sufficiently high activity, so its possible practical use is very unlikely.

In a different work, both of the newly characterized compounds, a glucosidic furanone derivative (**187**) and the γ-hydroxy-senecioic acid (**188**) showed no cytotoxicity toward the tested cell lines involving human colon carcinoma, HCT-116, human ovary carcinoma, IGROV-1 and human ovary adenocarcinoma, OVCAR-3, in MTT assays (Znati et al., 2014).

Finally, latisulfides A-E (**166**-**170**) were tested for their *in vitro* cytotoxic activity against human cancer cell lines including HeLa, HCT116, A2780 and A549 (Soltani et al., 2018). In this relation, the majority of the characterized compounds showed IC_{50} values > 100 μM and only latisulfide C (**168**) exerted a moderate cytotoxicity with IC_{50} values of 49, 65 and 87 μM against HeLa, HCT116 and A2780 cell lines, respectively, but resulted less effective toward A549 cell line. The compound (**168**) accounted for the 0.0012% of raw materials composition. Also in this case the the relative high value of IC_{50} and the relative low abundance in the plant materials, suggest a poor practical applicability of this compound.

7.8. Antibacterial and antimicrobial activity

Galal and collaborators (2001) demonstrated that 14-(4'-hydroxybenzoyloxy)dauc-4,8-diene (**92**), isolated along with jaeschkeanadiol *p*-hydroxybenzoate, exhibited antibacterial activity toward *Staphylococcus aureus* (SA) with IC_{50} values of 1.5 and 3.5 μg/mL, respectively, and methicillin-resistant *S. aureus* (MRSA) having IC_{50} values of 2.0 and 4.0 μg/mL, respectively. Tetracycline was used as positive control. The daucane derivative (**92**) accounted for 0.025% (w/w) of plant materials, while no data about the relative abundance of jaeschkeanadiol *p*-hydroxybenzoate have been reported in the original article. The easy isolation procedure of (**92**) from the plant materials plays in favor to the possibility of

obtaining this compound in pure form and the low values of IC_{50} against MRSA and SA make it a possible candidate as an antibacterial drug.

Actually, jaeschkeanadiol *p*-hydroxybenzoate, together with other known compounds, namely jaeschkeanadiol vanillate, kuhistanol D and kuhistanol A, were screened for the antimicrobical activity also in a different study by Tamemoto et al. (2001). In particular, these compounds were tested against eight Gram-positive and Gram-negative bacterial species, including methicillin-sensitive and methicillin-resistant *S. aureus* (MSSA, MRSA). The two jaeschkeanadiol derivatives, exhibited significant activity (MIC comprised between 8 and 31 μg/mL) against the Gram-positive *S. aureus* (MSSA, MRSA), *S. epidermidis*, *E. faecalis*, and *B. subtilis* with efficacies comparable to those of the standard antibiotics, ampicillin (MIC 0.125-2 μg/mL) and chloramphenicol (MIC 2-16 μg/mL). Unfortunately, these compounds were isolated in the order of 2.3 and 2.5 mg, respectively, for jaeschkeanadiol *p*-hydroxybenzoate and jaeschkeanadiol vanillate, from 600 g of plant materials, thus resulting minor components.

The antibacterial activities of the isolated compounds (**53-55** and **158-161**) were assayed against a panel of bacteria including multidrug-resistant (MDR) and methicillin-resistant *Staphylococcus aureus* (MRSA), and mostly exhibited weak activities (Liu et al., 2015). The best result obtained in this study was observed for the new compound (**158**) (yield 0.015% (w/w)) against the multidrug-resistant *S. aureus* (strain SA-1199B) with a MIC value of 16 mg/L, (37 mM) resulting more effective in respect to the antibiotic norfloxacin 32 mg/L, (100 mM) used as positive control.

Foetithiophene F (**174**) (yield 0.006% w/w) showed a low antifungal activity against *Candida albicans* with an MIC value of 200 μg/mL, and its highest antimicrobial activity was observed against the Gram-positive bacteria *B. cereus* with a MIC value of 50 μg/mL (Chitsazian-Yazdi et al., 2015). The other foetithiophenes C-E (**171-173**) were either inactive

or showed higher MIC values, i.e., ranging from 100 to 400 μg/mL. Even if these compounds showed a certain activity it was not so striking that it could justify a possible use.

7.9. Anti-inflammatory activity

The anti-inflammatory activity of sesquiterpene coumarins (**31**-**36**) was evaluated (Motai et al., 2004). Almost all of them inhibited the inducible NO-synthase expression more efficiently than quercetin as a positive control (only compound **31** resulted to be less active) in both lipopolysaccharide (LPS) and recombinant mouse interferon-γ-induced inflammation in a murine macrophage-like cell line (RAW 264.7). The recorded IC_{50} comprised between 8.9 and 19.5 μM suggests a great potential as an anti-inflammatory agents. The structural features necessary to exert the observed activity were reconducted to the presence of the following functionalization: α,β-unsaturated ketones; position and configuration of the double bond in the sesquiterpene unit (*Z* configuration enhances the inhibitory activity). Furthermore, these compounds showed no cytotoxicity in MTT assay. Unfortunately, they accounted for a very little quantity of the raw plant materials (5.9 kg) being isolated in amounts from 4.7 to 40 mg.

Other active anti-inflammatory constituents of the *Ferula* spp. was the newly characterized glucosidic furanone derivative (**188**) which showed only a moderate inhibitory activity (17 ± 1% at 80 μmol/L) but exerted toward a different enzymatic target, the 5-lipoxygenase an enzyme involved in the eicosanoids metabolism catalizing the production of other inflammatory mediators than prostaglandins, such as leukotrienes and lipoxins (Znati et al., 2014). In addition, in this case (**188**) accounted for a very little percentage of raw plant materials (0.00034% w/w) thus resulting a minor components not easily useful as active compound.

7.10. Inhibitory behavior of transcription-activating factors for iNOS mRNA

It has been shown that the four new sesquiterpene coumarins (**37**-**40**) inhibited the transcription-activating factors for iNOS mRNA in a dose-dependent manner with IC_{50} values of 30 ± 2 μM; IC_{50} = 29 ± 1 μM; IC_{50} = 31 ± 1 μM; IC_{50} = 27 ± 2 μM, respectively (Motai and Kitanaka, 2004). The cytotoxic potential of these compounds, tested by the MTT assay, was not significant (3-100 mM), as well. Unfortunately, they were obtained in mg amount (ranging from 13.7 to 23.0) from 5.9 kg of plant materials, thus resulting to be minor components.

7.11. Antiprolifertive/anticancer activity

The antiprolifertive activity of the compounds (**114**-**116**) in the estrogen-dependent MCF-7 cells was evaluated with contrasting results: Compound (**114**) and (**116**) exhibited proliferative activity, whereas (**115**) showed an antiproliferative action (Lhuillier et al., 2005). Genistein and β-estradiol were used as positive controls. Also in this case the isolated amounts (10.6, 7.5 and 5.6 mg) indicate that these are minor components in plant materials (5.4 kg).

On the other hand, Alkhatib et al. (2008) screened the antiproliferative activities of the isolated compounds elaeochytrins A and B (**128** and **129**, respectively) on K562R human chronic myeloid leukaemia (imatinib-resistant) and DA1-3b/$M2^{BCR-ABL}$ mouse leukemia (dasatinib-resistant) cell lines. According to the findings of this is study, of the two new compounds elaeochytrin A (**128**) was the more active compound on both cell lines (IC_{50} values 12 and 8 μM, respectively). It was also active against non-resistant human promyelocytic leukemia cells (HL60), having an IC_{50} value of 13 μM. However, the toxicity toward normal peripheral blood mononuclear cells was not observed at concentrations up to 100 μM, while elaeochytrin B (**129**) showed a low activity (IC_{50} = 65.0 μM) against DA1-3b/$M2^{BCR-ABL}$ and resulted inactive toward K562R. Compound (**128**) accounted for 0.28%

w/w on raw materials and therefore resulted to be contained in a sufficient amoun in the plant materials to justify a practical use i.e. for extractive purposes of the active compound.

In addition, Iranshahi et al. (2010a), determined the antiproliferative activity of the isolates against a small panel of cancer cell lines [M14 (human melanoma), MCF-7 (breast carcinoma), T98G (glioblastoma), A549 (lung carcinoma), Saos-2 (osteosarcoma), FRO (thyroid carcinoma), and U937 (leukemic monocyte lymphoma)] using the MTT assay. However, only the already known feselol was found to be active against one cell line (U937), with an IC_{50} value of 8 μM. Unfortunately, the newly characterized compounds (**45**-**47**) were found to be inactive.

The antiproliferative activity of the isolated compounds (**137**-**139**) was tested against several human tumor cell lines. The new compounds showed varying activities: 2α-acetoxy-6α-*p*-methoxybenzoyl-10α-hydroxy-jaeschkeanadiol (**137**) showed very little activity toward A549, HeLa and K562, with IC_{50} values > 100, 52 ± 2 and 70 ± 6 μM, respectively. However, this compound was more active against HL-60, Jurkat, RS 4;11 and SEM having IC_{50} values 15 ± 5, 9 ± 4, 27 ± 4 and 27 ± 2 μM, respectively. Furthermore, 2α-hydroxy-6α-*p*-methoxybenzoyl-10β-acetoxy-jaeschkeanadiol (**138**) showed promising activity against HL-60 and Jurkat (IC_{50} values of 24 ± 4 and 34 ± 6 μM, respectively) while for the other cell lines only moderate to little activity was observed with IC_{50} values ranging from 70 - >100 μM. Finally, 8,9-dihydro-8,14-dehydro-9-hydroxyferutinin (**139**) displayed the best cytotoxicity only against RS 4;11 and SEM cell lines, specifically with IC_{50} values of 29 ± 4 and 35 ± 2 μM, respectively, and exhibited low or moderate activity against the other tested cell lines, with IC_{50} values ranging from 43 - >100 μM (Dall'Acqua et al, 2011). These active compounds (**137**-**139**) resulted present in the analyzed raw plant materials (450 g) with the following amounts, respectively: 21.4, 8.2 and 13.2 mg.

An inseparable mixture of dihydrofuranocoumarin isomers (**66**, **67**) exerted antiproliferative activity against HT-29 and HCT 116 cell lines, with IC_{50} values of 0.290.05 and 1.6 ± 0.6 μM, respectively (Ben Salem et al., 2013). Unfortunately, in this report no indication about the isolated quantities were provided, therefore it is not possible to estimate their abundance in the plant materials and the potentiality for an effective practical application.

Li and colleagues (2014), tested the isolated compounds for their potential antiproliferative activity. Sinkiangenorin C (**187**) was found to be cytotoxic against the AGS human cancer cell line, with an IC_{50} value of 37 μM, while sinkiangenorins A and B resulted inactive against all the tested cell lines. Compound (**187**) was obtained in 9 mg yield from 4.2 kg of plant materials. Therefore, considering that it is a minor component and showed not extremely high bioactivity, its practical use is quite impossible.

In a related study, the two new compounds (**59, 60**) were tested for their antiproliferative activities against K562, HeLa, and AGS human cancer cell lines. Compound (**59**) showed a moderate cytotoxic activity against the AGS cell line, with an IC_{50} value of 27 ± 1 μM, while (**60**) was less effective (IC_{50} = 63 ± 3 μM), in comparison with the standard drug taxol (IC_{50} = 3.5 ± 0.04 μM) (Li et al., 2015b). Conversely, cell lines K562 and HeLa did not show any appreciable sensitivity towards these compounds (**59**, **60**). Furtermore, in this case these compounds resulted to be only minor components being isolated in 16.0 and 9.0 mg, respectively, from 4.2 kg of raw plant materials.

Lastly, the cytotoxic tests of the characterized sulfur containing foetithiophenes C-F (**171-173**) implied that none of the identified compounds showed cytotoxicity ($IC_{50} > 100$ μM) against MCF-7 and K562 cell lines (Chitsazian-Yazdi et al., 2015).

Accordingly to the data reported by Li and collaborators (2015a), the compound sinkiangenorin D (**58**) showed promising anticancer activity in AGS with an IC_{50} value of 20 ± 1 μM, while resulted moderately active against HeLa and K562 human cancer cell lines,

985 with IC_{50}values of 81 ± 1 and 105 ± 1 μM, respectively. A quantity of 13.0 mg of (**58**) was
986 obtained from 4.2 kg of plant materials together with ten known metabolites, also present in
987 mg scale.

988 *7.12. Antioxidant activity*
989

990 The antioxidant potential of a mixture of identified compounds (**66**, **67**) was assessed by
991 some standard assays including DPPH·, $ABTS^{\cdot+}$, singlet oxygen ($^1O_2$) and hydrogen peroxide
992 (H_2O_2), which resulted in IC_{50} values of 19, 13, 7.6, and 4.8 μM, respectively (Ben Salem et
993 al., 2013). They showed to be less active in respect to BHT, used as positive control, in both
994 DPPH· and $ABTS^{\cdot+}$ tests (IC_{50} = 9.02 ± 0.49 μg/mL and 6.85 ± 0.11 μg/mL, respectively).
995 Conversely, they showed an effectiveness comparable to BHT (IC_{50} = 7.26 ± 0.13 μg/mL)
996 against singlet oxygen and resulted more active than the positive control (IC_{50} = 6.38 ± 0.04
997 μg/mL) in hydrogen peroxide assay. The ability to act as antioxidant compounds was
998 attributed to the presence of the OH phenolic function in C-5 of both compounds.
999 Unfortunately, in this report no indication about the isolated quantities were provided,
1000 therefore it is not possible to estimate their abundance in the plant materials and the
1001 potentiality for an effective application.

1002 The new compounds (**63** and **64**), ferulone A and B, respectively, were tested for their
1003 antioxidant potential in DPPH· assay but showed only a low level of free-radical-scavenging
1004 activity with values of 0.25 and 0.56 mg/mL, respectively, in comparison to that observed for
1005 the positive control (quercetin, 0.004 mg/mL) (Razavi et al., 2016). Their amounts accounted
1006 for 0.0081 and 0.0089% w/w of plant materials.

1007 *7.13. The antileishmanial activity*
1008

1009 The antileishmanial activities of extract, fractions and pure compounds involving fnarthexone
1010 (**51**) and fnarthexol (**52**) together with three known natural compounds, namely

umbelliferone, conferone and conferol have been tested (Bashir et al., 2014a). As shown in this work, the new compounds (**51** and **52**) showed only moderate activity with IC_{50} values of 43.77 ± 0.56 and 46.81 ± 0.81 μg/mL, respectively. The most potent antileishmanial activity observed in this study was attributed to conferol with an IC_{50} value of 11.51 ± 0.09 μg/mL. It is interesting to note the different bioactivity level recorded for the two epimers fnartexol (**52**) and conferol, because the only structural difference between these two compounds stands in the opposite configuration at C-5′. This may obviously suggest an important influence of the stereochemistry at this site (this imply a different configuration of the fused rings in the *cis*-form) for what concerns the enhancing of the antileishmanial activity of sesquiterpene coumarins and could be an useful structural feature in projecting new synthetic active derivatives. The new fnarthexone (**51**) and the known fnarthexol (**52**) were isolated in the order of mg (18.0 and 24.0, respectively) from 8 kg of plant materials, thus providing a very low yield. On the contrary, conferol was isolated in huge amount (800 mg) accounting for 0.01 % w/w.

7.14. The ferulosis

In the context of bioactivities ascribed to *Ferula* spp., it is worth mentioning the case of "ferulosis", a lethal haemorragic syndrome affecting sheeps, cattle, horses and goats (and even humans) (Carta, 1951a) caused by consumption of giant fennel (*F. communis* L.) (Carta, 1951b; Carta and Delitala, 1951; Carta, 1955). This obviously leads to suffering of the affected animals that in many cases come to death, together with a negative impact on economy relying on animal resources. Several cases of ferulosis are reported in Sardinia (Appendino, 1997). The connection between the toxic symptoms and the consumption of giant fennel was demonstrated by the Sardinian veterinary Altara (Altara, 1925), who postulated the existence of two different chemotypes of giant fennel to explain the contrasting evidences of toxicity. The existence of two different chemotypes, undistinguishable by

morphology, has been unambiguously confirmed by several phytochemical studies (Valle et al., 1986; Appendino et al., 1988a; Appendino et al., 1988b). Furthermore, several analytical approaches have been conducted to discriminate the two chemotypes on the basis of the presence (or absence) of specific chemical markers (Sacchetti et al., 2003; Rubiolo et al., 2006; Alzweiri et al., 2015). Plants of the toxic chemotype showed the presence of prenylated 4-hydroxy-coumarins with haemorragic properties such as ferulenol, 15-hydroxy-ferulenol, ferprenin. Conversely, these coumarins were not detected from the non-poisonous chemotype, which instead contained daucane sesquiterpenoids, some of which endowed with estrogenic properties, i.e. ferutinin (Valle et al., 1986; Appendino et al., 1988a; Appendino et al., 1988b; Appendino et al., 2001). It is interesting to note that within the toxic chemotype, highly poisonous plants were also recognized, which contain the polyacetylene falcarindiol endowed with pronounced antiplatelet activity (Appendino et al., 1993) besides the prenylated coumarins. In these higly poisonous plants, the contemporaneous presence of both polyacetylene and prenylated coumarins is most likely responsible of a synergistic toxicity. Fortunately, the toxic components have been identified and several analytical methods developed to discriminate between the two chemotypes. This is one clear case which demonstrates the importance of phytochemical analysis in both natural product studies and bioactivity and the primary role they have in the analysis of plant raw materials employed in botanicals, food supplements and phytotherapy (Toniolo et al., 2014).

As just reported, a wide number of the newly described metabolites from *Ferula* spp. have been tested for their biological activities. Besides the quite common antioxidant characteristics, some of these compounds have showed a wide range of activities such as antimicrobial, antiviral (HIV), antibacterial (against multidrug-resistant and methicillin-resistant *S. aureus*) and antiprotozoal (against *Leishmania* and *Plasmodium*), thus offering new potentially useful compounds for the therapeutic treatment of various diseases. This is of

potential importance considering that traditional antibiotics are losing their efficacy due to the emergence of new resistant disease-causing strains. On the other hand, new active molecules are becoming available for the treatment of diseases that have not been yet considered as drugs of choice. Furthermore, there are many drugs with reduced therapeutic indices and therefore high intrinsic toxicity.

The antiprolifertive potential against several human cancer cell lines and the immunosuppresive activity, exerted by inhibition of the production of several cytokines, have been observed for several unusual metabolites from *Ferula*. In addition, there is the remarkable anti-inflammatory activity displayed by inhibition of both inflammation mediators and the mRNA expression of inflammatory factors such as iNOS, TNF-α, IL-6, IL-1β and COX-2. In this context, it is worth mentioning the antineuroinflammatory potential observed in microglial LPS-activated cells, since inflammatory and oxidative processes are considered as important factors in the etiopathogenesis of neurodegenerative diseases such as Alzheimer and Parkinson diseases and Multiple Sclerosis. Previous studies suggested that the ability to quench the induction of microglial activation might have interesting applications in several neurodegenerative and neuroinflammatory pathologies (Salemme et al., 2016) since it is known that microglia-dependent inflammation is strictly associated with the onset of neurodegenerative diseases, characterized by increased oxidative stress and neuroinflammation. Therefore, the *Ferula* metabolites, which act as inhibitors of microglial activation, possess interesting potentialities also as possible neuroprotective agents.

It should be also underlined that the majority of these compounds, in particular the newly described ones, are contained in their natural sources in very little amounts. Therefore, a possible estractive procedure to obtain them as pure compounds could be quite expensive considering the low yields that would be obtained. It is obviously not possible to exclude *a priori* that in the original works of their first description no exhaustive extraction has been

obtained and that further studies in this sense can improve the yields. Anyway, in many cases, the extraction of the pure compounds seems to be the only possibility to use them because, given their small presence in the plant material, it is unlikely that they can give a biological effect when using the plant materials or the crude extract since the effective doses would not be achieved (Gertsch, 2009). This is an even more probable eventuality for those compounds which showed high values of IC_{50} i.e. $\geq$ 25 μM (Cos et al., 2006). A second limiting condition is that the majority of the described compounds have been tested only in *in vitro* assays. Nothing is known about their fate when administered to a living organism. The pharmacokinetic profile is an important factor to establish if a compound will be absorbed in sufficient amount to reach the effective dose and target tissues/organs, if it is metabolized and inactivated as well as if the eventual metabolites are still active or not. This in our opinion could be the future development regarding the bioactivity potential of the numerous metabolites isolated from *Ferula* species: the study of their pharmacokinetics and *in vivo* tests in order to obtain a complete picture of their real therapeutic and toxicological aspects.

8. Propagation of *Ferula* species

In recent years, the possibility to reproduce plants of *Ferula* spp. has also been studied by means of biothechnologic methods. To the date, there are only a few papers dealing with these aspects. Anyway, we are of the advice that in the future this area of research will be developed due to the high interest in the active secondary metabolites and the wide uses of *Ferula* spp. in the traditional medicine of several countries worldwide together with the increased interest in the protection of endangered species. Single node explants from *F. orientalis* L. were studied by Tuncer (2017) and shoots induction was obtained by culturing in Murashige/Skoog (MS) medium with the addition of 2,4-dichlorophenoxyacetic acid (2,4-D) and 6-benzylaminopurine (BAP) (0.5 and 2.0 mg/L, respectively) as plant growth

1111 regulators. With this method, the production of three shoots was obtained for each explants,
1112 thus resulting to be a useful *in vitro* regeneration method. Explants of root, hypocotyl and
1113 cotyledon (embryonal leaves) of *F. assa-foetida* L. were studied to evaluate the effects of
1114 different variables such as explants type, medium and plant growth regulators (Roozbeh et
1115 al., 2012). The results obtained in this study showed that the best somatic embryogenesis or
1116 the highest percent of induction was obtained from explants of leaves treated with 2,4-D (0.2
1117 mg/L) and KT (kinetin) (0.2 mg/L) in MS medium, while no significant effect was observed
1118 for both explants from cotyledon and hypocotyls. The best indirect somatic embryogenesis
1119 was instead obtained from roots explants treated with 2,4-D (0.5 mg/L) and KT (0.2 mg/L) in
1120 B5 medium. The maximum percentage of seedling development from embryos was found
1121 with simultaneous use of 2,4-D (0.5 mg/L) and KT (0.2 mg/L) as plant growth regulators in
1122 B5 medium, while the highest callogenesis induction was observed in B5 medium added with
1123 naphthaleneacetic acid (NAA) (1 mg/L) and KT (1 mg/L). A similar study was conducted by
1124 Zhu and colleagues (2009) in *F. sinkiangensis* K. M. Shen to explore the effect of different
1125 culture conditions and hormone combinations on callus induction. In addition, in this study
1126 different explants types were employed involving young cotyledon, hypocotyl and radicles. It
1127 resulted that the optimum medium for hypocotyl induction was MS added with 2,4-D (1.0
1128 mg/L) and KT (1.5 mg/L), while for radicle induction was MS added of NAA (0.5 mg/L) and
1129 BAP (0.5 mg/L) as plant growth regulators. The best subculture medium was MS added with
1130 NAA (1.5 mg/L) and BAP (2.5 mg/L), as well. The results were similar to those reported in
1131 the previous study with *F. assa-foetida* L. explants. It was observed that NAA, 2,4-D and
1132 BAP resulted to exert the inductive effect, while BAP showed better results than the KT in
1133 the proliferation step, and the GA3 (giberellin A3) had a coinductive role in the process of
1134 subculture embryogenic callus production. Somatic embryos production was also studied in
1135 *F. gummosa* Boiss. (Bernard et al., 2007) by induction of callus in zygotic embryonic axes in

MS medium. The differentiation of tissues was obtained under induction with NAA and after the exposure to thermo-phototperiod of 16 h of light at 19 °C and 8 h in the dark at 7 °C. The maturation of embryos and development of plantlets were obtained in MS induction medium added with NAA or 2,4-D as plant growth regulators. However, better results were obtained after transfer in hormone free medium, even if a high percentage of abnormal embryos was recorded. A second study on *F. gummosa* Boiss. callus and organogenesis induction was conducted by Sarabadani et al. (2008). Moreover, various organs including roots, cotyledons, main leaf, hypocotyle, embryo and cutting embryo were used in the induction phase promoted by various combinations of plant growth regulators. In this relation, cutting embryos and roots were detected as best explants for callus induction with 1.2 mg/L-1 BAP and 10 mg/L-1 NAA as plant growth promoter, while shoot organogenesis was observed only under treatment with 1.5 mg/L-1 BAP and 0.5 mg/L-1 ADS (adenine sulfate) conditions.

