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The Nonvolatile and Volatile Metabolites of *Prangos ferulacea* and Their Biological Properties*

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ABSTRACT

Prangos ferulacea (L.) Lindl. (Fam. Apiaceae), an orophilous species of eastern Mediterranean and western Asia, possesses a number of biological properties that are worthy of exploitation in different fields. Phytochemical investigations revealed the presence of coumarins, prenyl-coumarins, and furano-coumarins as the main constituents of this species, as well as several flavonoids. Among prenyl-coumarins, osthol is a promising apoptotic agent quite selective toward cancer cells. In addition, the essential oils have been extensively investigated, and several chemotypes have been identified. This work reviews the literature on this species published between 1965 and 2018, describes its volatile and nonvolatile metabolites, and outlines its pharmacological effects.

Introduction

The Apiaceae family comprises a set of medicinal and aromatic plants that store important secondary metabolites in internal secretory structures known as ducts and vittae, which occur in all plant organs [1]. They have been used since ancient times in traditional medicine as well as in cooking for their bioactive compounds content, including coumarins, flavonoids, polyacetylenes, and essential oils [2]. The relatively safety of these compounds, along with the availability of the raw material from which they are obtained, make them exploitable in different fields [3]. The main examples of useful Apiaceae are anise, cumin, fennel, dill, caraway, and coriander [4]. Other Apiaceae, in particular the *Cachrys* group, deserve further exploration for possible use on the industrial level.

The *Cachrys* group (fam. Apiaceae, subfam. Apioideae) is divided into several genera: *Prangos, Alocacarpum, Cachrys, Bilacunaria, Ferulago, Diplotaenia, Eriocycla*, and *Azilia* [5].

According to the Plant List [6], there are 19 accepted *Prangos* species. They are mainly distributed in the eastern Mediterranean area, the Balkans, the Middle East, and western Asia and many of them are endemic in Turkey. Species of the genus *Prangos* found in Italy are *Prangos ferulacea* Lindl. and *Prangos trifida* (Miller) Herrnst. & Heyn, whereas in western Europe, only *P. trifida* occurs [7].

* Dedicated to Professor Dr. Cosimo Pizza in recognition of his important contributions to natural product research on the occasion of his 70th birthday in 2019.

The *Prangos* Lindl. genus [8] consists of perennial herbaceous plants. Its stems are well branched, without coasts, at the base, with a well-developed and persistent collar of fibrous parts. Its leaves are 4–7(3)-pinnate, glabrous, with numerous thread-like, acute leaflets. The umbels are composed of numerous flowers. The bracts and bracteoles are sometimes deciduous, and the flowers are hermaphrodite and male. The goblet has more or less evident teeth. Its petals are yellow, broadly ovate, with curved peak, and homogeneous. The fruits are oblong, more or less compressed laterally, and hairless. The mericarps are smooth, free of externally marked coasts, with semielliptical or semicircular sections, with spongy mesocarp; vittae are numerous and form a continuous ring. The seeds have the endosperm convoluted on the commissural face [9].

P. ferulacea (synonyms: *Cachrys alata* Hoffm., *C. alata* M. Bieb., *Cachrys ferulacea* [L.] Calest., *Cachrys goniocarpa* Boiss., *Cachrys prangoides* Boiss., *Laserpitium ferulaceum* L., *Prangos alata* Grossh., *Prangos biebersteinii* Karjagin, *Prangos carinata* Griseb. ex Grecescu) [6] is an orophilous species of the eastern Mediterranean and western Asia, where it grows in arid, stony, mountain pastures, preferentially on basic soils. In Sicily, it is fairly widespread on the carbonate mountains, above 1000 m of altitude; it flowers in May to June and fruits in July to August. In the Madonie Mountains (Sicily), the species is usually consumed by grazing cattle and sheep and imparts characteristic smells and flavors to their milk, which are transmitted to the derived dairy products such as cheese and salted ricotta, very appreciated and sought after by local communities [10]. In Turkey, *P. ferulacea* is known as “heliz” and is used as an ingredient of the very famous cheese, “otlu”, produced traditionally in eastern cities, particularly around Van province, as it provides characteristic appearance and special aroma as well as antimicrobial preservation [11]. In the central, southern, and eastern mountains of Turkey, where it is called “çaşir”, the young shoots of this plant are used as a vegetable, consumed boiled, fried, and pickled [12]. In Persian folk medicine, *P. ferulacea* has been used as a carminative, emollient tonic for gastrointestinal and liver disorders, and as anti-flatulent, sedative, anti-inflammatory, anti-viral, anti-helminthic, antifungal and antibacterial agent [13]. It is locally known as “jashir” and also serves as food and yogurt seasoning [14].