A new cryopreservation technique, based on vitrification of internal solutes, has been developed with the scope of conservation of seeds and embryonic axes obtained from *F. gummosa* Boiss. (Rajaee et al., 2012). The plant seeds were cultured to obtain the embryonic axes which were pre-treated in sucrose cultures prior to cryotreatment with liquid nitrogen by applying two different encapsulation-dehydration and vitrification methods. The major survival percentage of cryopreserved materials was obtained when the technique was applied on embryos. During this study, a higher percentage of germination was also recorded for embryonic axes in comparison with *Ferula* seeds subjected to natural germination. Dormancy break and germination induction were already studied earlier by Nadjafi and coworkers (2006) on the seeds of the same plant species (*F. gummosa* Boiss.) which were subjected to different treatments such as exposure to GA3, acid scarification with H_2SO_4 or HNO_3, chilling and soaking in water at different temperatures. Accordingly, germination

grade was noted after treatment with GA3 and dormancy breaking was efficiently obtained by chilling at 5 °C for two weeks.

Other two studies which could give interesting information for what concerns the cultivation and conservation procedures were more recently conducted on *F. jaeschkeana* Vatke, a severely threatened medicinal plant native of the Himalayan region by Yaqoob and Nawchoo (2017b, a). Seed dormancy was interrupted after contemporaneous treatment with kinetin and dry stratification for 60 days and the higher percentage of germination was obtained after 24 h of treatment with kinetin in sand:soil media (2:1). Differently, higher sprouting and rooting response in roots cuttings were observed after treatment with GA3 (500 ppm). Furthermore, the habitat variability impact on the reproductive success was studied. Several morphologic parameters (such as number of shoots per plant, root tuber dimensions, plant height, basal leaf length, pinnae number, pinnae length, pinnule length, number of flowering stems per plant, flowering stem length, sheath number per plant, sheath length, number of umbels, umbel diameter, umbels per flowering stem, umbellule's per umbel, number of flowers, fruit morphology and fruit number) were considered to evaluate the reproductive success of this plant species. The best environmental conditions were also determined for a possible cultivation of this species as well as to develop effective strategies in the conservation of the wild populations and possibly for their sustainable use. In this study, it was concluded that the better conditions of growth of this species are those of altitudes comprised between 1500 and 2000 m a.s.l..

9. Conclusion and future perspectives

The increasing trend of industrialization and emergence of unknown and persistent diseases are among the greatest challenges to scientists in near future. Plant derivatives have exhibited novel therapeutic characteristics as a result of a large number of scientific investigations over

the past few decades. Therefore, replacing chemical and synthesized drugs with natural-based plant products seems highly rational. The genus *Ferula* is the third largest genus of the Apiaceae family and comprises about 180 species mainly distributed in Asia, India and Mediterranean basin. Many of these species are endemic or indigenous entities with a consolidated use in the traditional medicines of the countries of origin. To date, a large number of bioactive compounds possessing interesting biological and medicinal activities have been separated from a wide array of *Ferula* plants. The present overview describes the large number of new compounds, which have been identified as components of *Ferula* species in recent decades, and makes note of the main ethnobotanical aspects of these species together with the pharmacological potentialities. The huge number of structures reported, belonging to different classes of natural products, highlighted the great variability in secondary metabolites in *Ferula* spp.. Several of them are metabolites restricted to this genus and, as such, are useful makers in the chemotaxonomy field. A great number of these new compounds resulted to be active as antibiotics against drug-resistant bacterial strains offering so new possible therapeutic approaches and new chemical structures, in comparison with those of traditional drugs, to develop new semisynthetic derivatives. Several *Ferula* metabolites resulted active against different tumor cell lines and, in the majority of the cases, showing little or no toxicity toward somatic cells. Both these two therapeutic areas, the microorganisms infections treatment and the chemotherapy of cancer, need new active molecules since the effectiveness of traditional drugs is decreasing due to the establishment of resistance and *Ferula* metabolites have demonstered to posses the potentiality to be effective drug candidates and to be useful starting materials to develop new semisynthetic derivatives. The inhibitory action in microglia-mediated neuroinflammation showed by some of the *Ferula* components is also worth of mention since this pathologic mechanism is widely considered responsible of the development of several neurodegenerative diseases. In this

specific pharmaceutical field, only a little number of compounds resulted effective and the search of new active molecules is still in the limelight. Finally yet importantly, is noteworthy the antiprotozoal activity exerted by some metabolites against *Leishmania* and *Plasmodium.* There are currently very few drugs available for antiprotozoal therapy and the majority have a reduced therapeutic index due to their intrinsic toxicity. Differently from bacteria the protozoa offer limited and non-selective molecular targets, and this is one of the reasons why only a few compounds are currently available as antiprotozoal drugs. Therefore, the potentialities of *Ferula* metabolites represent a resource to be exploited in projecting new antiprotozoal molecules. Moreover, since only a limited number of species have been analyzed until now, we are of the opinion that several new components, also endowed with currently unexplored bioactivities, might be discovered in other so far unanalyzed species of the genus. We are also of the advice that the high pharmaceutical potential of *Ferula* metabolites will not go unnoticed by the scientific community and that in the future different studies will bring new developments, especially in the practical application of the various biological activities found so far. In conclusion, the presence in *Ferula* species of unusual bioactive phytochemicals demonstrates that this genus is a precious source of active natural products and has great potential in the pharmaceutical and medicinal fields. What is lacking in the current state of the art, for what concerns the bioactivity tests, is an approach that effectively assesses the therapeutic potential of these secondary metabolites through studies conducted in *in vivo* systems, and above all, investigating the pharmacokinetic aspects of compounds already resulted active in *in vitro* experiments. We hope these studies will be a prevalent aspect of future research.

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Table 1

Some endemic and indigenous species of the genus *Ferula* growing wild in different parts of the world.

Country flora	Endemic/indigenous species		Ref.
	Number	Name	
Italy	3	*Ferula arrigonii* Bocchieri, *F. communis* L. and *F. glauca* L.	(Conti et al., 2005; Maggi et al., 2009b)
Iran	15	*F. pseudalliacea* Rech.f., *F. gabrielii* Rech.f., *F. kashanica* Rech.f., *F. persica* Wild., *F. macrocolea* (Boiss.) Boiss., *F. microcolea* (Boiss.) Boiss., *F. stenocarpa* Boiss. & Hausskn, *F. tabasensis* Rech.f., *F. behboudiana* Rech. f. & Esfand, *F. lutensis* Rech.f., *F. assa-foetida* L., *F. sharifii* Rech.f., *F. serpentinica* Rech.f., *F. flabelliloba* Rech. f. & Aell. and *F. xylorhachis* Rech.f.	(Mozaffarian, 1996)
Turkey	9	*F. amanicola* Hub.-Mor. Et Pesmen, *F. anatolica* (Boiss.) Boiss., *F. drudeana* Korovin, *F. halophila* Pesmen, *F. huber-morathii* Pesmen, *F. longipedunculata* Pesmen, *F. lycia* Boiss., *F. parva* Freyn et Bornm. and *F. tenuissima* Hub.-Mor. et Pesmen	(Pesmen, 1972; Sağiroğlu and Duman, 2010)
Tunisia	4	*F. communis* L., *F. tingitana* L., *F. tunetana* Pomel ex Batt. and *F. lutea* (Poir.) Maire	(Jabrane et al., 2010; Znati et al., 2012)
Algeria	2	*F. logipes* Coss. ex Bonnier and Maury (also named *F. cossoniana* Batt.) and *F. vesceritensis* coss. et Dur.	(Labed-Zouad et al., 2015)
Pakistan	15	*F. assa-foetida* L., *F. baluchistanica*, *F. communis* L., *F. costata*, *F. hindukushensis*, *F. jaeschkeana*Vatke, *F. kokanica* Rgl. et Schmalh., *F. lehmannii* Boiss., *F. microloba* Boiss., *F. narthex* (Falc.) Drude, *F.oopoda* (Boiss. Et Buhse) Boiss., *F. ovina* Boiss., *F. reppiae*, *F. rubicaulis*, and *F. stewartiana*	(Anonymous; Yaqoob and Nawchoo, 2016)
Saudi Arabia	4	*F. communis* var. *communis* L./var. *glauca* (L.) Rouy and Camus, *F. ovina* (Boiss.) Boiss., *F. rutbaensis* C.C. Townsend. and *F. sinaica* Boiss.	(Anonymous; Yaqoob and Nawchoo, 2016)
India	3	*F. narthex* (Falc.) Drude, *F. thomsoni* and *F. jaeschkeana* Vatke	(Hooker, 1897)

Table 2

Remedial traditional, pharmaceutical and medicinal properties of the different species from the genus *Ferula* growing wild in different parts of the world.

Ferula species	Organ/part	Properties	Used as/for; prescription mode	Country/continent	Ref.
F. assa-foetida L.	Different parts	Tonic, spice and as a strong antioxidant, antibacterial, antifungal, anti-coagulant, antimicrobial, anti-ulcer, anticonvulsant, antispasmodic, anti-inflammatory, antihelmintic, antidiabetic, aphrodisiac, alterative, hypotensive, sedative, laxative, stimulant, diuretic, neuroprotective and carminative remedy; widely administered to address asthma, impotence, bronchitis, flatulence, infection, stomachache, hysteresis; as a flavoring agent to table sauces and for seasoning the food products, to lower blood pressure, acting as a vermifuge when its decoction is taken orally	Decoction, extract, row, air dried, and fried	Iran, Asia	(Mahran et al., 1973; Zargari, 1990; Rafiq Siddiqui et al., 1995; Sefidkon et al., 1998; Dehpour et al., 2009; Iranshahy and Iranshahi, 2011; Mahendra and Bisht, 2012; Amiri, 2014)
	OGR [1]	Promising neuroprotective impact against the cultured neurons, a proper remedy for intestinal parasites, whooping cough, emmenagogue, influenza, gasterointestinal problems, insects and snake bites, respiratory malfunctions, an antifertility, antihepatotoxic, antihyperglycemic and antiviral drug, an acaricide, anticholesterol and anticarcinogenic plant	Raw	Iran, Asia	(Heravi, 1967; Mahran et al., 1973; Samsam Shariat and Moattar, 1990; Samsam-Shariat, 1992; Keshri et al., 1999; Mallikarjuna et al., 2003; Iranshahy and Iranshahi, 2011; Kanani et al., 2011; Moghadam et al., 2013; Ghannadi et al., 2014; Hadavand Mirzaei and Hasanloo, 2014; Homayouni Moghadam et al., 2014; Fatemikia et al., 2017)
		As a flavoring agent and condiment in the vegetarian diet of the Indian people and in Indian pickles	Raw	India, Asia	(Guenther, 1952)
		Effective against amenorrhea when is being chewed	Raw	Malaysia, Asia	(Buddrus et al., 1985)
F. gummosa Boiss. [2]	Aerial parts, flowers, leaves, seeds, stems and roots	Effective in the treatment of stomach problems, flatulence, chronic, antibacterial, bronchitis, colic, chorea as well as some neurological disorders, tonic, as an anti-hysteric, antihemolytic, anti-diarrhea, anti-parasitic, antinociceptive, antioxidant, emmenagogue, antispasmodic, anti-inflammatory, anti-convulsant, decongestant, analgesic, digestive, expectorant, uterine tonic drug, stimulant, epilepsy, and as an effective wound healing remedy, to withdraw morphine	Air dried, raw, poultice, and extract	Iran, Asia	(Zargari, 1990; Fazly-Bazzaz et al., 1997; Ramezani et al., 2001; Eftekhar et al., 2004; Mandegary et al., 2004; Iranshahi et al., 2010a; Nabavi et al., 2010; Kanani et al., 2011; Mozaffarian, 2012; Amiri, 2014; Mahboubi, 2016)
		Used as a carminative and softening agent, a proper remedy against seizure, earache, asthma, headache, chorea, epilepsy and stomachache, inflammation, in wound healing, and to address liver disorders and inability; industrial uses: to prepare varnishes and paints of high	Raw	Japan, Iran, Asia	(Howlett, 1980; Panda, 2003; Javidnia et al., 2005; Mortazaienezhad and Sadeghian, 2006;

	OGR	qualities, as a flavoring agent or emulsifier to food products and beverages and additive to some detergents and soaps			Mohammadzadeh Milani et al., 2007; Miyazawa et al., 2009; Mahboubi, 2016)
		To address some disorders and diseases like rheumatism, bronchitis, acne, poor circulation, muscle, aches, stretch marks and to improve scars, wounds, sores and cuts; serving as a proper aphrodisiac, antihysteric, anti-diabetic, anti-nociceptive, antiseptic, anti-catarrh, and as an analgesic drug	Raw, extract	Iran, Asia	(Sayyah et al., 2001; Mandegary et al., 2004; Kouyakhi et al., 2008; Fallah et al., 2015)
F. communis L. [3]	Aerial parts	As a medicinal plant from antiquity for the treatment of dysentery, an antihysteric agent	Raw and dried	Different parts of the world	(Heywood, 1971; Mohammadhosseini, 2016)
	Roots	Acting as a strong female sterilizing agent, an analgesic, anti-helmintic, and diuretic remedy as well as in the treatment of rheumatism, joins pains and in hair care	Raw	Morocco, Africa	(Nguir et al., 2016)
	Rhizomes	To treat skin disorders	Raw and dried	Saudi Arabia, Asia	(Collenette, 1985)
	Roasted flower	Effective against dysentery and hay fever			
	Fresh kernel	Treating of snakebite, hysteria, convulsion, diarrhea, diabetes, dizziness and stomachache, to improve muscle cramps, to stop bleeding	Dried and crushed	Some African countries	(Boulos, 1983; Dioscorides, 2000)
F. foetida Regel	Aerial parts	Edible with high diuretic, antispasmodic and anthelminthic potentials	Raw and dried	Iran, Asia	(Zargari, 1990)
	Roots	Effective to cure of backache and rheumatism			
F. microcolea (Boiss.) Boiss.	Aerial parts, flowers, leaves, and stems	As a spice, food additive and flavoring agent and acting as an antioxidant agent	Raw, dried, crushed, extracts	Iran, Asia	(Zargari, 1990; Amiri, 2014)
F. hermonis Boiss.	Different parts	As a tonic aphrodisiac agent [4]	Raw and dried	Lebanon and Syria, Asia	(Lev and Amar, 2002; Hadidi et al., 2003)
	Aerial parts	Recommended as a highly aphrodisiac in the American dietary supplement protocols	Raw and dried	United States of America	(Hadidi et al., 2003)
F. jaeschkeana Vatke	Resin	Antiseptic agent	Raw	India, Asia	(Anonymous, 1948)
F. galbaniflua Boiss. & Buhse	Galbanum	An additive to candy and to address intestinal malfunctions	Aerial parts and stems	Iran, Asia	(Sadraei et al., 2001; Radulović et al., 2013)
F. rubricaulis Boiss.		An additive to candy and to address intestinal malfunctions	Aerial parts and stems	Iran, Asia	(Sadraei et al., 2001; Radulović et al., 2013)
F. persica Wild.	Aerial parts, roots	To treat lumbago, backache, rheumatism and diabetes; as a potent carminative, laxative, and antihysteric agent	Raw, dried or powder form	Iran and Jordan, Asia	(Afifi and Abu-Irmaileh, 2000; Amiri, 2014)
F. sinkiangensis K. M. Shen	Aerial parts	Having immunopharmacological, anti-inflammatory, antibacterial, antiulcerative activities as well as remedial properties against stomach problems along with rheumatoid arthritis; an antioxidant, anti-tumor and a deodorant agent; in the preparation of a special Chinese food; acting as neuroinflammation inhibitors[5]	Raw and dried	Xinjiang, China, Asia	(Zhang and Hu, 1987; Yang et al., 2006; Xiaojin and Jiang Lin, 2007; Yang et al., 2007; Zhang et al., 2015; Li et al., 2016; Xing et al., 2017)
F. teterrima Kar. & Kir.	Aerial parts	For the treatment of rheumatoid arthritis along with intestinal (stomach) problems	Raw and dried	Xinjiang, China, Asia	(Yang et al., 2006)

F. ovina (Boiss.) Boiss.	Aerial parts	An anti-cholinergic, anti-spasmodic remedy with remarkable smooth muscle relaxant properties, as a condiment and spice	Air dried, raw, and extract	Jordan, Asia	(Al-Khalil et al., 1990; Aqel et al., 1992; Radulović et al., 2013)
	Aerial parts and roots	*In vitro* apoptosis and cytotoxic influences [6]; antimicrobial impacts	Raw and dried	Iran, Asia	(Amooaghaie, 2009; Matin et al., 2014)
F. iliensis Krasn. ex Korov	Aerial parts	Lowering blood pressure and enhancing intestinal muscle contractibility in rabbits and to cure inflammation	Juice, extracts and essential oils	Kazakhstan, Asia	(Aqel et al., 1992; Özek et al., 2017)
F. syreitschikowii Koso-Pol.	Aerial parts	To cure peptic disease	Raw and dried	China, Asia	(Tan et al., 2017)
F. latisecta Rech. f. & Aell	Different parts	To treat infant colic	Raw and dried	Iran, Asia	(Iranshahi et al., 2008)
	Resins	An antihysteric agent; used as an effective remedy against insects, dysentery, feminine sterility, hay fever, colon, asthma, spasm, epilepsy, rheumatism and malaria	Raw and dried	China, Asia; African countries	(Boulos, 1983; Trease and Evans, 1983; Martinetz and Lohs, 1988; Habibi et al., 2006b)
F. fukanensis K.M.Shen	Aerial parts	In the treatment of bronchitis along with rheumatoid arthritis	Raw and dried	Central Asia (arid lands)	(Motai and Kitanaka, 2005b; Xing et al., 2017)
F. orientalis L.	Aerial parts	To flavor the local pickles	Raw and dried	Turkey, Europe	(Kartal et al., 2007)
F. elaeochytris Korovin	Roots	Ruminant feeding (sheep and cattle); promotion of the rate of animal fertility	Dried powder	Turkey, Europe	(Miski et al., 1983; Klevenhusen et al., 2015)
F. flabelliloba Rech. F. et Aell	Aerial parts	As a sedative drug, effective against abdominal pain and diarrhea	Raw and dried	Iran, Asia	(Lahazi et al., 2015)
F. diversivittata Regel & Schmalh.	Aerial parts	As a sedative drug, effective against abdominal pain and diarrhea	Raw and dried	Iran, Asia	(Lahazi et al., 2015)
F. szowitsiana DC. [7]	Aerial parts	To relief pain due to its impact on different receptors involving adenosine, cannabinoid and cannabinoid	Raw and dried	Iran, Asia	(Saghravanian et al., 2016)
	Aerial parts, flowers and stems	Known as a strengthening agent and also an appetite stimulator; an antimicrobial agent	Raw and dried	Turkey, Europe	(Özek et al., 2008)
F. badrakema Koso-Pol.	Roots	Recommended against epilepsy and spasms	Raw and dried	Iran, Asia	(Asili et al., 2009)
F. badrakema Koso-Pol. and *F. gummosa* Boiss. (Mixed together)	Aerial parts	As a strong anti-hysteric, decongestant and anticonvulsant remedy, effective in treating some neurological disorders and a tonic herbal drug	Raw and dried	Tunisia, Africa	(Eigner and Scholz, 1990; Afifi and Abu-Irmaileh, 2000; Znati et al., 2017)
F. oopoda (Boiss. & Buhse) Boiss.	Different parts	Representing remarkable antiplasmodial and remedial features against migraine as well as cough	Extract, raw and dried	Iran, Asia	(Esmaeili et al., 2009)
F. heuffelii Griseb. ex Heuffel	Underground parts	Spasmolytic activity	Extract	Serbia, Europe	(Pavlović et al., 2014)
F. vesceritensis Coss. & Dur [8]	Aerial parts, leaves, flowers and	For the treatment of persistent headache, throat infections and fever, having antioxidant and antibacterial properties	Fresh and dried	Algeria, Africa	(Benchabane et al., 2012; Labed-Zouad et al., 2015)

	stems				
F. tingitana L	Different parts	As an abortive plant with high menstruation-inducing properties; recommended for the treatment of indigestion, fever, pains and sore throat	Fresh and dried	Libya, Africa	(Elghwaji et al., 2017)
F. cupularis (Boiss.) Spalik et S. R. Downie	Flowers, leaves and stems	To cure ulcer and also to preserve foodstuffs (oil and meat)	Dried parts	Iran, Asia	(Alipour et al., 2015)
F. alliacea Boiss.	Different parts	As one of the potential sources of asafoetida representing traditional and medical uses like *F. assa-foetida* L.	Raw and dried	Iran, Asia	(Kasaian et al., 2016)

[1] Oleo-gum-resin; [2] Known as "Barijeh" and "Ghasni" in the Iranian folk medicine; [3] Giant fennel formerly known as "Narthex" by the Romans; [4] Known as "Lebanese Viagra";[5] Due to the presence of sesquiterpene coumarins; [6] Related to ferutinin isolated from the roots of *F. ovina* (Boiss.) Boiss.; [7] Known as “Sivas Kasnisi” in Turkish traditional folk medicine; [8] Traditionally known as "Kelkha"

Table 3

Main components of essential oils, oleo-gum-resins, volatile constituents and extracts from different species of *Ferula* genus growing wild in different parts of the world.

Plant name (s)	Major constituents (%)	YEO [a]	Prevailing group	Extraction method (s)/Solvent	Analysis or characterization methods (s)	Organ(s)/Part(s)	Country	Identified		Ref.
								Number	%	
F. assa-foetida L.	Limonene (26.0%), *p*-cymene (14.3%), α-pinene (8.3%), and terpinen-4-01 (5.8%)	1.0	MH [b]	HD [c]	GC and GC-MS	Oleo-gum-resin	India	44	97.9	(Garg et al., 1989)
F. elaeochytris Korovin	Nonane (27.1%), α-pinene (12.7%), and germacrene B (10.3%)	0.27	NH [d]	HD	GC-MS	Fruits	Turkey	43	76.7	(Baser et al., 2000)
F. flabelliloba Rech. F. et Aell	δ-Cadinene (13.2%), α-cadinol (12.0%), and cadina-4,1(10.0)-dien-8β-ol (10.9%), and α-pinene (10.0%)	0.87	OS [e]	HD	GC and GC-MS	Aerial parts	Iran	20	80	(Rustaiyan et al., 2001b)
F. stenocarpa Boiss. & Hausskn	α-Pinene (48.8%) and β-pinene (30.1%)	0.33	MH	HD	GC and GC-MS	Aerial parts	Iran	26	97.8	(Rustaiyan et al., 2001a)
F. gummosa Boiss.	EO [f]: Limonene (14.0%), α-pinene (13.0%), myrcene (10.0%), terpinolene (10.0%), linalool (9.0%), δ-3-carene (9.0%), γ-terpinene (6.0%), phellandral (5.0%), butyl isovalerate (3.0%), α-terpinolene (2.5%), β-pinene (2.0%), and hexyl isovalerate (2.0%)	18	MH	HD	GC-FID and GC-MS	Oleo-gum resin	Iran	>30	88	(Sadraei et al., 2001)
	EE [g]: β-Pinene (62.0%), α-pinene (34.0%), and δ-3-carene (4.0%)	26	MH	Ether				3	100	
	PE [h]: Guaiole (31.0%), β-pinene (21.0%), valencene (14.0%), α-pinene (11.0%),	25	MH	Petroleum ether				6	99	

	δ-cadinene (11.0%), and pyrimidine (10.0%)									
	ME [i]: Benzene-1-3-dimethyl (38.0%), benzene-1-2-dimethyl (16.0%), benzene ethyl (12.0%), and benzene-1-ethyl-2-methyl (4.0%)	15	NH	MeOH				4	70	
F. gummosa Boiss.	β-Pinene (50.1%), α-pinene (18.3%), δ-3-carene (6.7%), α-thujene (3.3%), and sabinene (3.1%)	6-7	MH	HD	GC and GC-MS	Fruits	Iran	17	94.6	(Sayyah et al., 2001)
F. ovina (Boiss.) Boiss.	Carvacrol (9.0%), α-pinene (8.2%), geranyl isovalerate (7.2%), and geranyl propionate (7.0%)	1.0	OM [j]	HD	GC-MS	Aerial parts	Iran	43	86.7	(Ghannadi et al., 2002)
F. galbaniflua Boiss. et Buhse.	β-Pinene (46.4%), *cis*-chrysanthenyl acetate (6.1%), (*E*)-nerolidol (5.2%), and α-pinene (2.8%)	1.2	MH	HD	GC and GC-MS	Stem	Iran	41	87.4	(Rustaiyan and Monfared, 2002)
	β-Pinene (58.8%), *cis*-chrysanthenyl acetate (6.1%), and (*E*)-nerolidol (5.2%)	3.0				Root		34	86.1	
F. microcolea (Boiss.) Boiss.	α-Pinene (19.2%), nonane (13.2%), and β-pinene (13.0%)	1.5	MH	HD	GC and GC-MS	Aerial parts	Iran	30	88.9	(Akhgar et al., 2005)
F. hirtella Boiss.	α-Pinene (15.4%), and thymol (14.9%)	0.4						35	84.8	
F. communis L.	Myrcene (53.5%), and aristolene (8.5%)	NR [k]	MH	HD	GC, GC-MS and ^{13}C-NMR	Leaves	Corsica	47	95.0	(Ferrari et al., 2005)
F. persica Wild.	Dill-apiole (57.3%), and elemicine (5.6%)	0.2		HD	GC and GC-MS	Aerial parts	Iran	61	93.7	(Javidnia et al., 2005)
F. assa-foetida L.	(*E*)-1-Propenyl *sec*-butyl disulfide (40.0%), and germacrene B (7.8%)	1.13	NH	HD	GC and GC-MS	NR	Iran	25	94	(Khajeh et al., 2005)
	(*E*)-1-Propenyl *sec*-butyl disulfide (50.3-59.4%) [l]	0.8-5.5		SFE [m]: Supercritical fluid extraction				16-22	91.8-99	

F. macrocolea (Boiss.) Boiss.	β-Pinene (15.9%), α-pinene (10.4%), and β-caryophyllene (8.6%)	NR	MH	HD	GC-MS	Aerial parts	Iran	42	86.3	(Rustaiyan et al., 2005)
F. ferulaoides Korov.	Guaiol (58.8%), (*E*)-nerolidol (10.2%), and α-eudesmol (3.0%)	2.4-3.2	OS	HD	GC-MS	Air-dried roots	Mongolia	42	95.8	(Shatar, 2005)
F. gummosa Boiss.	β-Pinene (43.8%), α-pinene (27.3%), and myrcene (3.4%)	4.0	MH	HD	GC-MS	Air-dried fruits	Iran	73	96.9	(Ghasemi et al., 2005)
F. szowitsiana DC. [n]	α-Pinene (12.6%), germacrene D (12.5%), β-pinene (10.1%), *epi*-α-cadinol (8.9%), myrcene (7.0%), bicyclogermacrene (5.6%), and β-phellandrene (5.6%)	0.3	SH [o]	HD	GC and GC-MS	Aerial parts	Iran	23	100	(Habibi et al., 2006a)
F. latisecta Rech. f. & Aell	(*Z*)-Ocimenone (32.4%), (*E*)-ocimenone (20.3%), and *cis*-pinocarvone (11.4%)	0.4	OS	HD	GC and GC-MS	Aerial parts	Iran	22	87.7	(Habibi et al., 2006b)
F. persica Willd. var. *persica*	Dimethyl trisulphide (18.2%), myristicin (8.9%), dimethyl tetrasulphide (7.6%), α-terpinyl *n*-pentanoate (5.8%), lavandulyl 2-methyl butanoate (3.7%), α-terpinyl isovalerate (3.5%), and α-barbatene (3.1%)	0.15	NH	HD	GC and GC-MS	Root	Iran	39	82.0	(Iranshahi et al., 2006)
F. szovitsiana D.C.	Neryl acetate (33.0%), β-caryophyllene (8.9%), α-pinene (8.0%), β-pinene (6.7%), bicyclogermacrene (4.5%), caryophyllene oxide (4.1%), limonene (4.6%), and α-terpineol (3.2%)	0.18	OM	HD	GC and GC-MS	Stem/Leaves	Iran	51	97.7	(Dehghan et al., 2007)
	Neryl acetate (41.5%), bicyclogermacrene (9.0%), α-pinene (5.5%), β-pinene (3.9%), γ-cadinene (3.5%), and calarene (3.2%)	0.2				Flower/fruits		47	95.9	

F. latisecta Rech. F. et Aell.	*sec*-Butyl-(*Z*)-propenyl disulphide (65.2%), *sec*-butyl-(*E*)-propenyl disulphide (6.8%), and di-*sec*-butyl disulphide (2.1%)	2.0	NH	HD	GC and GC-MS	Fruits	Iran	41	88.9	(Iranshahi et al., 2008)
F. gummosa Boiss.	β-Pinene (26.8-69.2%), and α-pinene (1.4-33.9%)	1.66-3.85	MH	HD	GC and GC-MS	Fruits	Iran	9-21	79.4-100	(Kouyakhi et al., 2008)
F. badrakema Koso-Pol.	β-Pinene (45.8%), α-pinene (10.9%), *cis*-isolongifolanone (4.1%), β-phellandrene (2.7%), myrcene (2.4%), and carvacrol methyl ether (2.4%)	4.0	MH	HD	GC, GC-MS and ^{13}C-NMR	Fruits	Iran	74	98.2	(Asili et al., 2009)
F. assa-foetida L.	Phenol, 2-methyl-5-(1-methyl ethyl) (18.2%), α-bisabolol (10.4%), and arsine triethyl (8.7%)	0.94	NH	HD	GC-MS	Aerial parts	Iran	61	98.8	(Dehpour et al., 2009)
F. glauca L. [p]	(*E*)-Caryophyllene (24.9%), and caryophyllene oxide (14.3%)	0.02-0.07	SH	HD	GC-FID and GC-MS	Leaves	Italy	60	87.3	(Maggi et al., 2009a)
	Germacrene D (14.2%), myrcene (13.6%), and α-pinene (11.7%)		SH			Flowers		82	96.8	
	α-Pinene (24.2%), and β-pinene (14.7%)		MH			Fruits		19	68.7	
	(*E*)-β-Farnesene (10.0%), elemicin (9.0%), and myristicin (7.4%)		SH			Roots		23	79.7	
F. glauca L.	(*E*)-Caryophyllene (20.5%), caryophyllene oxide (13.9%), and germacrene D (6.8%)	0.05	SH	HD	GC-FID and GC-MS	Leaves	Italy	74	89.8	(Maggi et al., 2009b)
	Germacrene D (16.4%), myrcene (10.1%), (*E*)-caryophyllene (9.4%), and α-pinene (6.8%)	0.06	SH			Flowers		95	92.8	
	α-Pinene (36.6%), β-pinene (17.8%), and myrcene (4.1%)	0.09	MH			Fruits		55	79.1	

	Elemicin (9.0%), (*E*)-β-farnesene (8.4%), α-zingiberene (6.9%), myristicin (6.0%), and β-barbatene (4.0%)	0.03	SH			Roots		54	76.3	
F. assa-foetida L.	Sample 1 [q]: (*E*)-1-Propenyl *sec*-butyl disulfide (30.7%), 10-*epi*-γ-eudesmol (12.7%), (*Z*)-1-propenyl *sec*-butyl disulfide (12.4%), methyl l-(methylthio) propyl disulfide (10.9%), eudesmol (7-*epi*-α) (4.8%), and agarospirol (2.8%)	0.8	NH	HD	GC and GC-MS	Roots	Iran	26	98.5	(Mirzaei and Hasanloo, 2009)
	Sample 2 [r]: (*E*)-1-Propenyl *sec*-butyl disulfide (18.8%), 10-*epi*-γ-eudesmol (18.7%), (*Z*)-1-propenyl *sec*-butyl disulfide (9.2%), 7-*epi*-α-eudesmol (8.2%), agarospirol (5.1%), and methyl l-(methylthio) propyl disulfide (4.3%)	1.6						26	93.3	
F. lycia Boiss	α-Pinene (59.9%), β-pinene (19.0%), limonene (3.2%), and bornyl acetate (2.1%)	NR	MH	HD	GC-MS	Roots	Turkey	36	96.8	(Kose et al., 2010)
F. latisecta Rech. f. and Aell.	*sec*-Butyl-(*Z*)-propenyl disulfide (50.5%), sesquicineol-2-one (7.2 %), *sec*-butyl-(*E*)-propenyl disulfide (6.2%), and δ-cadinene (2.9%)	0.3	NH	HD	GC-MS	Roots	Iran	14	73.3	(Sahebkar et al., 2010)
F. oopoda (Boiss. & Buhse) Boiss.	β-Phellandrene (22.4%), thymol-methyl ether (15.3%), and myrcene (8.7%)	0.9	MH	HD	GC and GC-MS	Leaves	Iran	16	97.3	(Akhgar et al., 2011)
	Myrcene (36.1%), β-phellandrene (28.2%), and germacrene D (5.5%)	1.1				Seeds		20	98.2	
F. badghysi	β-Phellandrene (21.7%), thymol-methyl ether	0.7				Leaves		17	95.8	

(Korovin.)	(13.8%) and myrcene (13.5%), α-ylangene (11.3%)									
	Myrcene (32.8%), β-phellandrene (24.1%), and germacrene D (6.8%)	1.2				Seeds		22	94.7	
F. hermonis Boiss.	α-Pinene (43.3%), α-bisabolol (11.1%), and 3,5-nonadiyne (4.4%)	1.5	MH	HD	GC-FID, GC-MS and ^{13}C-NMR	Rhizome and roots	Jordan	79	92.8	(Al-Ja'Fari et al., 2011)
F. ovina (Boiss.) Boiss.	Fresh: Limonene (16.9%), α-pinene (15.2%), β-myrcene (7.7%), *cis*-β-ocimene (6.1%), isosylvestrene (5.1%), and β-pinene (4.4%)	0.4	MH	HD	GC and GC-MS	Aerial parts	Iran	42	95.0	(Azarnivand et al., 2011)
	Dried: α-Pinene (20.2%), spathulenol (9.6%), germacrene D (6.3%), β-caryophyllene (5.1%), α-terpineol (5.0%), and caryophyllene oxide (4.4%)	0.25						21	91.1	
F. foetida (Bunge) Regel	2,3,4-Trimethylthiophene (49.0%), 2,5-diethylthiophene (27.5%), elemicine (8.1%), and α-pinene (3.4%)	NR	NH	HD	GC-FID and GC-MS	Aerial parts	Iran	14	97.3	(Kanani et al., 2011)
F. assa-foetida L.	1-Methylpropyl (1*E*)-prop-1-en-1-yl disulfide (32.8%), α-pinene (11.3%), 1-methylpropyl (1*Z*)-prop-1-en-1-yl disulfide (9.1%), and β-pinene (6.1%)		NH					18	81.3	
F. behboudiana (Rech. f. & Esfand.) Chamberlain	Sabinene (75.3%), (*E*)-caryophyllene (16.1%), and α-pinene (2.0%)		MH					13	99.1	
F. flabelliloba Rech. f. & Aell.	*epi*-α-Cadinol (17.8%), (*E*)-γ-bisabolene (8.0%), and α-pinene (5.4%)		SH					33	84.2	
F. hirtella Boiss.	Germacrene B (15.5%),		SH					16	87.0	

	bicyclogermacrene (12.9%), α-pinene (9.9%), γ-elemene (8.5%), germacrene-D (8.5%), β-elemene (6.3%), β-pinene (4.6%), and limonene (4.4%)									
F. latisecta Rech. f. & Aell.	α-Pinene (51.6%), β-pinene (13.7%), limonene (10.0%), and sabinene (5.5%)		MH					23	96.9	
F. persica Willd. var. *latisecta*	α-Pinene (33.5%), spathulenol (8.2%), citronellyl acetate (5.3%), and β-elemene (5.1%)		MH					24	96.6	
F. persica Willd. var. *persica*	α-Pinene (55.0%), camphene (20.5%), limonene (4.8%), limonene (4.8%), and sabinene (4.1%)		MH					17	98.7	
F. szowitsiana DC.	1-Methylpropyl (1*Z*)- prop-1-en-1-yl disulfide (88.1%), and 1-methylpropyl (1*E*)-prop-1-en-1-yl disulfide (5.0%)		NH					8	98.8	
F. diversivittata Regel & Schmalh.	Verbenone (69.4%), and *ar*-curcumene (6.2%)		OM					22	87.3	
F. galbaniflua Boiss. & Buhse	β-Pinene (59.0%), and α-pinene (36.6%)		MH					12	99.9	
F. gummosa Boiss.	β-Pinene (66.3%), α-pinene (20.3%), and δ-3-carene (8.6%)		MH					10	98.8	
F. stenocarpa Boiss. & Hausskn.	β-Pinene (40.7%), β-phellandrene (22.7%), α-pinene (16.2%), and δ-cadinene (7.2%)		MH					16	93.2	
F. hezarlalehzarica	α-Pinene (37.3%), and β-pinene (36.2%)		MH					18	97.3	

Y. Ajani										
F. macrocolea (Boiss.) Boiss.	(*Z*)-β-Ocimene (41.7%), and myrcene (35.3%)		MH					11	85.3	
F. microcolea (Boiss.) Boiss.	α-Pinene (21.9%), β-pinene (17.8%), (*Z*)-caryophyllene (6.2%), caryophyllene oxide (4.6%), (*E*)-caryophyllene (4.4%), and limonene (4.3%)		MH					18	89.3	
F. orientalis Boiss.	α-Pinene (41.2%), nonane (16.0%), β-pinene (13.8%), myrcene (4.7%), limonene (4.4%), and sabinene (4.3%)		MH					16	99.4	
F. ovina (Boiss.) Boiss.	Nonane (45.6%), α-pinene (32.1%), and 2- methyl octane (19.4%)		NH					12	99.4	
F. ovina (Boiss.) Boiss.	α-Pinene (61.0%), myrcene (6.3%), limonene (6.3%), and camphene (5.6%)		MH					16	91.5	
F. ovina (Boiss.) Boiss.	α-Pinene (63.8%), camphene (6.5%), and limonene (4.9%)		MH					11	83.7	
F. ovina (Boiss.) Boiss.	α-Pinene (68.7%), myrcene (4.7%), camphene (4.2%), β-pinene (4.2%), and limonene (4.1%)		MH					12	90.1	
F. ovina (Boiss.) Boiss.	α-Pinene (65.4%), and β-pinene (5.1%)		MH					18	92.1	
F. oopoda (Boiss. & Buhse) Boiss.	α-Terpinyl acetate (73.3%), sabinene (19.7%), and α-pinene (1.1%)		MH					10	99.0	
F. sinkiangensis K. M. Shen	*n*-Propyl *sec*-butyl disulfide (55.8%)	3.8	NH	HD	GC-MS	Seeds	China	26	99.1	(Li et al., 2011)
F. fukangensis K. M. Shen	*n*-Propyl *sec*-butyl disulfide (49.8%)	1.2						21	100	

F. ovina (Boiss.) Boiss.	*n*-Propyl *sec*-butyl disulfide (53.8%)	1.8						25	99.5	
F. vesceritensis coss. et Dur.	Viridiflorol (13.4%), δ-cadinene (10.1%), and farnesol (8.1%)	0.1	OS	HD	GC and GC-MS	Leaves	Algeria	89	96.8	(Benchabane et al., 2012)
F. behboudiana (Rech. f. & Esfand.) Chamberlain	A mixture of 1-*sec*-butyl-2-[(*E*)-3-(methilthio) prop-1-enyl] disulphane and 1-*sec*-butyl-2-[(*Z*)-3-(methilthio) prop-1-enyl] disulphane (59.4%), glubolol (12.5%), α-pinene (8.8%), α-bisabolol (6.1%), and β-pinene (3.9%)	0.9	NH	HD	GC, GC-MS, ^{1}H-NMR, ^{13}C-NMR, DEPT, H-H-COSY, C-H-COSY and HMBC	Aerial parts	Iran	27	97.2	(Yousefi et al., 2011)
F. lutea Poiret	2,3,6-Trimethyl benzene (25.0%), *cis*-chrysanthenol (20.8%), α-pinene (10.9%), and thymol (10.2%)	1.0	OM	HD	GC and GC-MS	Aerial parts	Algeria	21	84.9	(Chibani et al., 2012)
F. assa-foetida L.	(*E*)-1-Propenyl-*sec*-butyl disulfide (62.7%), β-ocimene (21.7%), and β-pinene (5.0%)	7.0	NH	HD	GC-MS	Latex	Iran	11	99.9	(Kavoosi et al., 2012)
F. assa-foetida L.	Sample 1 [s]: (*E*)-1-Propenyl *sec*-butyl disulfide (25.5%), (*Z*)-1-propenyl *sec*-butyl disulfide (23.0%), bis [(1-methylthio) propyl] disulfide (11.0%), bulnesol (4.3%), agaruspirol (4.0%), germacerene B (3.2%), hinesol (2.5%), and guaiol acetate (2.3%)	2.3	NH	HD	GC and GC-MS	Seeds	Iran	41	93.5	(Mirzaei and Hasanloo, 2012)
	Sample 2 [t]: (*Z*)-1-propenyl *sec*-butyl disulfide (23.9 %), bis [(1-methylthio) propyl] disulfide (19.4%), (*E*)-1-propenyl *sec*-butyl disulfide	2.85						42	97.3	

	(18.8%), bulnesol (6.7%), and α-bisabolol (3.1%)									
F. heuffelii Griseb. ex Heuffel	Elemicin (35.4%), and myristicin (20.6%)	0.08	NH	HD	GC and GC-MS	Underground parts	Serbia	67	94.4	(Pavlović et al., 2012)
F. assa-foetida L.	*epi*-α-Cadinol (23.2%), germacrene B (11.0%), α-gurjunene (6.2%), (*Z*)-1-propenyl *sec*-butyl disulfide (5.9%), 5-*epi*-7-*epi*-α-eudesmol (4.9%), δ-cadinene (4.8%), γ-cadinene (3.4%), and germacrene D (3.1%)	0.3	SH	SDSE [u]	GC-MS	Fruit	Iran	54	96.9	(Bahramia et al., 2013)
F. assa-foetida L.	(*E*)-1-Propenyl-*sec*-butyl disulfide (62.7%), β-ocimene (21.7%), and β-pinene (5.0%)	NR	NH	HD	GC-MS	Leaves and latex	Iran	NR	NR	(Kavoosi and Purfard, 2013)
F. assa-foetida L.	OGR [v]1: (*E*)-1-Propenyl *sec*-butyl disulfide (23.9%), 10-*epi*-γ-eudesmol (15.1%), (*Z*)-1-propenyl *sec* butyl disulfide (8.0%), (*Z*)-β-ocimene (5.6%), α-eudesmol (4.5%), α-pinene (4.4%), β-pinene (4.2%), β-dihydroagarofuran (4.1%), γ-eudesmol (3.5%), guaiol (3.0%), agarospiral (3.0%), limonene (2.9%), α-phellandrene (2.9%), (*E*)-β-ocimene (2.5%), 5-*epi*-7-*epi*-α-eudesmol (2.1%), and β-eudesmol (1.1%)	9.0	NH	HD	GC and GC-MS	OGR	Iran	45	99.7	(Kavoosi and Rowshan, 2013)
	OGR2: (*Z*)-1-Propenyl *sec*-butyl disulfide (27.7%),	6.0	NH					45	99.9	