This work reviews reports published between 1965 and 2018 on the volatile and nonvolatile secondary metabolites and the biological activities of *P. ferulacea* with the aim of stimulating further research that may open the way to new applications of this species.

Nonvolatile Metabolites

Occurrence

The roots from different *P. ferulacea* populations growing in Armenia, Bulgaria, Iran, Russia, Sardinia, and Turkey have been the subject of extensive phytochemical investigations (▶ **Table 1**). They were shown to be extremely rich in coumarins, the main class of secondary metabolites detected so far. In addition, the aerial parts contain not only coumarin derivatives, but also several flavonoid glycosides and the trisaccharide umbelliferose (**46**) (in a Sardinian population) (▶ **Table 1**). The structures of all the metabolites are depicted in ▶ **Figs. 1**, **2**, and **3**.

Coumarins are widely distributed plant metabolites. Starting from the parent structure, coumarin (1,2-benzopyrone), which was isolated around 200 y ago, several biogenetic modifications can occur on the basic skeleton. A quite common feature is the presence of an oxygen substituent on C-7, as can be observed in all the structures reported in the present review (**1**–**39**). Oxygenation can also occur at 1 or more of the remaining positions of the coumarin skeleton. These oxygen atoms can be present as phenol (**1, 3, 4**) or ethereal groups (**2, 5**–**39**).

Another common feature in most of the coumarin-based structures is the presence of a prenyl group, variedly oxidized, that can be linked to a carbon atom of the skeleton (**4**–**12**) or to an oxygen atom (**13, 24**–**36, 39**). The oxidative ring closure of the prenyl group with a close oxygen results in the formation of hydroxyisopropylfuran moiety (**20**–**23, 37, 38**). Further loss of acetone leads to a furan ring (**16**–**19, 24**–**36, 39**). The biochemical activities, dietary sources and intake, and potential health risks of furanocoumarins have been recently reviewed [40]. An alternative cyclization of the C-prenyl group can afford pyrano-coumarins (**14, 15**).

Biological properties of *P. ferulacea* extracts and nonvolatile metabolites

Cytotoxic activity

The cytotoxic potential of coumarins isolated from *P. ferulacea* on PC3, SKNMC, and H1299 (p53 null) human carcinoma cell lines was evaluated. Osthol (**5**) was shown to be a potent cytotoxic agent against PC3 cells (IC_{50} = 20.1 µM), whereas isoimperatorin (**31**) exhibited moderate inhibitory effects against SKNMC and PC3 cell lines (IC_{50} = 182 µM and 119.4 µM, respectively). On the other hand, oxypeucedanin (**34**) and braylin (**14**) did not display any cytotoxic activity. Furthermore, the apoptotic properties of osthol (**5**) and isoimperatorin (**31**) were investigated, with quite interesting results. Osthol (**5**) induced apoptosis in PC3 and SKNMC cell lines via both mitochondrial and extrinsic pathways, whereas it induced the apoptotic cell death via a p53 independent pathway in H1299 cells [24]. Osthol (**5**) and osthol derivatives also showed growth inhibitory activity against MCF-7 and MDA-MB-231 human breast carcinoma cell lines [41]. Remarkably, osthol (**5**) is not toxic to normal cells (HEK-293 and Vero cell lines) [26, 41]. Osthol (**5**) was also shown to have cytotoxic effects on A2780S human ovarian carcinoma cell line (IC_{50} = 0.54 mM) and isoimperatorin (**31**) was shown to be a nontoxic cyclooxygenase-2 inhibitor [26]. Pre-treatment with nontoxic concentrations of osthol (**5**) protected PC12 cells from DOX-mediated apoptosis by inhibition of ROS (radical oxygen species) production [42]. In another paper, several coumarins obtained from *P. ferulacea* root, namely osthol (**5**), psoralen (**16**), isoimperatorin (**31**), pranferol (**27**), gosferol (**28**), oxypeucedanin (**29**), oxypeucedanin hydrate (**30**), and oxypeucedanin methnolate (**36**), were reported to exhibit moderate cytotoxic and anti-HIV properties [27].