	(*E*)-1-propenyl *sec*-butyl disulfide (20.3%), α-pinene (10.7%), β-pinene (10.2%), (*Z*)-β-ocimene (7.8%), 10-*epi*-γ-eudesmol (5.3%), (*E*)-β-ocimene (2.9%), and β-dihydroagarofuran (1.8%)									
	OGR3: β-Pinene (47.1%), and α-pinene (21.3%), 1, 2-dithiolane (18.6%), nitrite propyl (3.6%), thionol (2.6%), (*Z*)-β-ocimene (2.4%), and (*E*)-β-ocimene (1.4%)	4.0	MH					45	100	
F. assa-foetida L.	β-Pinene (47.1%), α-pinene (21.4%), and 1,2-dithiolane (18.6%), nitrite propyl (3.7%), thionol (2.6%), and *cis*-β-ocimene (2.4%)	NR	MH	HD	GC and GC-MS	Latex	Iran	15	98.5	(Kavoosi et al., 2013)
F. microcolea (Boiss.) Boiss	α-Pinene (27.3%), β-pinene (16.4%), nonanal (8.7%), β-caryophyllene (8.5%), and thymol (6.7%)	1.1	MH	HD	GC and GC-MS	ADHP [w]	Iran	22	93.6	(Amiri, 2014)
F. assa-foetida L.	(*E*)-1-Propenyl *sec* butyl disulphide (56.0%), 1-(1-propenylthio) propyl methyl disulfide (16.9%), and 1,2-dithiolane (5.7%) [x]	10.6	NH	HD	GC-MS	Resins	India	14	NR	(Divya et al., 2014)
	(*E*)-1-Propenyl *sec*-butyl disulfide (28.8%), (*Z*)-1-propenyl *sec*-butyl disulfide (14.4%), and 1-(1-propenythio) propyl methyl disulfide (10.1%) [y]	1.9						16	NR	
F. vesceritensis Coss. & Dur	β-Pinene (24.3%), α-pinene (17.3%), limonene (10.0%), β-myrcene (6.6%), and carotol (6.1%)	1.4	MH	HD	GC-FID and GC-MS	Seeds	Algeria	50	96	(Bouratoua et al., 2014)
F. ovina (Boiss.)	α-Pinene (25.7%), myristcin	0.28	MH	HD	GC and GC-MS	Aerial parts	Iran	14	100	(Mohammadhosse

Boiss.	(10.1%), limonene (9.6%), camphene (9.5%), δ-3-carene (9.3%), linalool (7.4%), and citronellol (5.6%)									ini and Nekoei, 2014)
	Myristcin (14.7%), limonene (12.2%), α-pinene (9.6%), myrcene (9.5%), *endo*-fenchyl acetate (5.7%), and camphene (4.3%)	0.24		SFME [z]				30	95.6	
	α-Pinene (23.9%), limonene (17.0%), myrcene (16.0%), camphene (8.3%), myristcin (4.9%), and bornyl acetate (4.0%)	0.33		MWHD [aa]				20	97.4	
	Myrcene (26.0%), α-pinene (17.6%), limonene (18.4%), camphene (4.3%), and *endo*-fenchyl acetate (3.0%)	-		HS-SPME [ab]				28	98.2	
F. orientalis L.	α-Cadinol (10.4%), δ-cadinene (8.1%), germacrene D-4-ol (6.8%), *epi*-α-muurolol (5.9%), and α-pinene (5.7%)	NR	OS	HD	GC and GC-MS	Leaves	Turkey	69	83.4	(Ozkan et al., 2014)
	α-Cadinol (11.7%), germacrene D-4-ol (11.9%), δ-cadinene (9.3%), α-pinene (7.2%), and *epi*-α-muurolol (6.1%)					Flowers		68	84.3	
F. cupularis (Boiss.) Spalik et S. R. Downie	Limonene (25.0%), δ-2-carene (15.8%), sabinene (8.0%), β-phellandrene (6.9%), α-terpinolene (5.6%), δ-3-carene (5.2%), *p*-mentha-1-en-9-ol (2.8%), and γ-terpinene (2.2%)	0.36	MH	HD	GC and GC-MS	Flowers	Iran	30	98.6	(Alipour et al., 2015)
	β-Pinene (13.9%), β-ocimene (9.0%),	0.45	MH			Leaves		36	93.7	

	bornyl angelate (6.6%), *allo*-ocimene (6.1%), *trans*-isolimonene (5.8%), dihydro-linalool acetate (5.0%), β-phellandrene (4.2%), *p*-mentha-1,5,8-triene (4.0%), α-terpinyl isobutyrate (3.7%), terpin-4-ol (3.4%), *cis*-dihydro- α-terpinyl acetate (3.1%), δ-2-carene (2.9%), camphene (2.7%), *neo*-*allo*-ocimene (2.7%), citronellyl *n*-butyrate (2.6%), decane (2.4%), and α-phellandrene (2.4%)									
	α-Terpinyl isobutyrate (8.7%), δ-3-carene (8.4%), bornyl angelate (7.4%), *trans*-sabinol (6.9%), sothol (6.0%), *p*-cymen-9-ol (5.5%), terpinyl acetate (5.2%), linalool isobutyrate (3.4%), camphor (3.0%), β-bourbonene (2.7%), *p*-menth-1-en-9-ol acetate (2.6%), citronellyl butyrate (2.6%), myrcenone (2.4%), *trans*-sabinyl acetate (2.2%), and *iso*-verbanol acetate (2.2%)	0.39	OM			Stem		32	91.9	
F. vesceritensis Coss. & Dur.	α-Pinene (32%), carotol (13.9%), fenchyl acetate (10.4%), α-phellandrene (8.5%), and aristolene (5.4%)	1.8	MH	HD	GC-FID and GC-MS	FF [ac]	Algeria	42	97.9	(Labed-Zouad et al., 2015)
	α-Phellandrene (24.3%), α-	1.6	MH			DF [ad]		37	88.6	

	pinene (16.1%), carotol (10.7%), and elixene (6.3%)									
	Carotol (18.8%), α-pinene (11.5%), β-pinene (8.1%), caryophyllene oxide (7.6%), fenchyl acetate (7.3%), aristolene (7.2%), and elixene (5.4%)	1.6	OS			FS [ae]		48	96.4	
	α-Pinene (17.4%), carotol (10.8%), β-pinene (8.9%), fenchyl acetate (8.8%), and aristolene (6.8%)	1.4	MH			DS [af]		36	87.4	
	S1: (*E*)-Propenyl *sec*-butyl disulfide (40.4%), (*Z*)-propenyl *sec*-butyl disulfide (23.1%), β-pinene (9.7%), (*E*)-β-ocimene (5.5%), and α-pinene (4.7%) [ag]	7.79	NH	HD	GC and GC-MS	Resin	Iran	18	97.4	(Moghaddam and Farhadi, 2015)
	S2: (*E*)-Propenyl *sec*-butyl disulfide (40.3%), (*Z*)-propenyl *sec*-butyl disulfide (22.1%), β-pinene (10.7%), α-pinene (5.0%), *n*-propyl *sec*-butyl disulfide (4.1%), and (*E*)-β-ocimene (3.2%) [ah]	10.07						24	97.7	
	S3: (*E*)-Propenyl *sec*-butyl disulfide (44.4%), (*Z*)-propenyl *sec*-butyl disulfide (22.8%), β-pinene (9.6%), (*E*)-β-ocimene (6.3%), and α-pinene (4.2%) [ai]	8.52						16	97.2	
	S4: (*E*)-Propenyl *sec*-butyl disulfide (50.0%), β-pinene (14.9%), (*Z*)-propenyl *sec*-butyl disulfide (13.5%), α-pinene (5.1%), *n*-propyl *sec*-butyl disulfide (3.6%), and (*E*)-β-ocimene (2.6%) [aj]	7.39						22	98.9	
	S5: (*E*)-Propenyl *sec*-butyl disulfide (49.1%), (*Z*)-	8.36						19	97.3	

	propenyl *sec*-butyl disulfide (12.1%), β-pinene (12.0%), α-pinene (6.2%), *n*-propyl *sec*-butyl disulfide (3.7%), and (*E*)-β-ocimene (2.5%) [ak]									
	S6: (*E*)-Propenyl *sec*-butyl disulfide (37.3%), (*Z*)-propenyl *sec*-butyl disulfide (17.8%), β-pinene (11.8%), α-pinene (6.7%), (*E*)-β-ocimene (4.0%), and *n*-propyl *sec*-butyl disulfide (2.5%) [al]	7.24						27	96.3	
	S7: (*E*)-Propenyl *sec*-butyl disulfide (42.6%), (*Z*)-propenyl *sec*-butyl disulfide (17.2%), β-pinene (14.4%), α-pinene (5.1%), *n*-propyl *sec*-butyl disulfide (5.0%), and (*E*)-β-ocimene (2.6%) [am]	8.10						16	98.1	
	S8: (*E*)-Propenyl *sec*-butyl disulfide (52.2%), (*Z*)-propenyl *sec*-butyl disulfide (13.2%), β-pinene (9.5%), α-pinene (4.2%), *n*-propyl *sec*-butyl disulfide (4.0%), and (*E*)-β-ocimene (2.9%) [an]	8.53						30	99.0	
	S9: (*E*)-Propenyl *sec*-butyl disulfide (54.0%) and (*Z*)-propenyl *sec*-butyl disulfide (12.7%), β-pinene (8.0%), α-pinene (5.6%), *n*-propyl *sec*-butyl disulfide (4.0%), and (*E*)-β-ocimene (3.0%) [ao]	9.52						26	97.3	
F. gummosa Boiss.	γ-Elemene (14.1%), germacrene B (11.8%), (*E*)-γ-bisabolene (10.7%), viridiflorene (8.1%), and	0.32	SH	HD	GC and GC-MS	Aerial parts	Iran	42	96.5	(Mohammadhosseini et al., 2015)

	epizonaren (6.2%)									
	Aromadendrene (17.6%), germacrene B (16.2%), γ-elemene (6.5%), (*E*)-γ-bisabolene (6.3%), and β-elemene (5.1%)	0.4	SH	SFME				39	98.4	
F. lutea (Poir.) Maire	δ-3-Carene (72.6%), α-pinene (5.8%), myrcene (5.1%), and α-phellandrene (4.0%)	0.09	MH	HD	GC(FID), GC-MS and ^{13}C-NMR	Roots	Tunisia	9	95.1	(Ben Salem et al., 2016)
F. alliacea Boiss.	10-*epi*-γ-Eudesmol (22.3%), valerianol (12.5%), hinesol (8.3%), guaiol (7.3%), and *Z*-propenyl-*sec*-butyl trisulphide (6.5%)	0.13	OS	HD	GC-MS	Roots	Iran	76	99.5	(Kasaian et al., 2016)
F. communis L.	α-Pinene (10.5%), hedycariol (8.4%), and γ-terpinene (7.6%)	0.13	MH	HD	GC-FID and GC-MS	Flowers	Italy	80	95.1	(Maggi et al., 2016)
	α-Pinene (55.9%), β-pinene (16.8%), and myrcene (5.9%)	0.03	MH			Fruits		102	97.7	
	β-Eudesmol (12.1%), α-eudesmol (12.1%), and hedycariol (10.3%)	0.06	OS			Leaves		73	95.5	
	(*E*)-β-Farnesene (9.5%), β-cubebene (8.2%), and (*E*)-caryophyllene (7.2%)	0.02	SH			Roots		50	70.9	
F. communis L.	Camphor (18.3%), α-pinene (15.3%), β-eudesmol (9.3%), caryophyllene oxide (8.0%), and myrcene (5.0%)	0.18	OS	HD	GC and GC-MS	Flowers	Tunisia	32	97.3	(Nguir et al., 2016)
	β-Eudesmol (28.1%), δ-eudesmol (11.1%), and α-eudesmol (9.6%)	0.15	OS			Stems		39	91.3	
	Dillapiole (7.9%), guaiol (7.3%), spathulenol (6.8%), myristicin (6.0%), and T-cadinol (5.9%)	0.024	OS			Roots		20	90.4	

	α-Eudesmol (25.2%), β-eudesmol (20.7%), δ-eudesmol (10.1%), and caryophyllene oxide (7.2%)	0.11	OS			Leaves		28	94.7	
F. communis L.	Bizerte: Chamazulene (9.3%), α-humulene (6.4%), α-cubebene (6.4%) and caryophyllene (4.0%)	0.022	SH	HD	GC-MS	Leaves	Tunisia	53	88.9	(Rahali et al., 2016)
	Rades: α-Terpinene (7.4%) and germacrene B (7.1%)	0.38	SH					54	78.70	
	Gammarth: α-Eudesmol (12.3%), caryophyllene oxide (5.5%), α-pinene (5.0%), *ar*-curcumene (5.0%), γ-cadinene (5.0%) and γ-terpinene (5.0%)	0.22	OS					59	75.5	
	Soliman:	0.11	OS					97	98.7	
F. akitschkensis B.Fedtsch. ex Koso-Pol.	Sabinene (58.7%), α-pinene (15.4%), β-pinene (8.5%), terpinen-4-ol (3.9%), eremophilene (1.4%), 2-himachalen-7-ol (1.3%), and *trans*-sabinene hydrate (1.0%)	0.7	MH	HD	GC and GC-MS	Umbels + seeds	Kazakhstan	52	98	(Schepetkin et al., 2016)
	Myristicin (67.9%), and elemicine (0.8%)	0.02	NH			Stems		21	96.6	
F. clematidifolia Koso-Pol.	Myrcene (34.3%), limonene (30.1%), sabinene (16.5%), β-phellandrene (7.0%), α-pinene (2.5%), and β-pinene (1.6%)	0.1	MH	HD	GLC-MS	Leaves	Tajikistan	29	100	(Sharopov et al., 2016)
	β-Pinene (36.9%), α-pinene (29.3%), sabinene (8.1%),bicyclogermacrene (5.5%), myrcene (3.9%), germacrene D (3.2%), and (3*E*,5*Z*)-1,3,5-undecatriene (2.0%)	0.4				Roots		33	99.4	
F. gummosa	β-Pinene (50.1%), α- pinene (14.9%), δ-3-Carene	NR	MH	HD	GC-MS	Resins	Iran	17	98	(Fatemikia et al., 2017)

Boiss.	(6.7%), α-thujene (3.3%), sabinene (3.1%), and *allo*-ocimene (2.9%)									
F. gummosa Boiss.	β-Pinene (31.8%), α-pinene (11.4%), β-eudesmol (8.9%), and caryophyllenol (7.4%)	0.22	MH	HD	GC-MS	Roots	Iran	31	97.9	(Najafabadi et al., 2017)
	β-Pinene (23.9%), α-pinene (13.0%), β-eudesmol (8.4%), and α-bisabolol (6.7%)	0.36				Stems		35	94.2	
	β-Pinene (36.3%), α-pinene (16.3%), limonene (3.7%), and α-bisabolol (3.6%)	1.2				Flowers		33	90.9	
	β-Pinene (20.2%), α-pinene (8.9%), bornyl acetate (9.9%), and fenchyl acetate (8.4%)	0.1				Leaves		34	90.2	
	β-Pinene (38.6%), α-pinene (13.0%), β-eudesmol (7.5%), and fenchyl acetate (6.9%)	14.7				Galbanum		32	98.4	
F. tingitana L.	α-Thujene (13.5%), elemol (8.9%), and cadinol (2.2%)	0.06	OS	HD	GC-MS	Flowers	Libya	28		(Elghwaji et al., 2017)
	Cadinol (13.8%), eudesmol (9.7%), elemol (8.3%), and α-thujene (2.3%),	0.1	OS			Leaves		32		
F. iliensis Krasn. ex Korov	(*E*)-Propenyl *sec*-butyl disulfide (15.7-39.4%) and (*Z*)-propenyl *sec*-butyl disulfide (23.4-45.0%) [ap]	NR	NH [aq]	HD	GC-MS	Dried plant material	Kazakhstan	25-46	84-91.7	(Özek et al., 2017)
F. tunetana Pomel ex Batt.	α-Pinene (39.8%), β-pinene (11.5%), and (Z)-β-ocimene (7.5%)	0.12	MH	HD	GC, GC-MS and ^{13}C-NMR	Seeds	Tunisia	18	84.6	(Znati et al., 2017)

[a] YEO: Yield of essential oil; [b] MH: Monoterpene hydrocarbon; [c] HD: Hydrodistillation; [d] NH: Non-terpene hydrocarbon; [e] OS: Oxygenated sesquiterpene; [f] EO: Essential oil; [g] EE: Etheric extract; [h] PE: Petrolic extract; [i] ME: Methanol extract; [j] OM: Oxygenated monoterpene; [k] NR: Not reported; [l] Over run 1-9; [m] SFE: Supercritical fluid extraction; [n] Syn. *F. khorasanica* Rech. F. et Aell. and *F. microloba* Boiss.; [o] SH: Sesquiterpene hydrocarbon; [p] Formerly considered as a subspecies of *F. communis*; [q] From Gonabad, Iran; [r] From Tabas, Iran; [s] From Razavi Khorsan Province, Iran (Tabas); [t] From Kohsorkhe-Kasmar, Iran; [u] SDSE: Steam distillation solvent extraction method; [v] OGR: Oleo-gum-resin; [w] ADHP: Air-dried herbal parts; [x] From Pathani, India; [y] From Irani, India; [z] SFME: Solvent free microwave extraction; [aa] MWHD: Microwave hydrodistillation; [ab] HS-SPME: Headspace-solid phase microextraction; [ac] FF: Fresh flowers; [ad] DF: Dry flowers; [ae] FS: Fresh stems; [af] DS: Dry stems; [ag] S1: From Koohpaye, Iran; [ah] S2: From

Jangale Ghaem, Iran; [ai] S3: From Joopar, Iran; [aj] S4: From Khomroot, Iran; [ak] S5: From Pabdana, Iran; [al] S6: From Rayen, Iran; [am] S7: From Sardoo, Iran; [an] S8: From Sirjan, Iran; [ao] S9: From Shahr Babak, Iran; [ap] From flowers, leaves, stems, roots in the flowering period as well as seeds and umbels (fruits) together with roots in the fruiting period; [aq] Mainly composed of sulfur-containing compounds

Fig. 1. The photographs taken from *F. assa-foetida* L., A: in the marginal parts of Semnan province, Iran; B: separated leaves and flowers; C: fresh aerial parts.

Fig. 2. A: Photograph of *F. assa-foetida* L. taken by E. Karimi (PhD candidate in agriculture) in the full flowering stage, B and C: local foods prepared by dried stems and aerial parts of *F. assa-foetida* L.

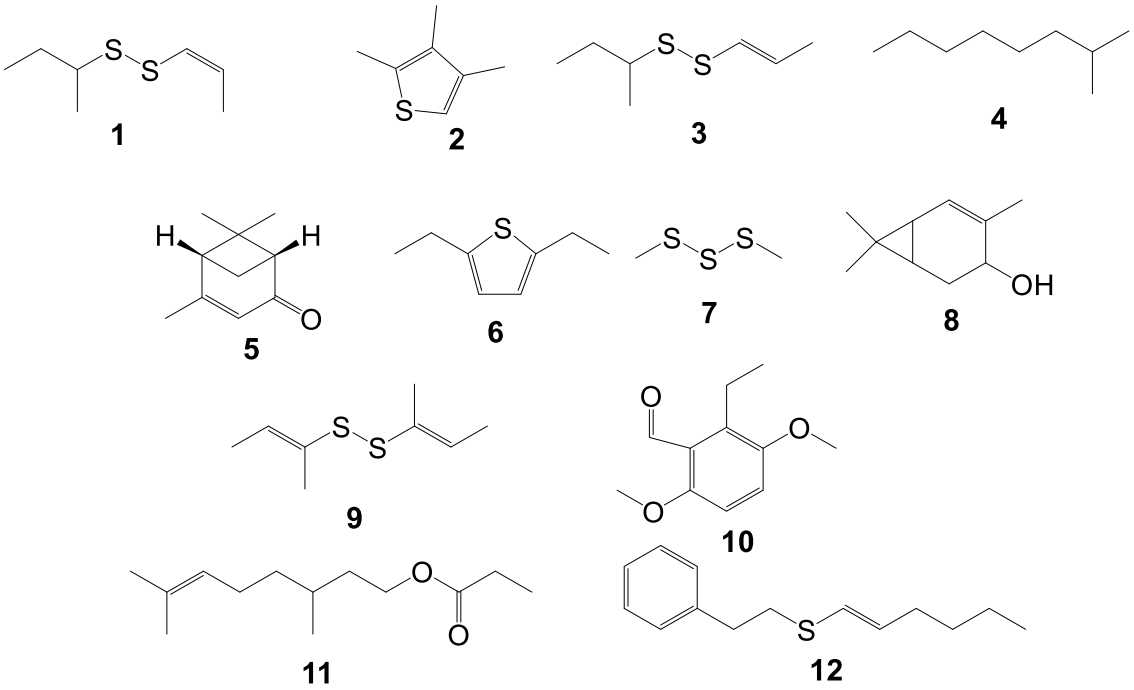


Fig. 3 Sulfur-containing, aliphatic, cyclic and aromatic compounds identified in the essential oils of 18 *Ferula* species: (*Z*)-1-(*sec*-butyl)-2-(prop-1-en-1-yl)disulfane (**1**), 2,3,4-trimethylthiophene (**2**), (*E*)-1-(*sec*-butyl)-2-(prop-1-en-1-yl)disulfane (**3**), 2-methyloctane (**4**), (1*R*,5*R*)-4,6,6-trimethylbicyclo[3.1.1]hept-3-en-2-one (**5**), 2,5-diethylthiophene (**6**), 1,3-dimethyltrisulfane (**7**), 4,7,7-trimethylbicyclo[4.1.0]hept-4-en-3-ol (**8**), 1,2-di((*E*)-but-2-en-2-yl)disulfane (**9**), 2-ethyl-3,6-dimethoxybenzaldehyde (**10**), 3,7-dimethyloct-6-en-1-yl propionate (**11**) and (*E*)-hex-1-en-1-yl(phenethyl)sulfane (**12**) (Kanani et al., 2011).

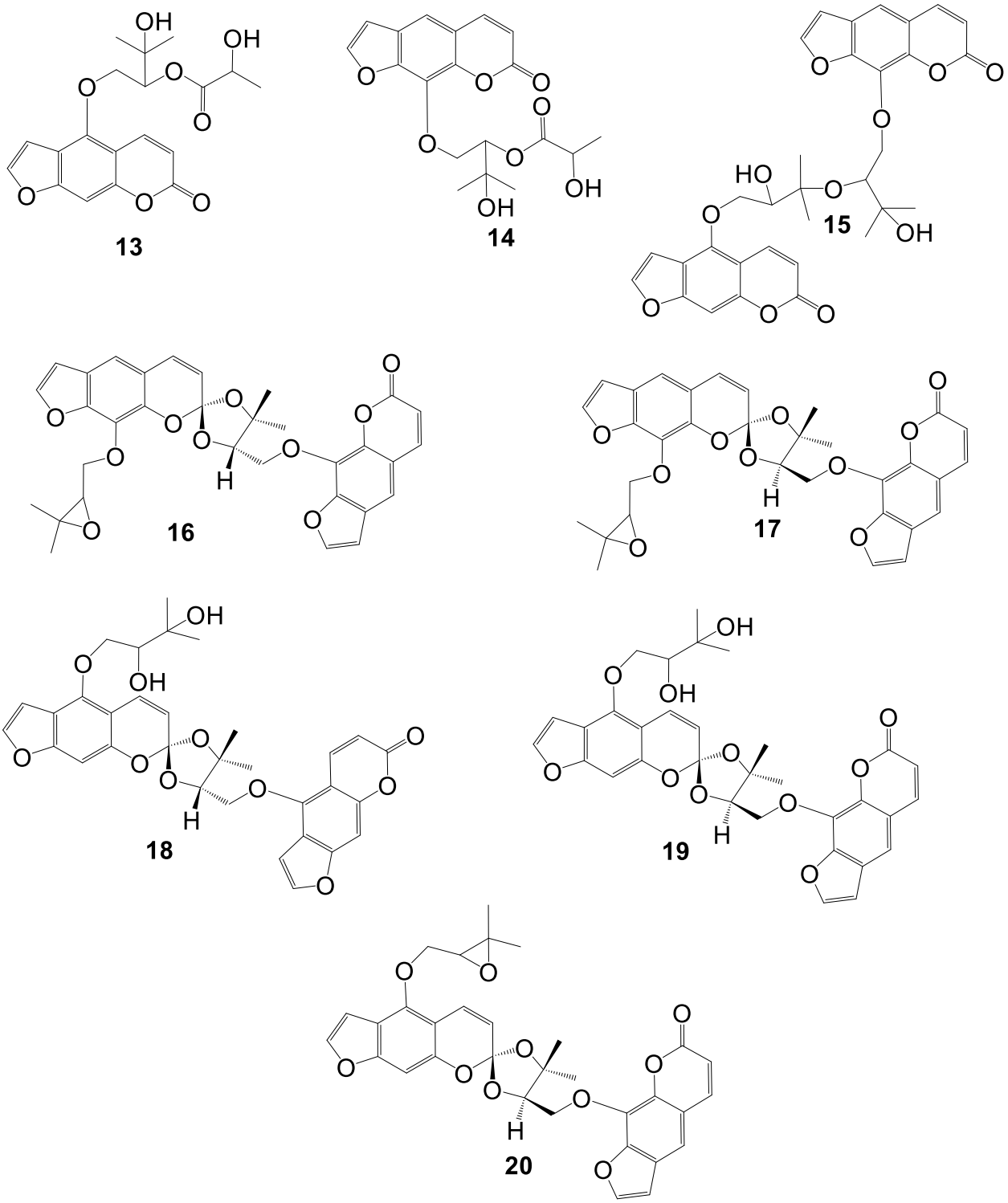
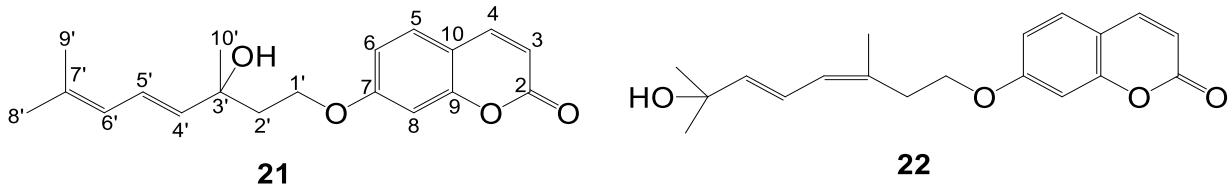


Fig. 4. Eight bioactive hemiterpene coumarin derivatives, fesumtuorin A-H (**13-20**), separated from *F. sumbul* (Kauffm.) Hook.f. (Zhou et al., 2000).



21 **22**

Fig. 5. The molecular structures of the isolated ferulagol A (**21**) and ferulagol B (**22**) in the extract of *F. assa-foetida* L. (roots) (El-Razek et al., 2001).

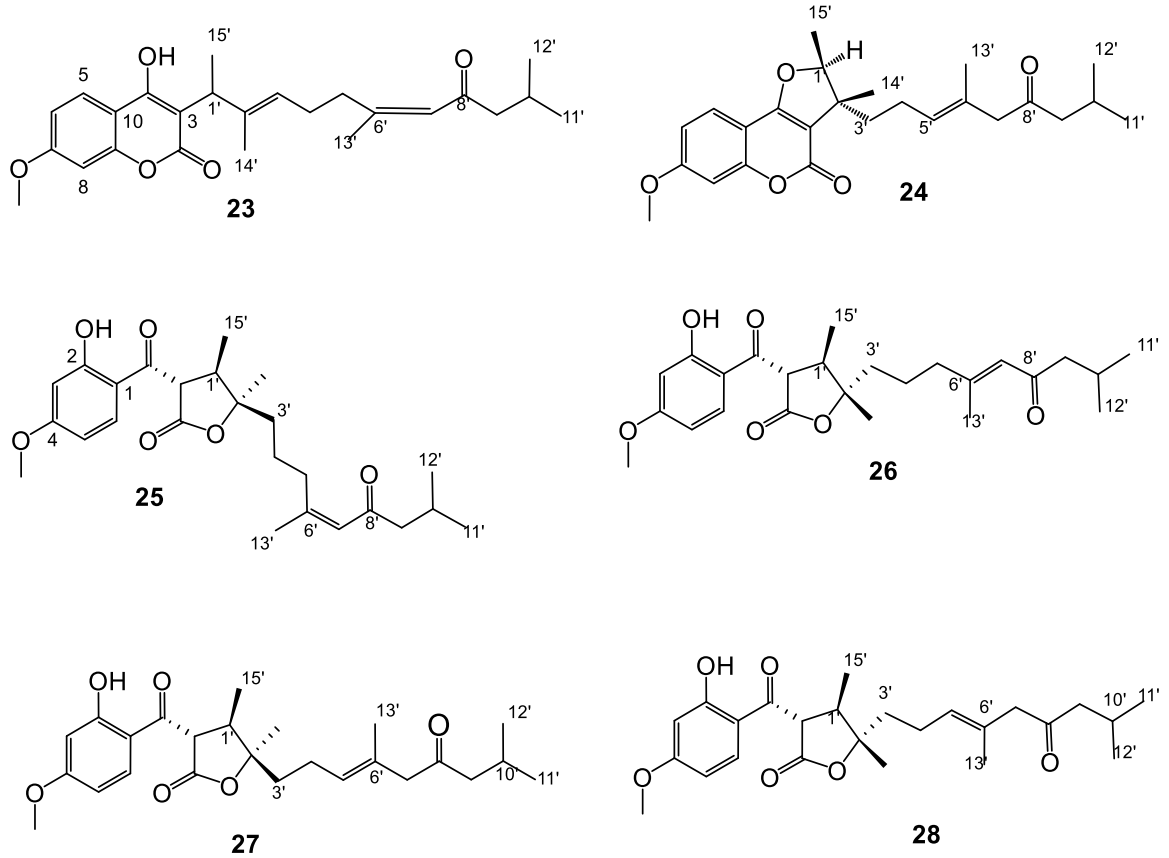


Fig. 6. The characterized sesquiterpenoids pallidones A-F (**23-28**) and isolated in the ethyl acetate extract obtained from *F. pallida* Korovin roots (Su et al., 2000).

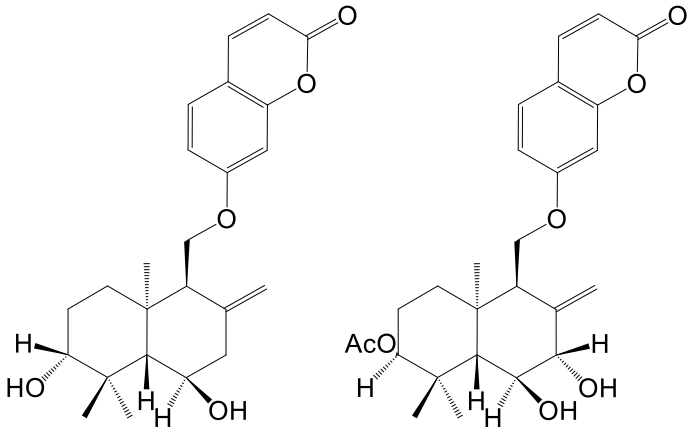


Fig. 7. The molecular structures of the isolated assafoetidnol A (**29**) and assafoetidnol B (**30**) in the extract of *F. assa-foetida* L. (roots) (Abd El-Razek et al., 2001).

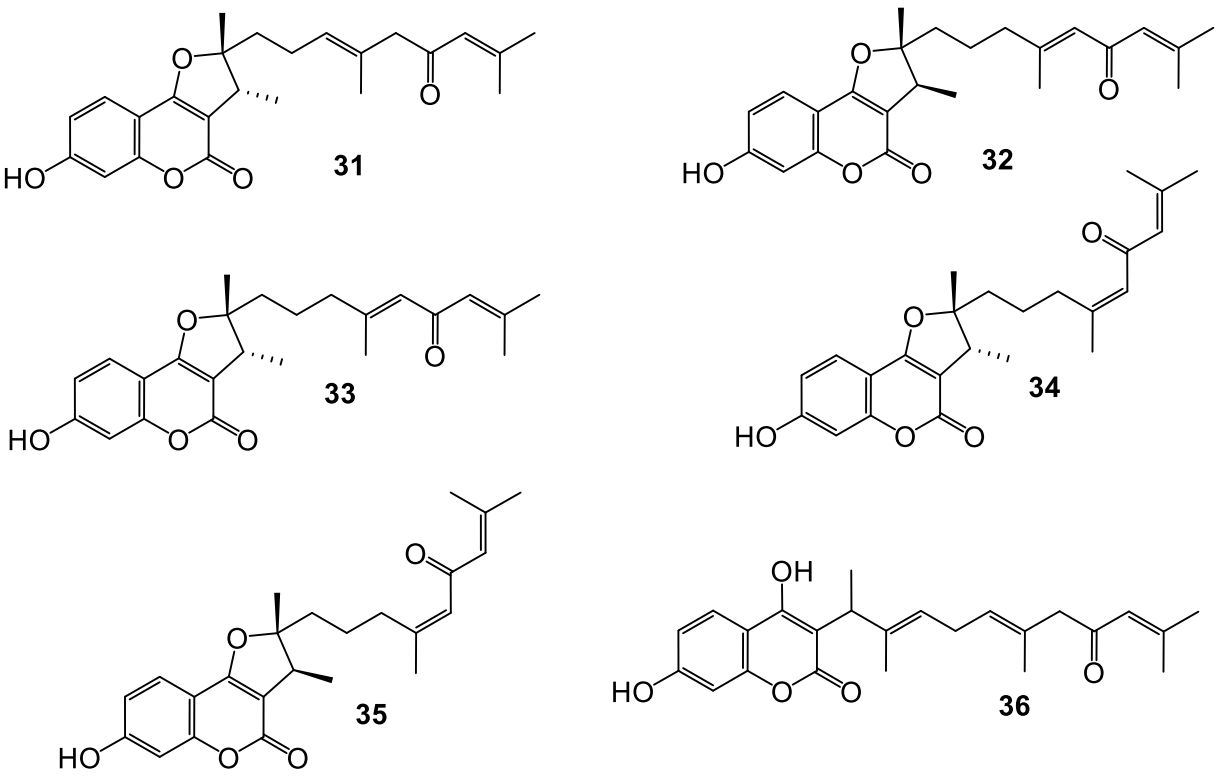


Fig. 8. The main bioactive compounds (**31-36**) separated from *F. fukanensis* K.M.Shen (Motai et al., 2004).

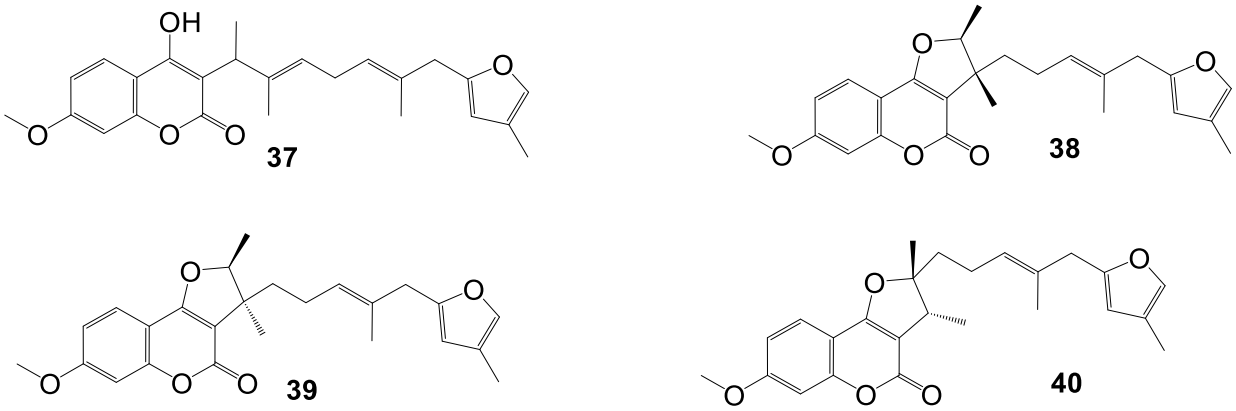


Fig. 9. The molecular structures of the four sesquiterpene coumarins (**37-40**) obtained from the 80% aqueous methanol extract of the roots of *F. fukanensis* K.M.Shen (Motai and Kitanaka, 2004).

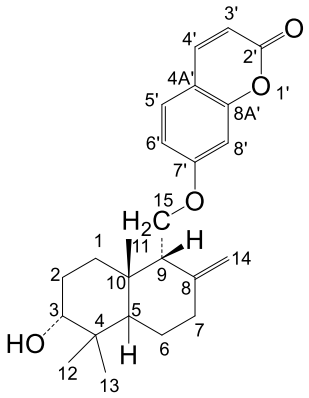


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Fig. 10. The molecular structure of saradaferin (**41**) separated from the EtOAc extract of *F. assa-foetida* L. (OGR) (Bandyopadhyay et al., 2006).

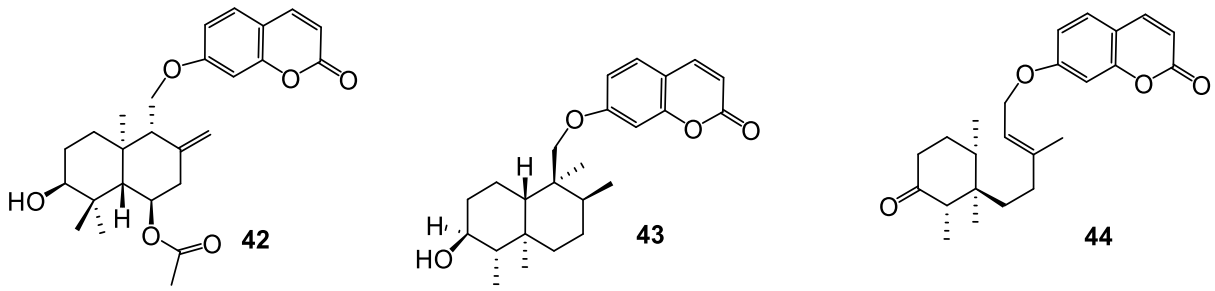


Fig. 11. The sesquiterpenoid coumarins (**42**-**44**) isolated from the ethanol extract obtained from *F. teterrima* Kar. & Kir. and *F. sinkiangensis* K. M. Shen roots (Yang et al., 2006).

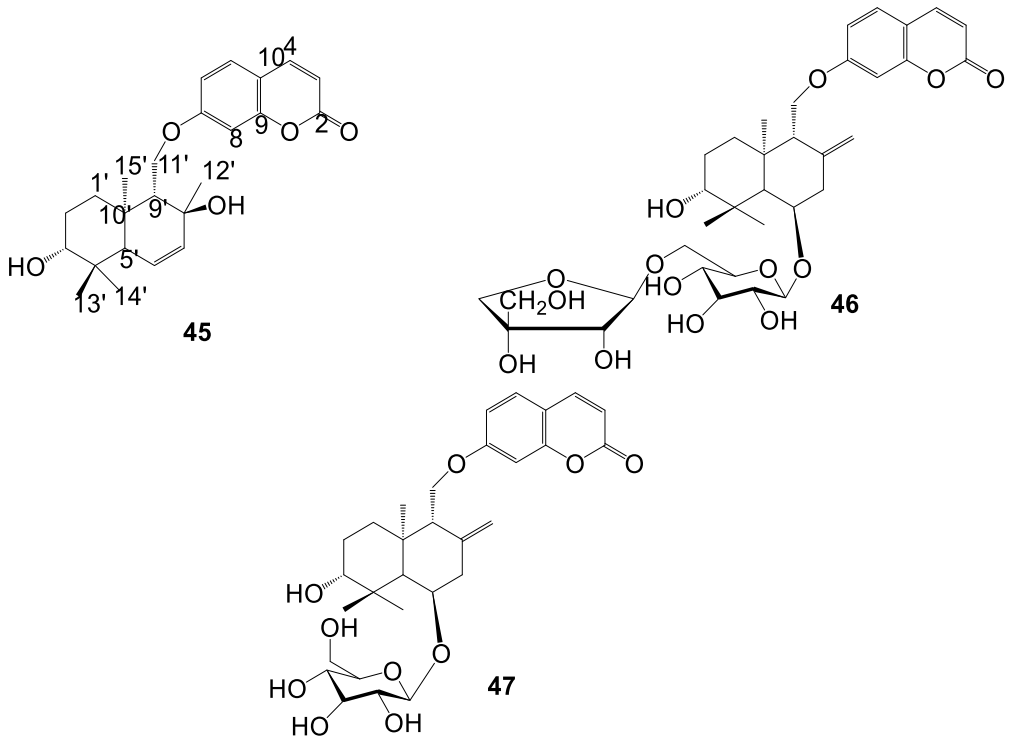


Fig. 12. The main sesquiterpene derivatives (**45**-**47**) characterized in the methanol extract from the roots of *F. gummosa* Boiss. (Iranshahi et al., 2010a).

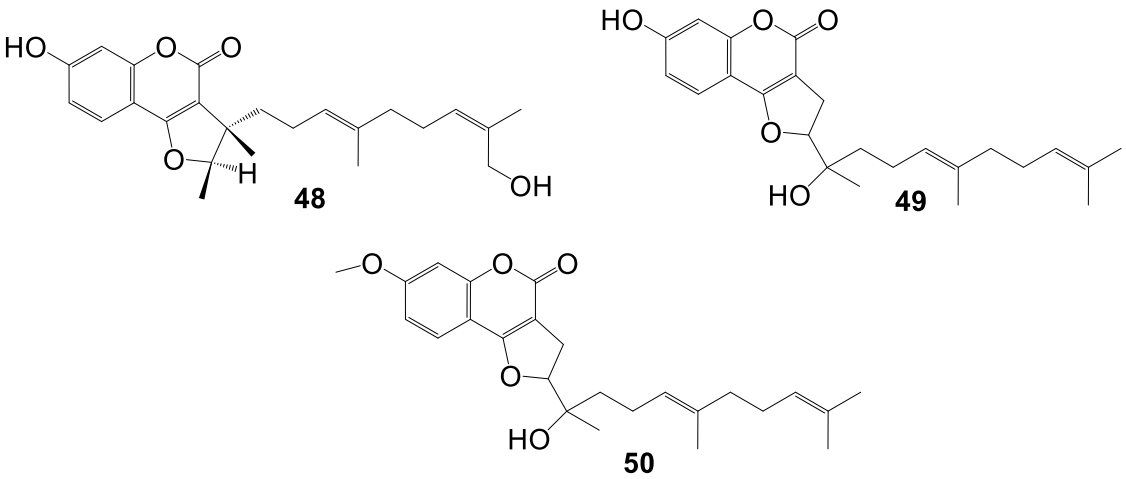


Fig. 13. The molecular structures of three newly characterized sesquiterpenoid coumarins, ferulin A-C (**48**-**50**), extracted from the roots of *F. ferulaeoides* (Steud.) Korov (Meng et al., 2013a).

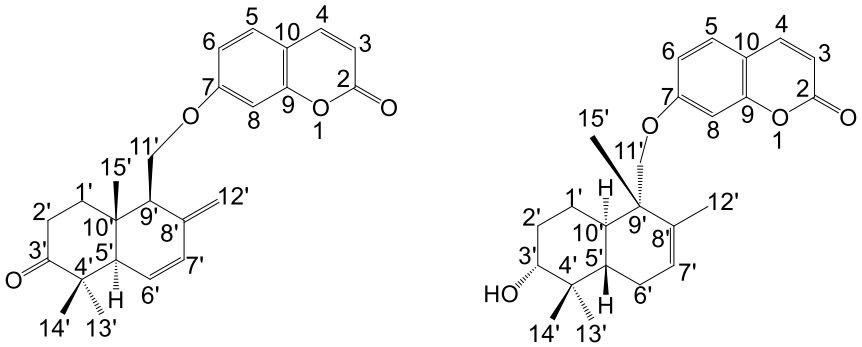


Fig. 14. The structures of sesquiterpene coumarins (**51**-**52**) from *F. narthex* Boiss (Bashir et al., 2014a).

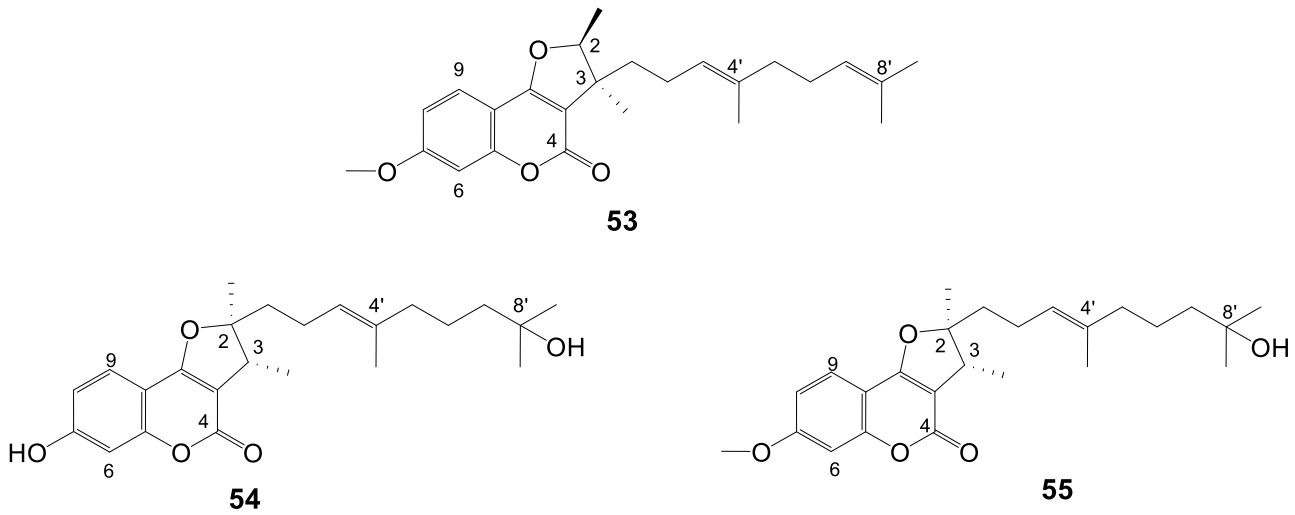


Fig. 15. The structures of the three sesquiterpenoid coumarins (**53-55**) separated from the roots of *F. ferulioides* (Steud.) Korovin (Liu et al., 2015).