Investigations of the safety of osthol (**5**) have found that it is moderately toxic substance when administered i. p. in rodents. The no-observed adverse-effect level of osthol (**5**) for both male and female rats is considered to be less than 5 mg/kg [43]. These

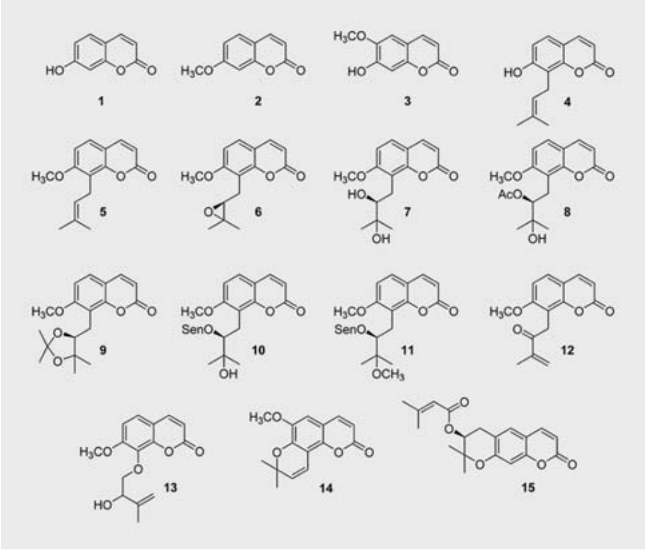
▶ **Table 1** Occurrence of nonvolatile metabolites in different populations of *P. ferulacea*.

Parts	Origin	Other metabolites	Coumarins	Ref.
roots	Armenia		pranferol (**32**)	[15]
roots	Armenia		osthol (**5**), meransin (**6**), meransin hydrate (**7**), xanthotoxin (**17**), prangeferol (marmesin) (**20**), isoimperatorin (**31**), pranferol (**32**), oxypeucedanin (**34**), oxypeucedanin hydrate (**35**)	[16, 17]
stems	Armenia		osthol (**5**), isoimperatorin (**31**), oxypeucedanin (**34**)	[16]
roots	Armenia		prangone (**12**), ferudenol (**13**)	[18]
aerial parts	Azerbaijan	quercetin 3-*O*-*β*-glucoside (**41**), isorhamnetin 3-*O*-*β*-glucoside (**42**), isorhamnetin 3-*O*-glucorhamnoside (**43**)	celereoside (**23**)	[19]
roots	Bulgaria		osthol (**5**), psoralen (**16**), bergapten (**18**), pranchimgin (**21**), imperatorin (**24**), isoimperatorin (**31**)	[20]
aerial parts	Egypt	*β*-D-gluco-*β*-sitosterol	umbelliferone (**1**), herniarin (**2**), scopoletin (**3**), osthenol (**4**), osthol (**5**), xanthotoxin (methoxsalen) (**17**), imperatorin (**24**)	[21]
aerial parts	Iran, Tochal	quercetin (**40**), quercetin 3-*O*-glucuronide (**44**)	imperatorin (**24**), heraclenin (**26**), oxypeucedanin (**34**), sprengelianin (**38**), xanthotoxin (methoxsalen) (**17**), oroserol (**37**), isopimpinellin (**19**), prangeferol (marmesin) (**20**), phellopterin (**27**), heraclenol (**28**), oxypeucedanin hydrate (**35**), [3-hydroxy-2-methyl-4-(7-oxofuro[3,2 g]chromen-9-yl) oxybutan-2-yl] (*Z*)-2-methylbut-2-enoate (**29**), 8-[2-(3-methylbutyroxy)-3-hydroxyl-3-methylbutoxylpsoralen (**30**), rivulobirin A (**39**)	[22]
aerial parts	Iran, West-Azerbaijan	quercetin 3-*O*-*β*-glucoside (**41**), isorhamnetin 3-*O*-*β*-glucoside (**42**), caffeic acid glucosyl ester (**47**)	imperatorin (**24**), ferudenol (**13**)	[23]
roots	Iran		osthol (**5**), braylin (**14**), isoimperatorin (**31**), oxypeucedanin (**34**)	[24, 25]
roots	Iran		osthol (**5**), psoralen (**16**), isoimperatorin (**31**), pranferol (**32**), gosferol (**33**), oxypeucedanin (**34**), oxypeucedanin hydrate (**35**), oxypeucedanin methnolate (**36**)	[26, 27]
whole plant	Iran	quercetin 3-*O*-glucuronide (**44**), isorhamnetin 3-*O*- *β*-glucuronide (**45**)		[28]
roots	Italy, Sardinia		osthol (**5**), decursin (**15**), imperatorin (**24**), heraclenin (**26**), isoimperatorin (**31**), oxypeucedanin (**34**)	[29]
seeds	Italy, Sardinia		osthol (**5**), decursin (**15**), imperatorin (**24**), heraclenin (**26**), isoimperatorin (**31**), oxypeucedanin (**34**)	[29]
fruits	Italy, Sardinia	umbelliferose (**46**)		[30]
fruits	Italy, Sicily		osthol (**5**), bergapten (**18**), imperatorin (**24**), isoimperatorin (**31**)	[31]
roots	Russia, Bichenak Mt		osthol (**5**), meransin hydrate (**7**), isoimperatorin (**31**), oxypeucedanin (**34**), oxypeucedanin hydrate (**35**)	[32]
roots	Russia, Bichenak Mt		pranferol (**32**)	[33]
fruits	Russia, Bichenak Mt		osthol (**5**), isoimperatorin (**31**), oxypeucedanin (**34**)	[34]
roots	Russia, Bichenak Mt		pranferin (**9**)	[35, 36]
roots	Russia, Bichenak Mt		gosferol (**33**)	[37]
roots	Russia, Nakhichevan		umbelliferone (**1**), meransin hydrate monoacetate (**8**), ferudiol (**10**), 3′-O-methylferudiol (**11**), ferudenol (**13**), lindiol (**22**), feruliden (**25**)	[18, 38]
roots	Turkey		imperatorin (**24**), oxypeucedanin hydrate (**35**), pranchimgin (**21**), isoimperatorin (**31**)	[39]