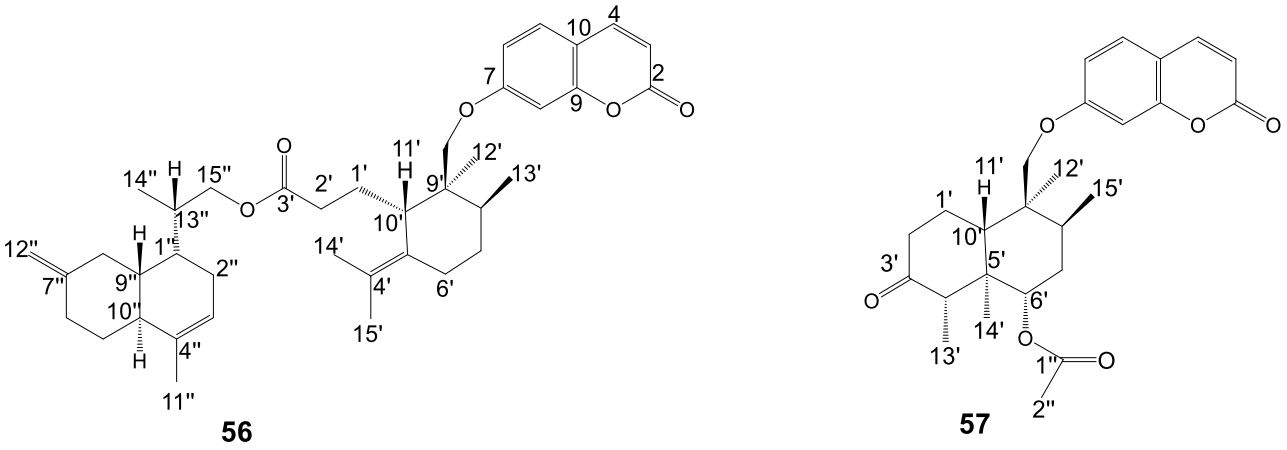
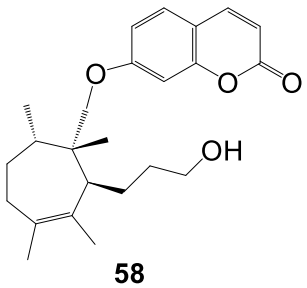
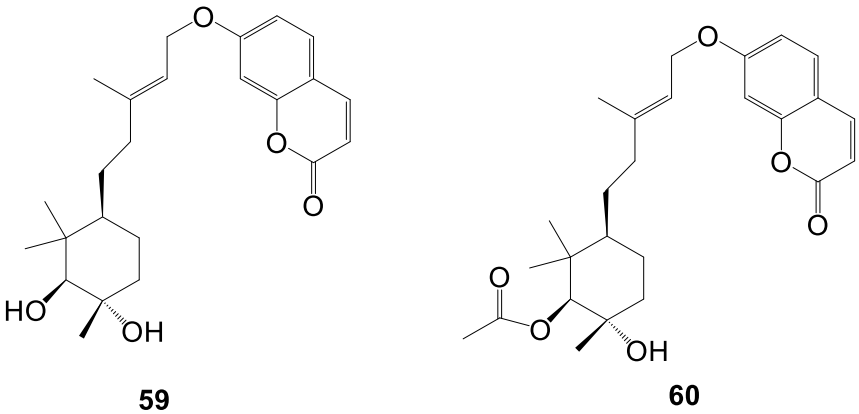


Fig. 16. The molecular structures of newly characterized disesquiterpene coumarins (**56**-**57**) separated from *F. pseudalliacea* Rech.f. (Dastan et al., 2012).



58

Fig. 17. The molecular structure of sinkiangenorin D (**58**) as a newly characterized sesquiterpene coumarin separated from the seeds of *F. sinkiangensis* K. M. Shen (Li et al., 2015a).



59 **60**

Fig. 18. The sesquiterpene coumarins (**59**-**60**) isolated from *F. sinkiangensis* K. M. Shen (Li et al., 2015b).

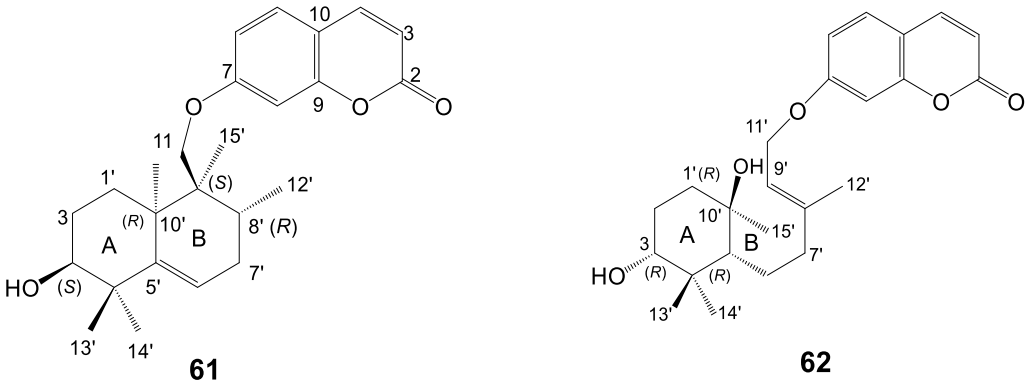
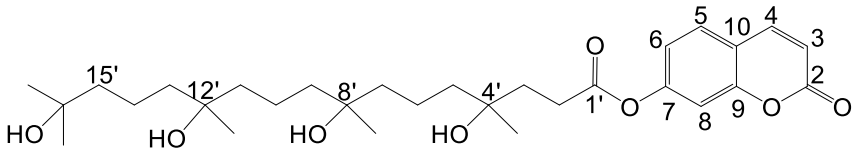
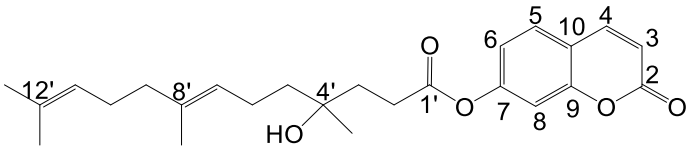


Fig. 19. The main bioactive compounds (**61-62**) separated from *F. sinkiangensis* K. M. Shen (Xing et al., 2017).

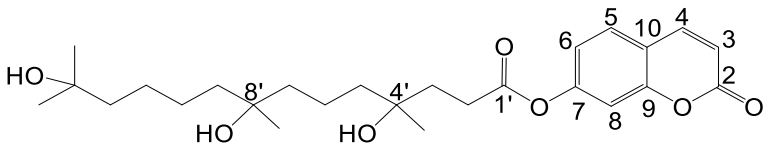


63



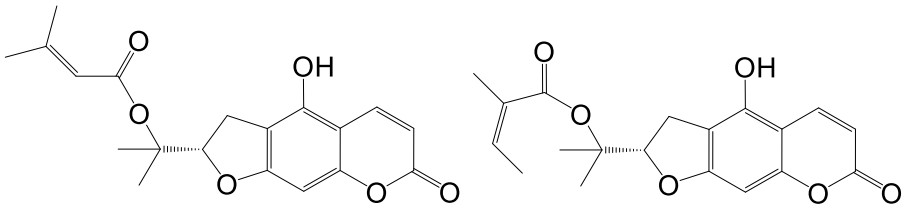
64

Fig. 20. The molecular structures of characterized coumarin esters derivatives (**63**-**64**) separated from *F. orientalis* L. (Razavi et al., 2016).



65

Fig. 21. The molecular structure of ferulone C (**65**), a ester coumarin, isolated from roots of *F. persica* Wild (Razavi and Janani, 2015).



66 **67**

Fig. 22. The molecular structures of the two dihydrofuranocoumarin esters obtained from the roots of *F. lutea* (Poir.) Maire, (−)-5-hydroxyprantschimgin (**66**) and (−)-5-hydroxydeltoin (**67**) (Ben Salem et al., 2013).

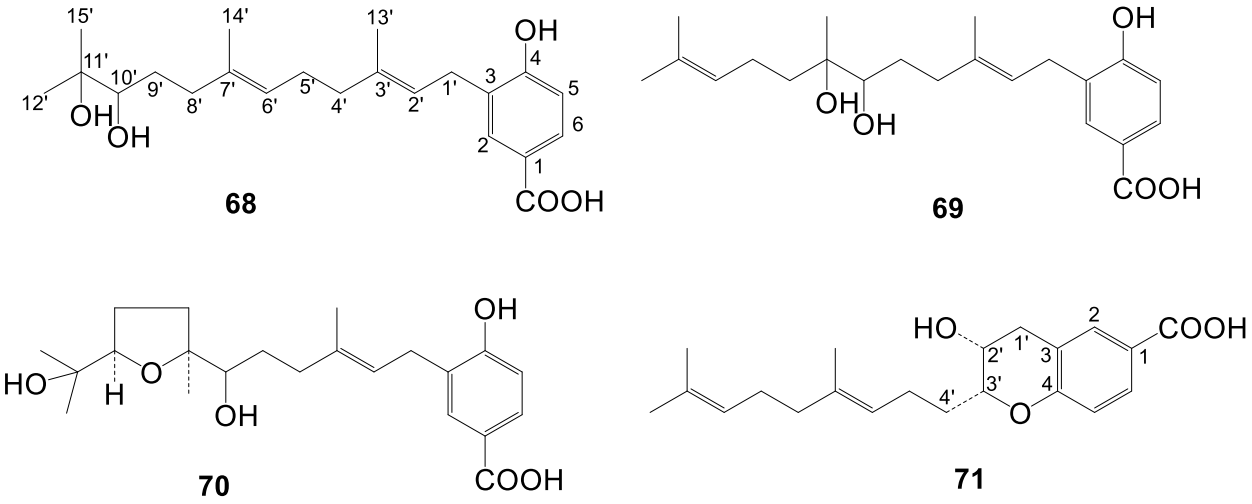


Fig. 23. The molecular structures of kuhistanols A-D (**68-71**) from *F. kuhistanica* Korovin (Chen et al., 2000a).

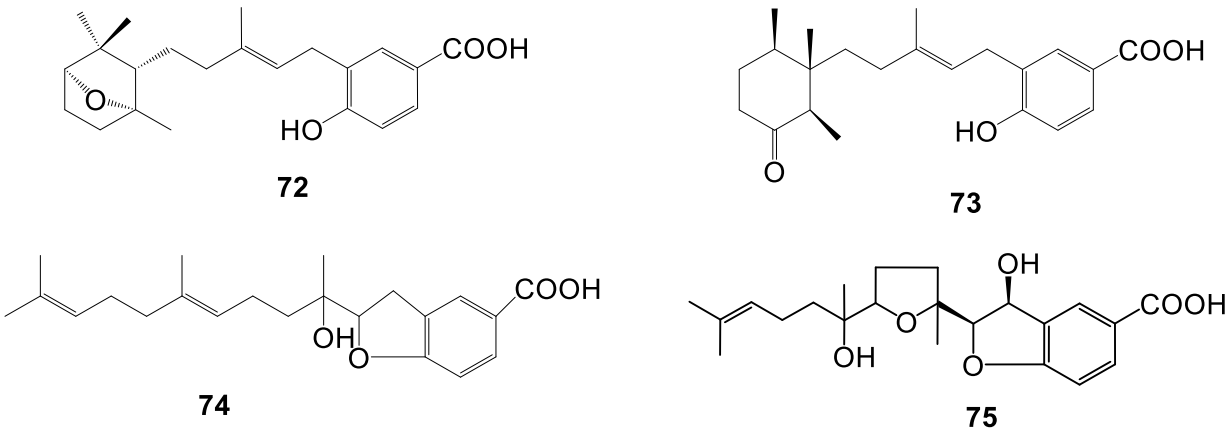


Fig. 24. The molecular structures of the farnesyl hydroxybenzoic acid derivatives (**72-75**) in the *F. kuhistanica* Korovin MeOH extract of roots (Chen et al., 2001).

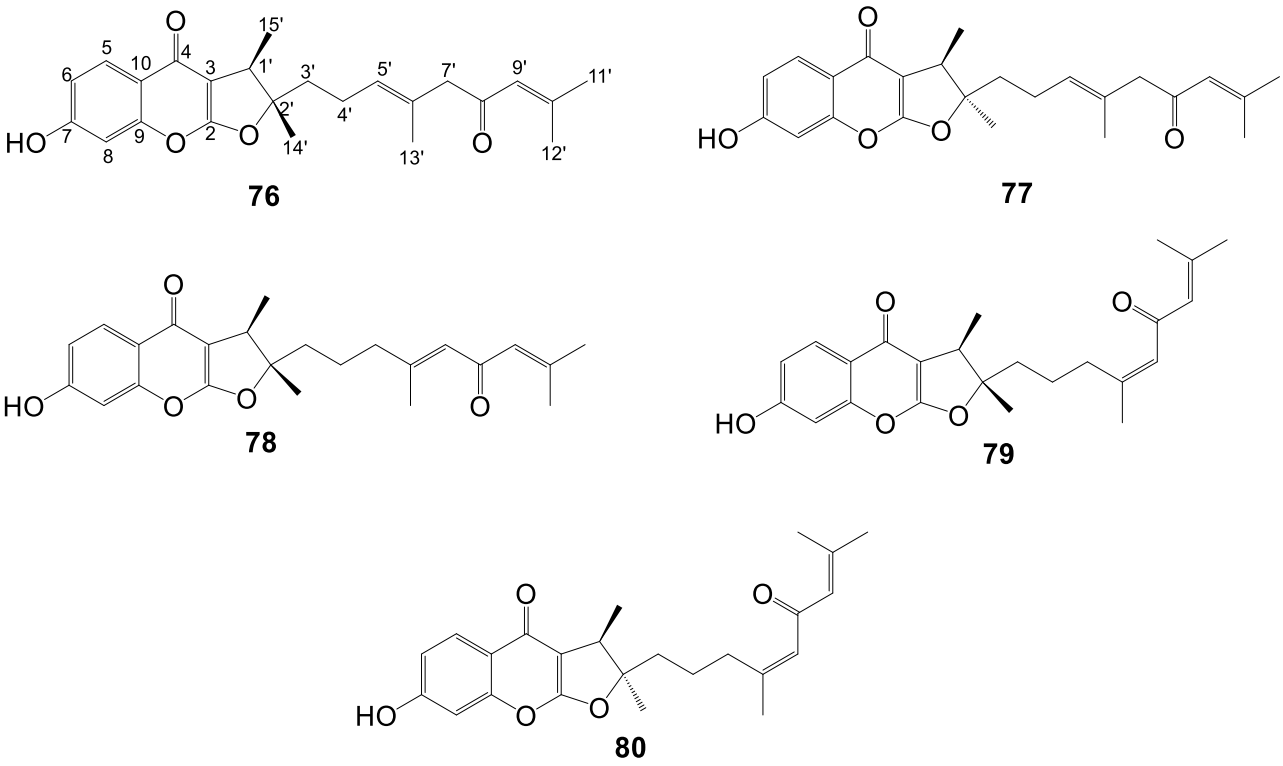


Fig. 25. The main sesquiterpene chromone derivatives (**76-80**) separated from a water-methanol extract of *F. fukanensis* K.M.Shen (roots) (Motai and Kitanaka, 2005a).

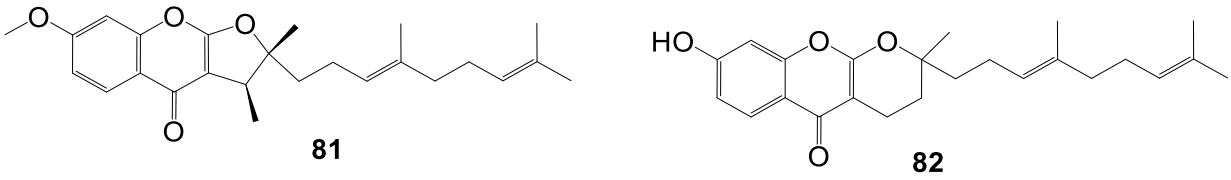


Fig. 26. The molecular structures of the two sesquiterpene chromone derivatives, ferulin D,E (**81**-**82**) extracted from the roots of *F. ferulaeoides* (Steud.) Korov (Meng et al., 2013a).

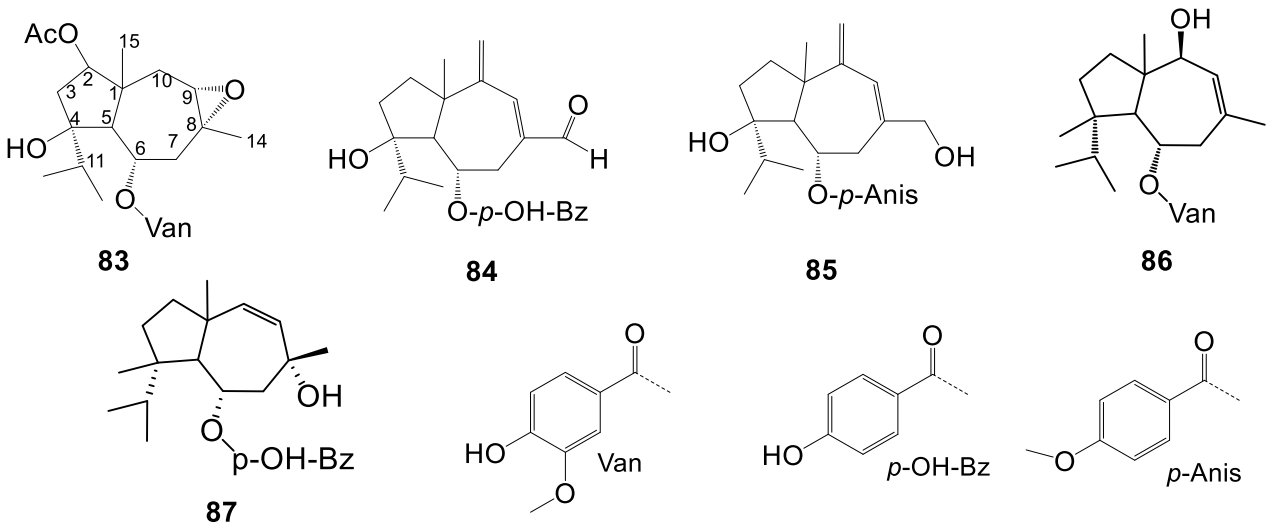
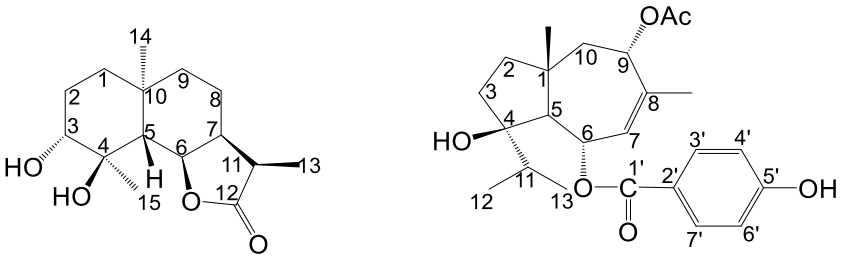
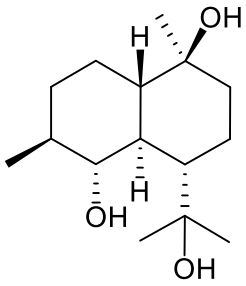


Fig. 27. The molecular structures of five daucane-type sesquiterpenes (**83-87**) characterized in the methanolic extract of *F. kuhistanica* Korovin (stems and roots) (Chen et al., 2000b).



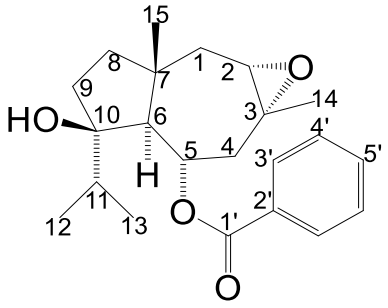
88 **89**

Fig. 28. The molecular structures of the eudesmanolide (**88**) and carotene (**89**) derivatives in the organic extract of *F. sinaica* Boiss. (Ahmed et al., 2001).



90

Fig. 29. The molecular structure of (1*S*,4*S*,5*R*,6*S*,7*S*,10*S*)-5,10,11-cadinanetriol (**90**) separated from an acetone extract of the air-dried ground roots of *F. communis* L (Appendino et al., 2001).



91

Fig. 30. The molecular structure of 2,3-α-epoxyjaeschkeanadiol-5-benzoate (**91**) separated from a methylene chloride extract of *F. hermonis* Boiss (roots) (Diab et al., 2001).

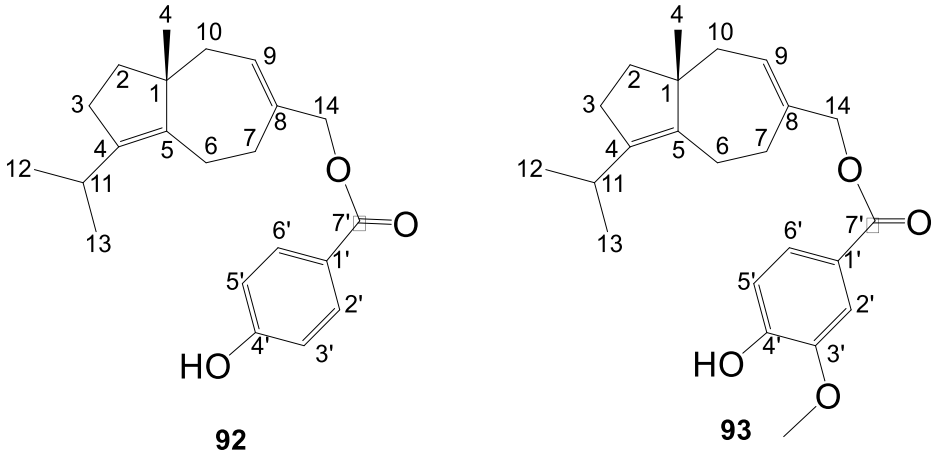


Fig. 31. The main daucane esters (**92-93**) separated from a hexane extract of *F. hermonis* Boiss (roots) (Galal et al., 2001).

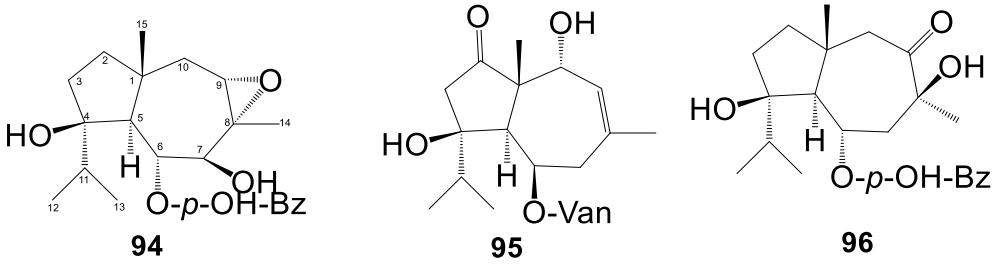


Fig. 32. The main daucane esters (**94-96**) separated from an EtOAc extract of *F. kuhistanica* Korovin. (dried fruits) (Tamemoto et al., 2001).

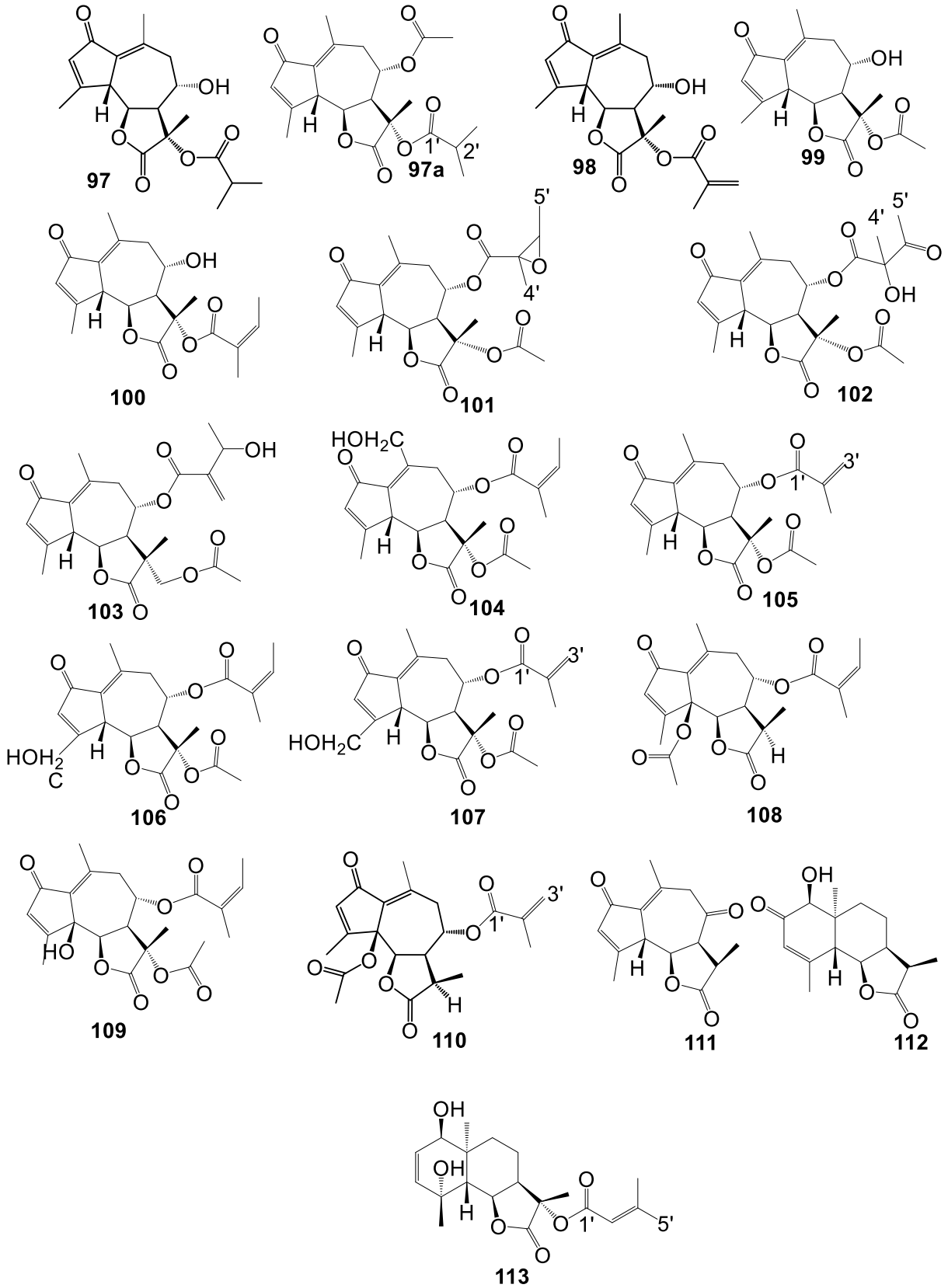


Fig. 33. Seventeen bioactive sesquiterpene compounds (**97-113**) separated from *F. penninervis* Regel and Schmalh (Shikishima et al., 2002).

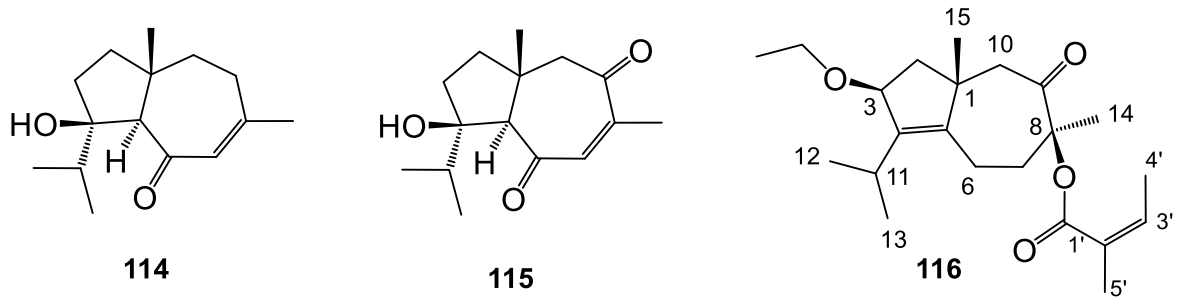


Fig. 34. The molecular structures of three daucane sesquiterpenes (1*R*,4*R*)-4-hydroxydauca-7-ene-6-one (**114**), (1*R*,4*R*)-4-hydroxydauca-7-ene-6,9-dione (**115**), and (1*R*,3*S*,8*S*)-3-ethoxy-8-angeloyloxydauca-4-en-9-one (**116**), separated from an hexane extract of *F. hermonis* Boiss (roots) (Lhuillier et al., 2005).

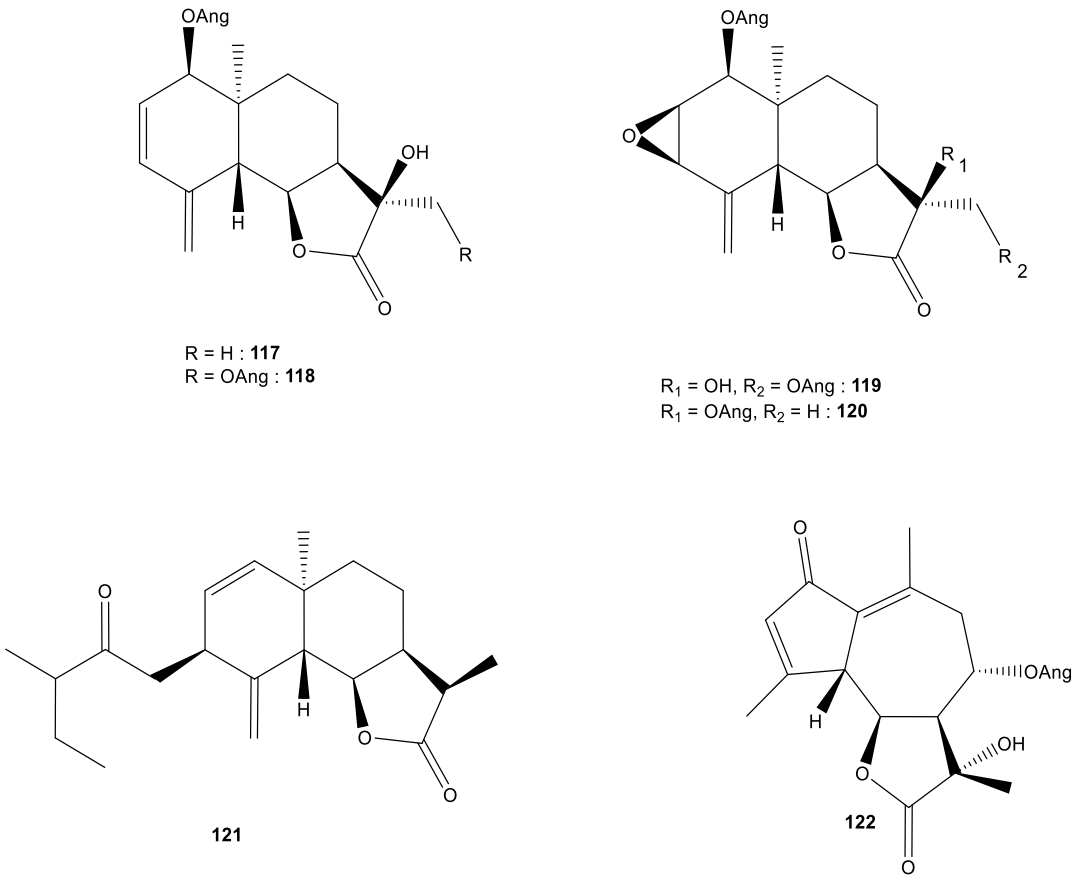


Fig. 35. The molecular structures of the six sesquiterpene lactones (**117-122**) obtained from from the roots of *F. varia* (Schrenk) Trautv. (Suzuki et al., 2007).

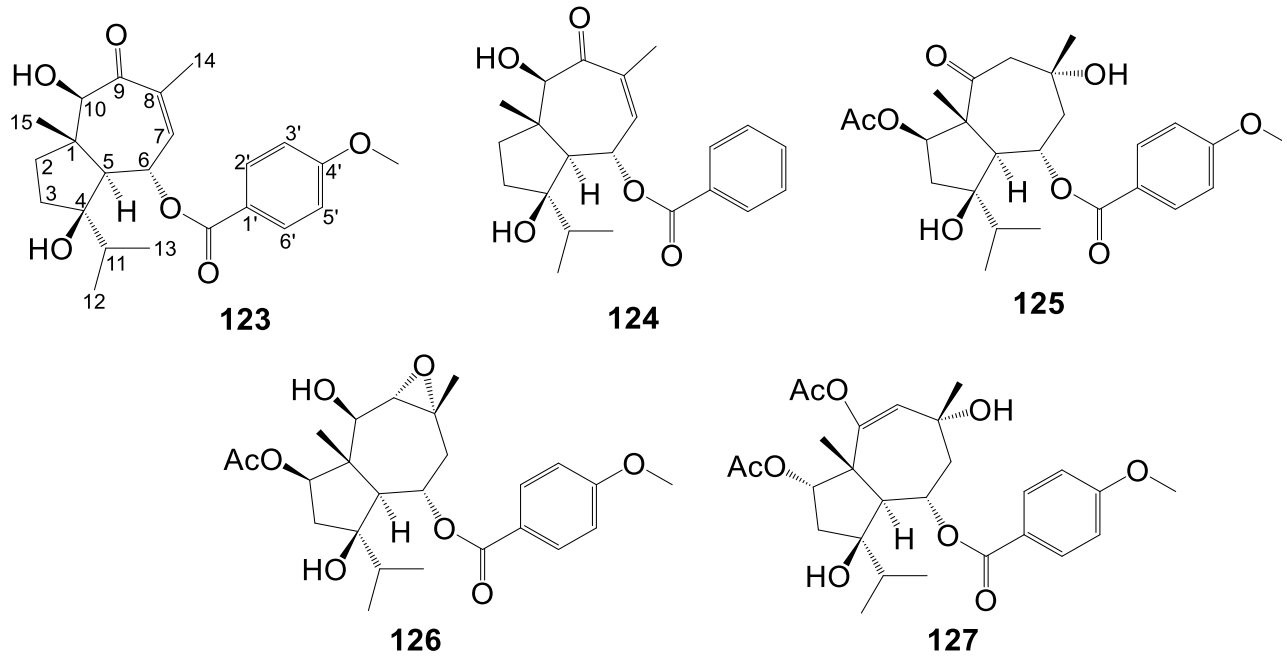
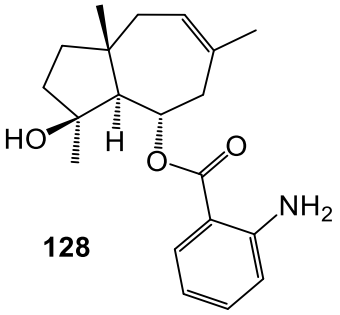
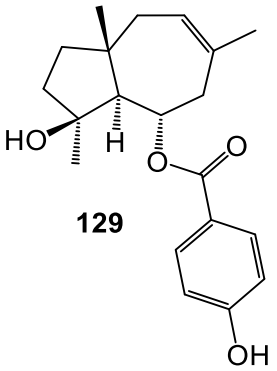


Fig. 36. The molecular structures of five characterized sesquiterpene derivatives (**123**-**127**) separated from the dichloromethane extract of *F. vesceritensis* Coss. & Dur, organ: aerial parts (Oughlissi-Dehak et al., 2008).

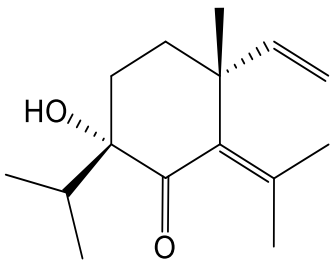


128



129

Fig. 37. The molecular structures of the two sesquiterpene esters obtained from the roots of *F. elaeochytris* Korovin, 6-anthraniloyljaeschkeanadiol (elaeochytrin A) (**128**) and 4β-hydroxy-6α-(*p*-hydroxybenzoyloxy)dauc-9-ene (elaeochytrin B) (**129**) (Alkhatib et al., 2008).



130

Fig. 38. The molecular structures of the sesquiterpene, badrakemonin (**130**), obtained from the roots *F. badrakema* Koso-Pol (Iranshahi et al., 2009).

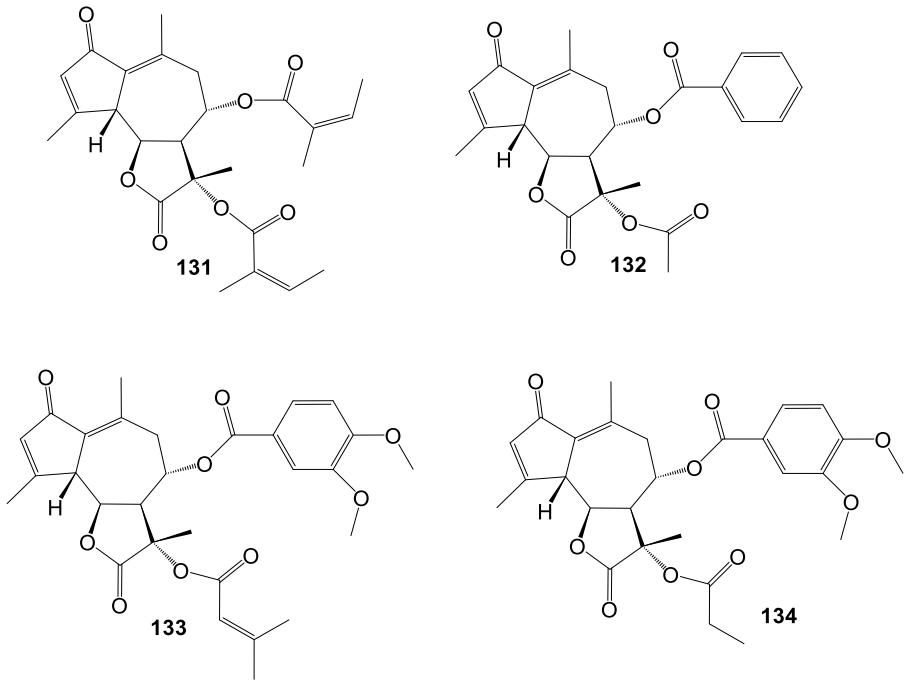


Fig. 39. The molecular structures of the four sesquiterpene lactones (**131-134**) obtained from from the roots of *F. diversivittata* Regel & Schmalh. (Iranshahi et al., 2010b).

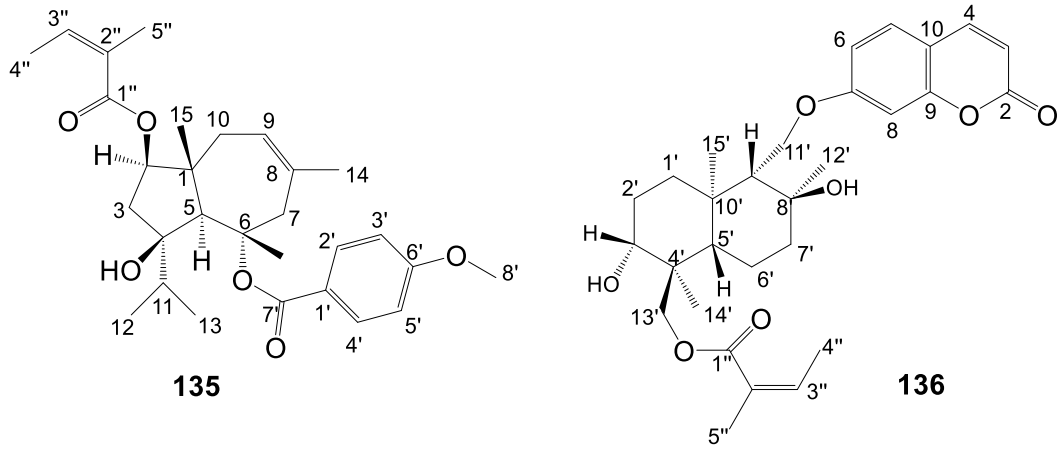


Fig. 40. Molecular structures of a characterized ester (**135**) and a coumarin sesquiterpene derivative (**136**) from the roots of *F. tunetana* Pomel ex Batt (Jabrane et al., 2010).

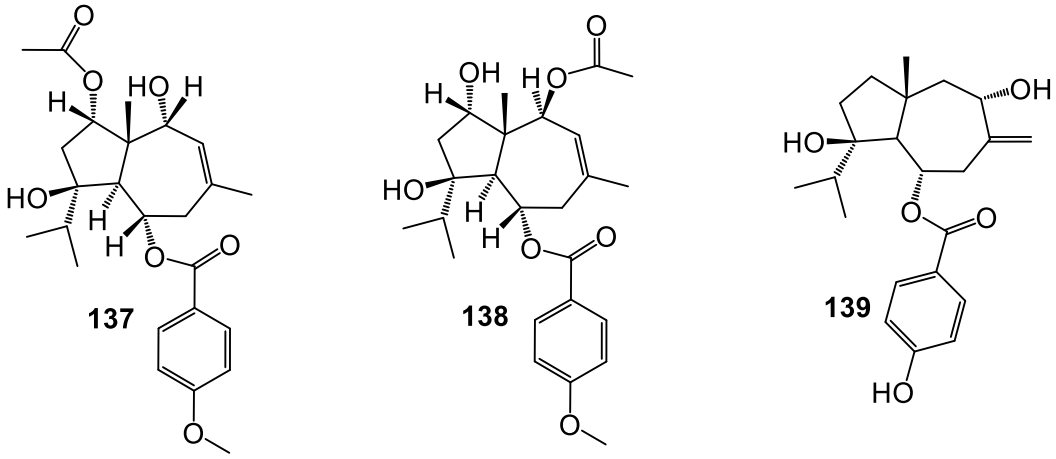


Fig. 41. The molecular structures of three daucane sesquiterpenes (**137**-**139**) isolated from the roots of *F. communis* subsp. *communis* (Dall'Acqua et al, 2011).

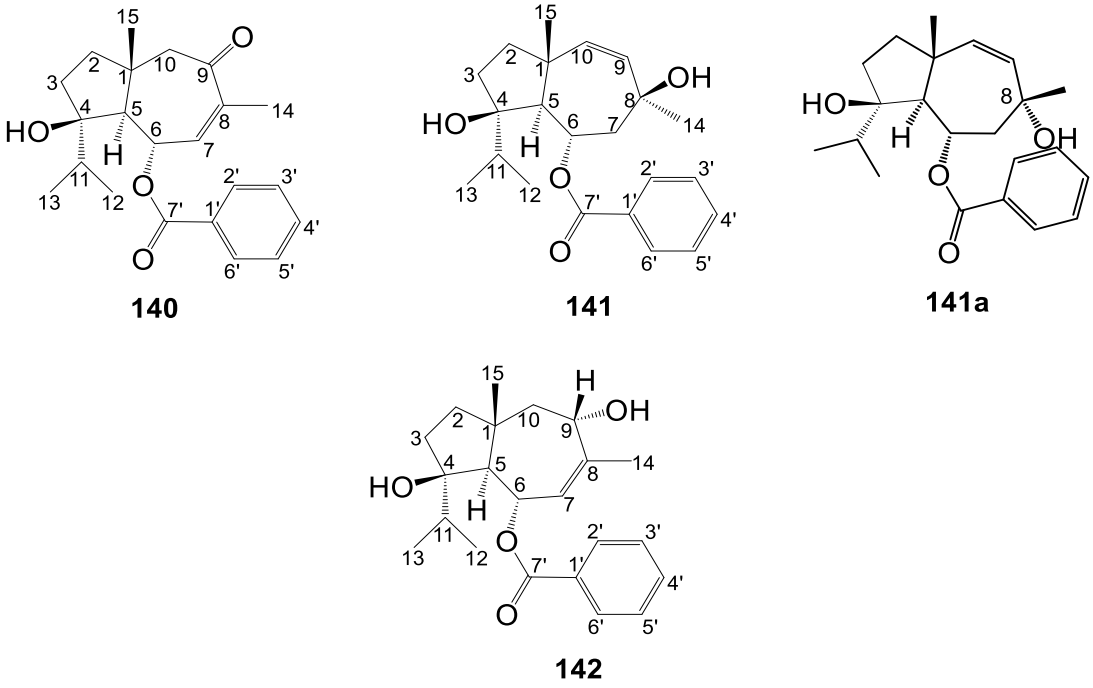


Fig. 42. The molecular structures of three daucane esters (**140**-**142** and **141a**) separated from an *n*-hexane-ethyl acetate (1:1) extract of the ground seeds of *F. hermonis* Boiss (Auzi et al., 2008; Ibraheim et al., 2012a).