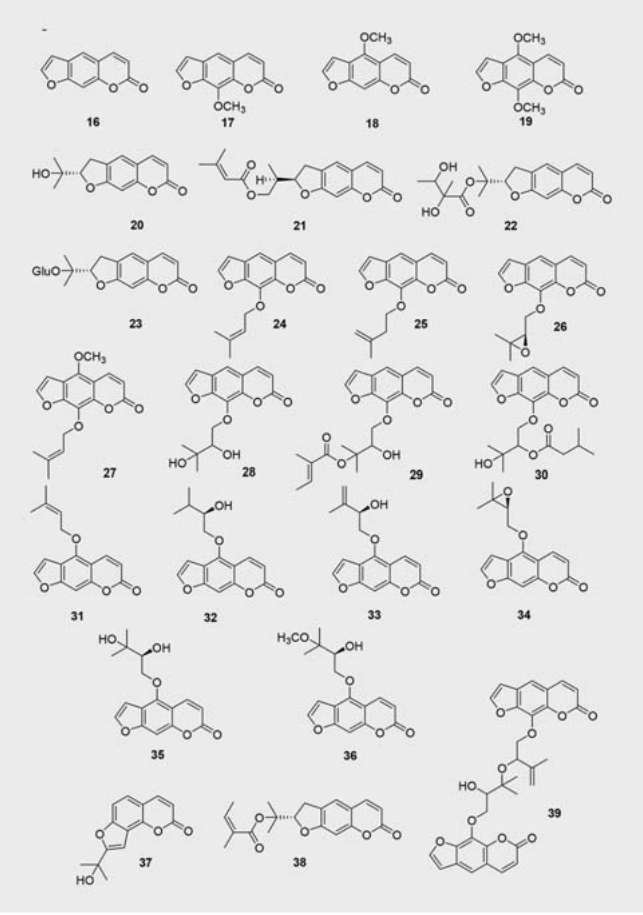
findings suggest that osthol (**5**) might prove to be useful as a therapeutic agent in carcinoma treatment mainly in phenotypic-resistant cell lines due to defect in p53 function. Randomized clinical trials are important to evaluate the safety and efficacy of osthol in patients with different types of cancers.

Antioxidant and antimicrobial activities

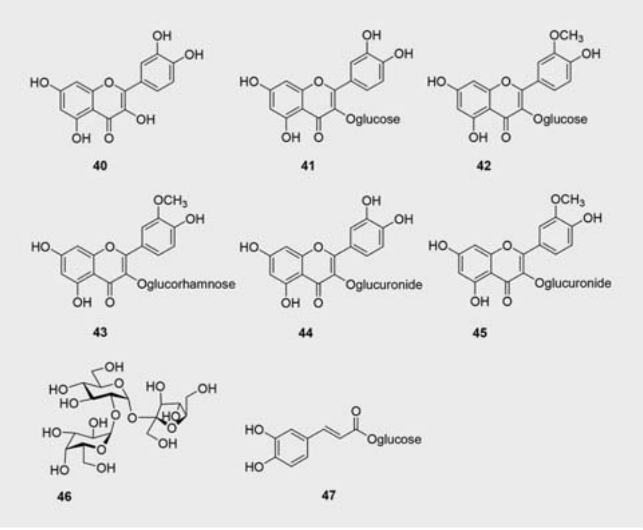
The methanolic extract from aerial parts of *P. ferulacea* collected in eastern Turkey was found to be a good antioxidant with 50 % inhibitory concentration values at 0.242 and 0.152 mg/mL in DPPH (2,2-Diphenyl-1-picrylhydrazyl) radical scavenging and lipid per-



▶ **Fig. 1** Chemical structures of coumarins of *P. ferulacea*.



▶ **Fig. 2** Chemical structures of furo- and dihydrofuro-coumarins of *P. ferulacea*.



▶ **Fig. 3** Chemical structures of other metabolites of *P. ferulacea*.

oxidation inhibition assays, respectively. It was also evaluated for its effect on glutathione-S-transferase activities showing an IC_{50} value of 79.25 µg/mL [44, 45].

Various solvent extracts (water, methanol, ethanol, and ethyl acetate) of different herbs, traditionally used in eastern Turkey to enhance the aromatic properties of cheese, were tested for their antioxidant properties. The methanolic extract of *P. ferulacea* showed the highest DPPH and ABTS (2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt) radical-scavenging activities. Furthermore, a moderate antimicrobial activity against *Enterococcus faecalis* (MIC [minimal inhibitory concentration] value of 250 µg/mL) was observed [11]. Quercetin glucoside (**41**) and isorhamnetin glucoside (**42**), isolated from the methanolic extract of *P. ferulacea* aerial parts collected in Eastern Azerbaijan province, Iran, exhibited strong antioxidant activity in the DPPH assay with RC_{50} values of 36.2 and 64.4 µg/mL, respectively [19]. Cytotoxic, phytotoxic, antimicrobial, and antioxidant effects of quercetin glucoside (**41**) isolated from aerial parts of *P. ferulacea* and characterized by HPLC were studied by MTT assay, lettuce germination assay, disk diffusion, and DPPH methods. Quercetin glucoside (**41**) exhibited the highest antioxidant activity in the DPPH assay with an RC_{50} value of 22 µg/mL, whereas no activity against *Bacillus cereus, Escherichia coli, Staphylococcus epidermidis, Pseudomonas aeruginosa*, and *Candida kefyr* was detected [46].

The antibacterial effects of 4 extracts (ethanolic, methanolic, aqueous, and hexanic) of *P. ferulacea* against several gram-positive bacteria such as *B. cereus, Bacillus subtilis, Micrococcus luteus*, and *Staphylococcus aureus* were evaluated. The highest inhibitory effects were observed against *M. luteus* and *S. aureus* for ethanolic (16 and 16 mm inhibition zone diameters, respectively) and methanolic extracts (12 and 16 mm inhibition zone diameters, respectively) [47].

Recently, a clinical trial showed that *P. ferulacea* vaginal cream, containing its extract plus oral metronidazole, prepared in the laboratory of the School of Pharmacy of Shahid Beheshti Univer-

sity of Medical Sciences, accelerated the recovery of patients with bacterial vaginosis. Thus, it can be used effectively as a complementary treatment with oral metronidazole in cases of medication resistance [48].

Hypoglycemic activity

The hypoglycemic and hypolipidemic effects of the *P. ferulacea* root hydroalcoholic extract in alloxan-induced diabetic rats were studied. A 4-wk treatment of diabetic rats with a hydroalcoholic extract of roots (100 mg/kg) caused significant decrease in blood glucose (from 383 to 309 mg/dL), similar to the results obtained with 1 IU/kg of insulin (298 mg/dL). On the basis of these results, it was concluded that the *P. ferulacea* extract can be used in the treatment of diabetes to reduce the blood glucose and lipid profile. Furthermore, the extract was found to influence changes of aminotransferases and to prevent the histopathological changes of liver in diabetic rats [49, 50]. Other researchers confirmed these results; in fact, a 3-wk diet with *P. ferulacea* hydroalcoholic extract (500 mg/kg) resulted in a significant decrease in blood glucose in diabetic male Wistar rats (from 380 to 160 mg/dL) and also in ALT (alanine aminotransferase), AST (aspartate aminotransferase), and creatinine, but no significant decrease in ALP (alkaline phosphatase), albumin, urea, and BUN (blood urea nitrogen) levels. Consequently, it may possibly serve to alleviate the liver and kidney damage caused by streptozotocin-induced diabetes mellitus [51]. These results could be ascribed to the presence in the extract of coumarins, such as umbelliferone (**1**), whose antihyperlipidemic and antidiabetic properties have already been proven [52].