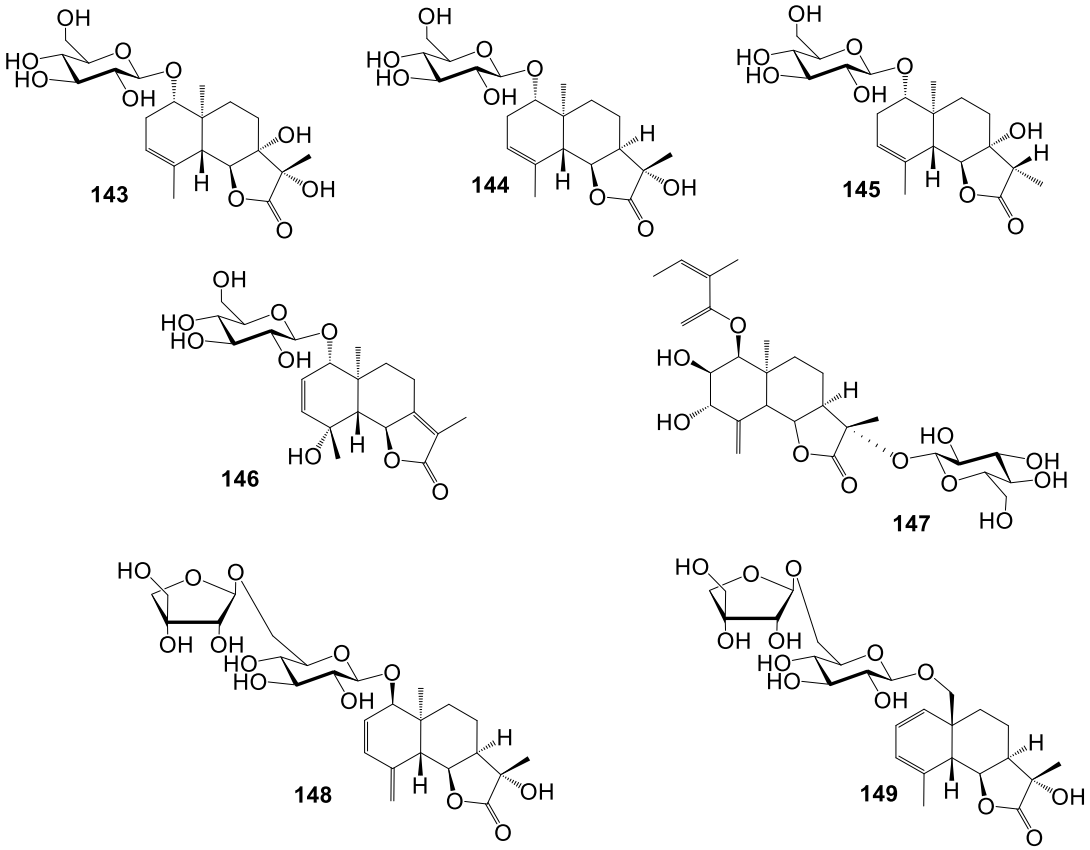


Fig. 43. The components, sesquiterpene lactone glycosides (**143-149)**, separated from the water-soluble fraction obtained from the methanol extract of *F. varia* (Schrenk) Trautv. roots (Kurimoto et al., 2012b).

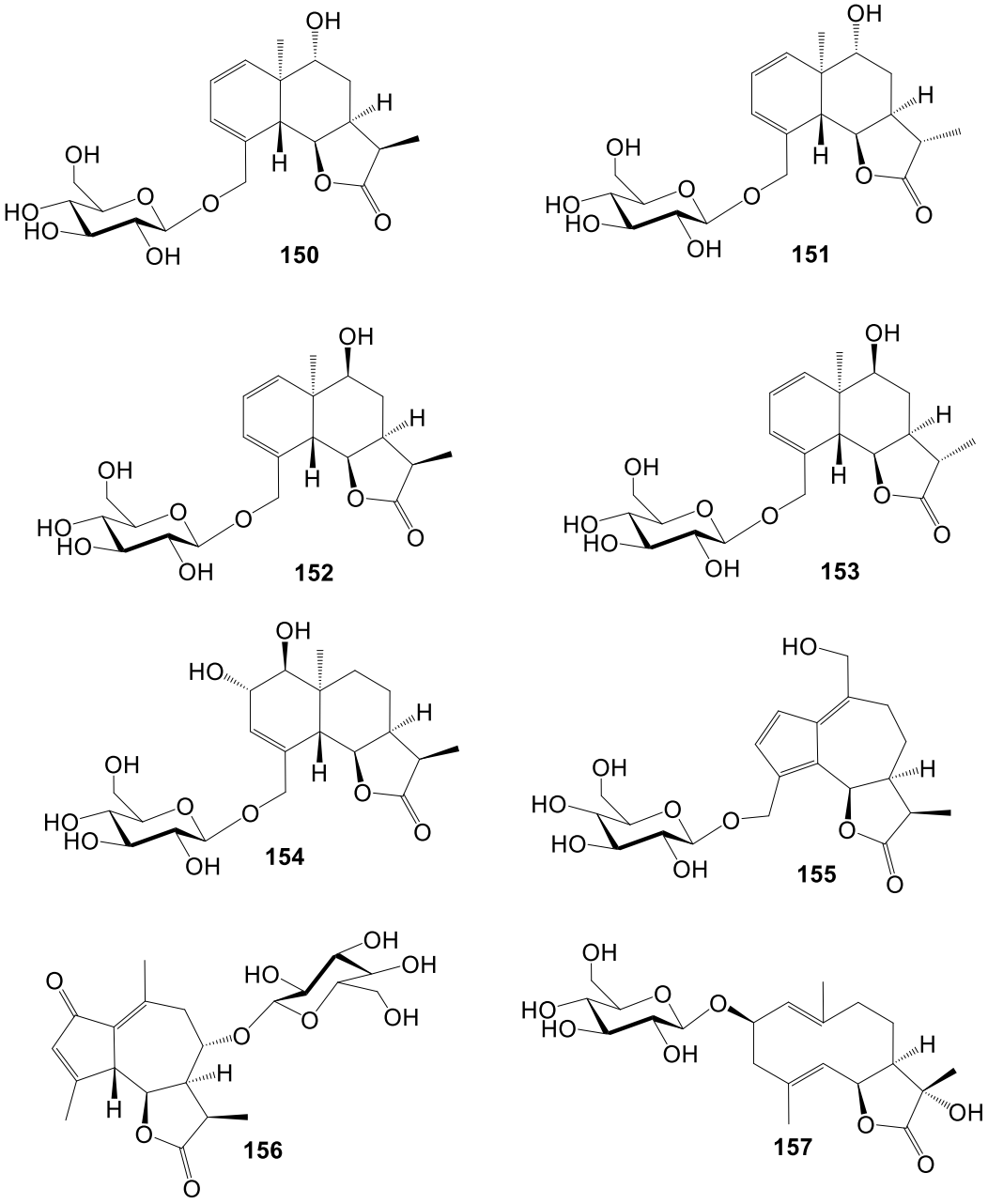
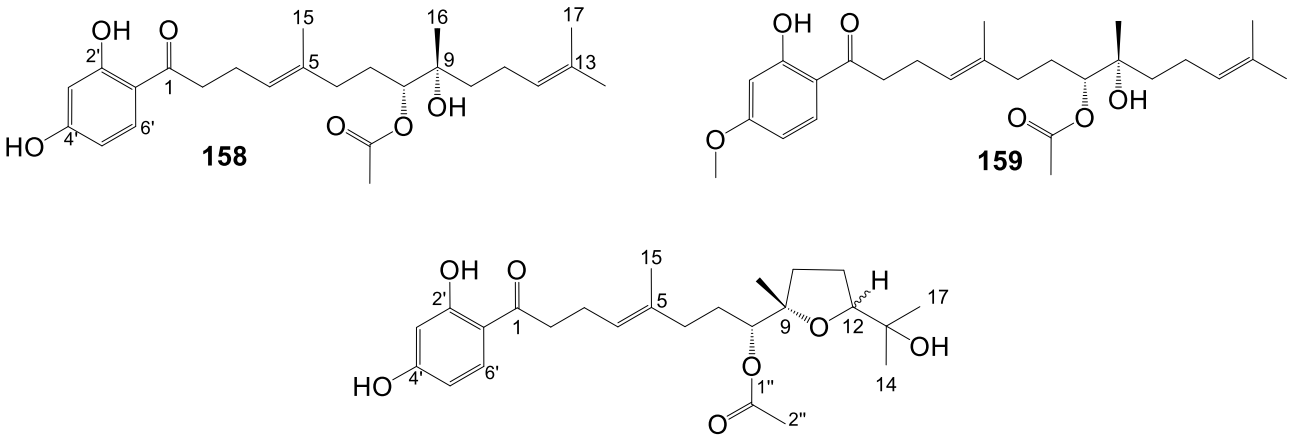


Fig. 44. bioactive compounds (**150**-**157**) separated from a water extract of *F. varia* (Schrenk) Trautv roots (Kurimoto et al., 2012a).



160 (12*R*), *cis*-furan
161 (12*S*), *trans*-furan

Fig. 45. The structures of the four sesquiterpene resacetophenones (**158**-**161**) separated from the roots of *F. ferulioides* (Steud.) Korovin (Liu et al., 2015).

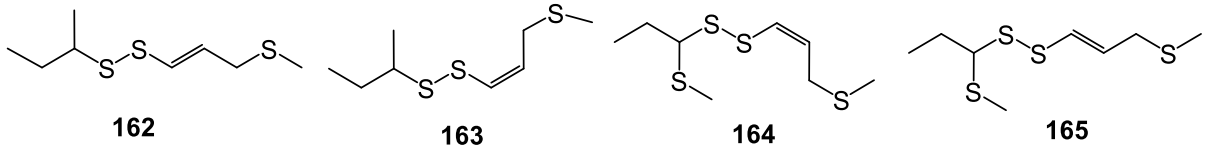


Fig. 46. The molecular structures of the four polysulphanes (**162**-**165**) isolated from the aerial parts of *F. behboudiana* Rech. f. Esfand (Yousefi et al., 2010).

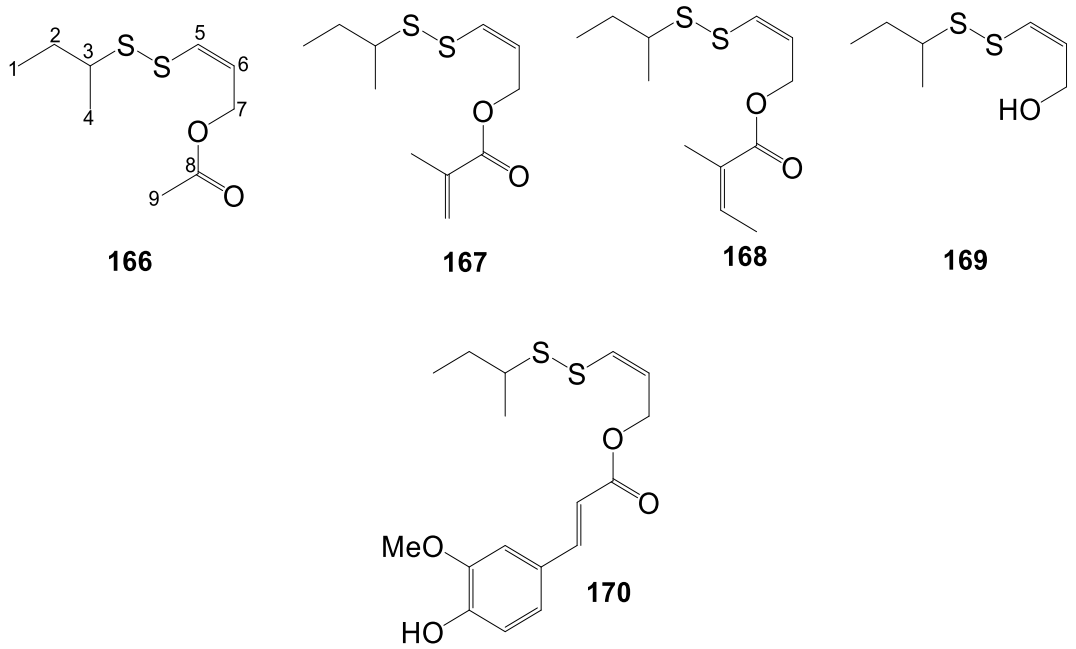
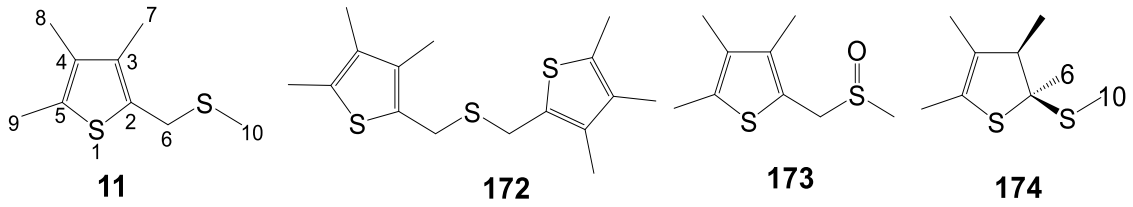
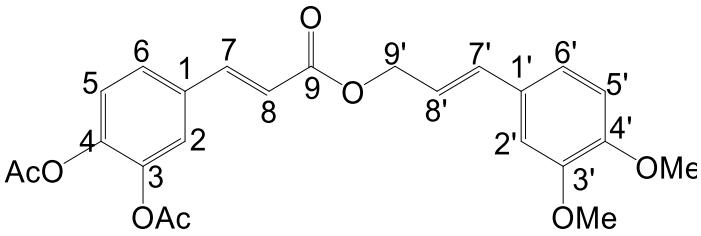


Fig. 47. The main bioactive sulfur-containing compounds (**166**-**170**) separated from a dichloromethane extract of *F. latisecta* Rech.f. & Aellen (Soltani et al., 2018).



11 **172** **173** **174**

Fig. 48. The molecular structures of the isolated sulfur-containing compounds foetithiophenes C-F (**171-174**) in the petroleum ether extract from the roots of *F. foetida* Regel (Chitsazian-Yazdi et al., 2015).



175

Fig. 49. The main bioactive compound, a caffeic acid cinnamyl ester, namely (2*E*)-3,4-dimethoxycinnamyl-3-(3,4-diacetoxyphenyl) acrylate (**175**) separated from *F. assa-foetida* L. (Abd El-Razek, 2007).

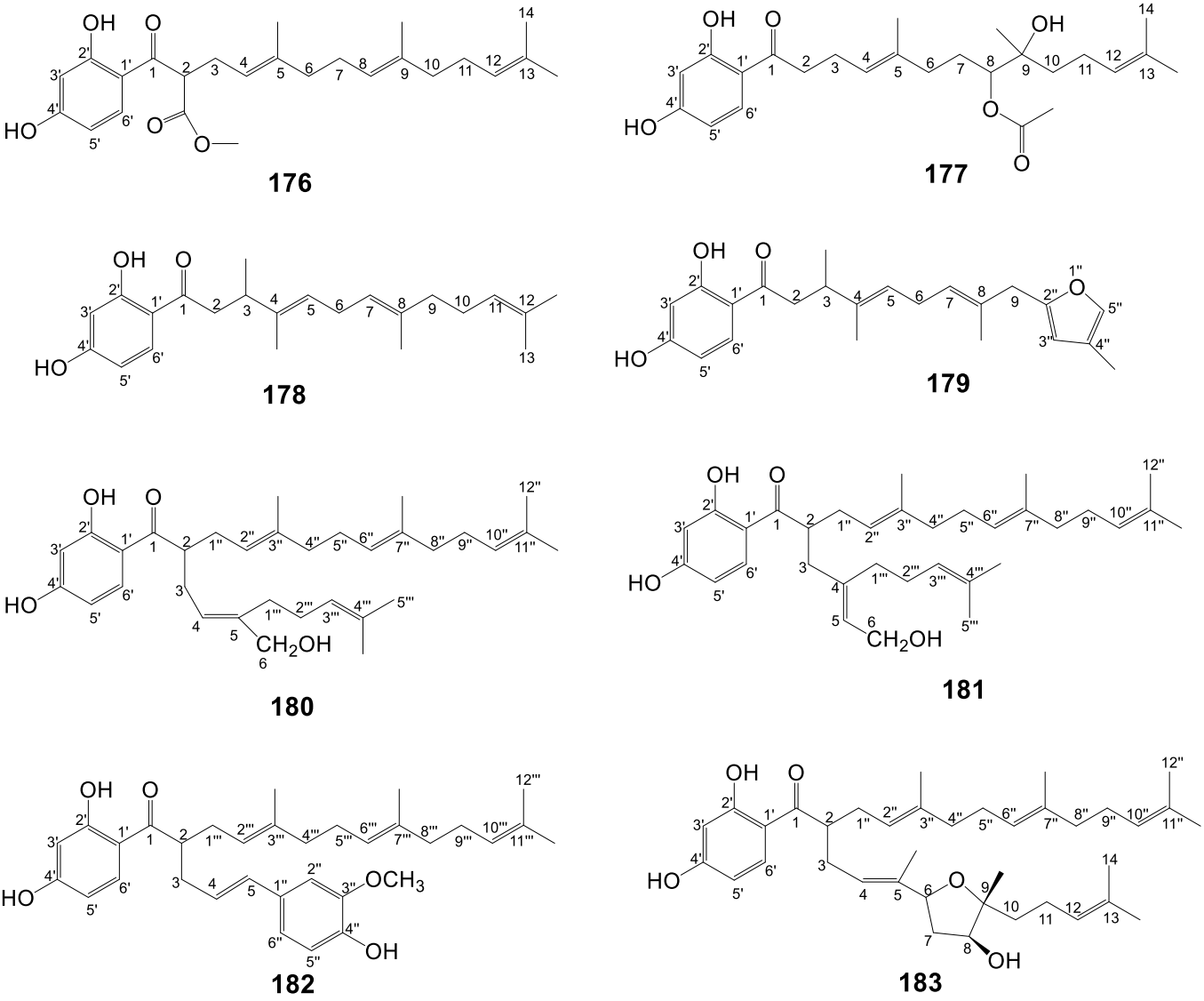
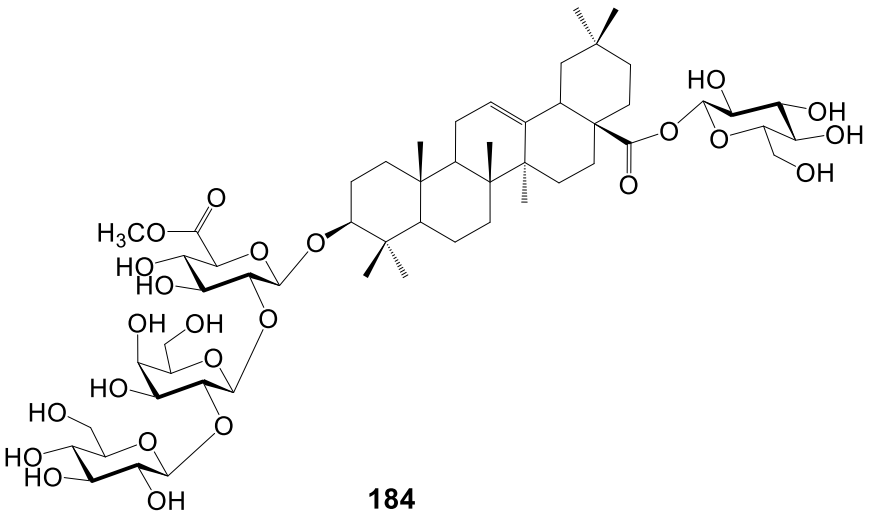


Fig. 50. Eight bioactive sesquiterpenoids--ferulaeone A-H (**176**-**183**)—isolated from aqueous-ethanol (5:95, v/v) extracts of the roots of *F. ferulaeoides* (Steud.) Korov (Meng et al., 2013b).



184

Fig. 51. The molecular structure of the saponin (sandrosaponin XI) (**184**) isolated from the root of *F. hermonis* Boiss. (Ibraheim et al., 2012b).

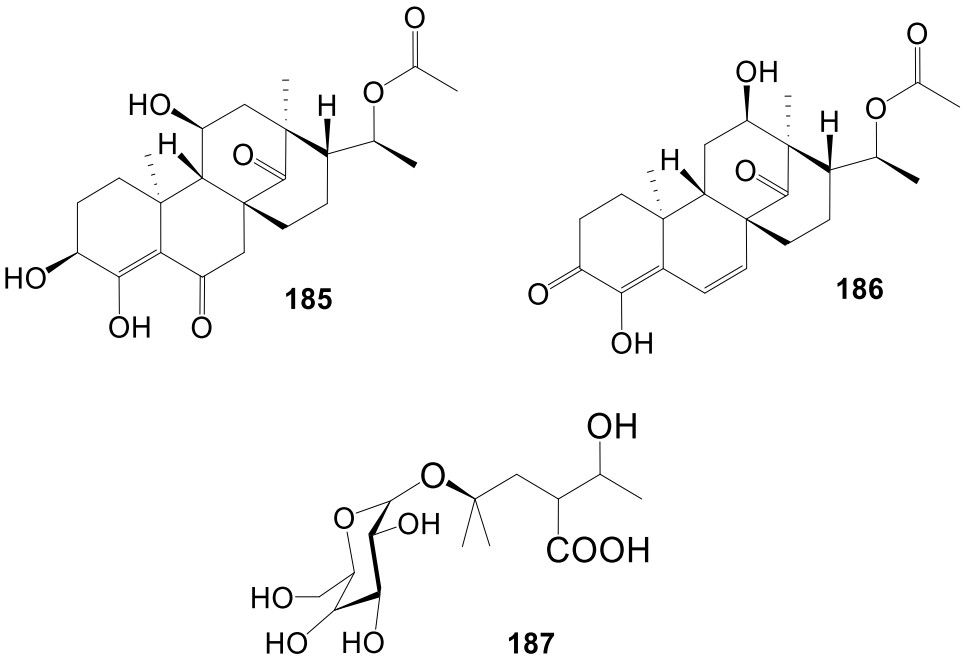
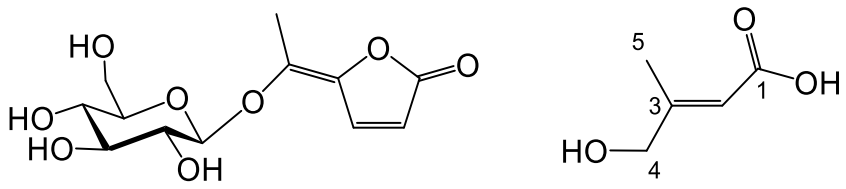


Fig. 52. The molecular structures of steroidal esters sinkiangenorin (**185**), sinkiangenorin B (**186**) and sinkiangenorin C (**187**), isolated from the seeds of *F. sinkiangensis* K. M. Shen (Li et al., 2014).



188 **189**

Fig. 53. Two compounds (**188, 189**) separated from *F. lutea* (Poir.) Maire (Znati et al., 2014).