Analgesic effects

The analgesic effects of aqueous and methanolic extracts of *P. ferulacea* on formalin-induced pain in female rats were examined. The results showed that both extracts exerted analgesic properties through peripheral and central analgesia [53].

Noteworthy antispasmodic effects of the *P. ferulacea* acetone extract and its main constituents, namely osthol (**5**) and prenylated coumarins, on rat ileum contraction and uterus smooth muscle motility have also been reported. The relaxation effects of osthol (**5**) might be mediated through Ca^{2+} channel blocking activity, as it inhibited the response to KCl [14, 54].

Other properties

P. ferulacea is used in Iranian traditional medicine for the treatment of gastrointestinal disorders. However, it seems to exert an abortifacient effect on pregnant women. A study by Kazerooni and Mousavizadeh [55] showed that the leaf aqueous and hydroalcoholic extracts of *P. ferulacea* did not significantly increase the rate of abortion in pregnant rats. However, further investigations should be conducted to test the safety of these extracts in other animals [56].

The *n*-hexane extract was evaluated for inhibitory activity on acetylcholinesterase enzyme (AChE), a key target for the discovery of new treatments of Alzheimer's disease. This extract showed a significant AChE inhibitory activity, with 75.6% inhibition at a concentration of 50 µg/mL. A further bio-assay-guided fractionation showed that the fraction containing imperatorin (**24**), oxypeucedanin (**34**), oxypeucedanin hydrate (**35**), oroserol (**37**), rivulobirin A (**39**), quercetin (**40**), and quercetin 3-*O*-glucuronide (**44**) was the most active against AChE, showing an IC_{50} value of 25.2 µg/mL as well as good docking scores of its constituents [22].

Volatile Metabolites

Essential oils

With regard to the composition of the essential oils obtained from different parts of *P. ferulacea* from different geographic origin, several papers have been published. Most of them refer to natural populations growing in Iran, while a few studies have been performed on those from Turkey, Greece, Montenegro, and Italy (▶ **Table 2**). The essential oil derived from whole aerial parts contains different chemotypes. Terpinolene (38.1–56.3%) [57], *δ*-3-carene (45.9%), limonene (55.1%) [58] and *β*-pinene (43.0%) [59] were found as the major constituents in the oils obtained from samples during the vegetative stage. *α*-Pinene (41.3%) and *δ*-3-carene (34.6%) [58], (*E*)-caryophyllene (48.2%) [60], *α*-pinene (37.1%), and *β*-pinene (33.8%) [59] were found as the most abundant volatile components in flowering aerial parts. *α*-Pinene (31.7%) and *β*-pinene (38.5%) were the major components in the oil obtained from aerial parts during the fruiting stage [59]. The leaf oil was mostly characterized by linalool (36.7%) [61], (*E*)-*β*-ocimene (13.6–28.2%) [62, 63], and *β*-pinene (29.6%) [64], with minor contributions of limonene (12.2–15.2%) and 2,3,6-trimethylbenzaldehyde (12.7%), and *α*-pinene (19.8%) and *δ*-3-carene (11.4%). Interestingly, a significant variation was found when the leaf oil sample obtained from the vegetative stage was compared with that from the flowering stage [65]. Indeed, the former was characterized by α-pinene (57.0%), whereas the latter was dominated by (*E*)-anethole (95.5%). The oil obtained from umbels was characterized by α-pinene (42.2%) [66], linalool (19.0%) and lavandulyl acetate (16.0%) [61], and *β*-pinene (20.6%) and *δ*-3-carene (10.4%) [64, 67]. Fruit oil exhibited a different chemical profile, with *α*-pinene (18.0–26.3%) [66, 68], chrysanthenyl acetate (26.5%) [69], and *γ*-terpinene (27.8–30.2%) [70, 71] as the major constituents. The stem oil was characterized by 1,8-cineole (19.0%) and *α*-pinene (10.3%) [61]. The root oil was found to be rich in *β*-phellandrene (11.8–32.1%) and *δ*-3-carene (22.5–25.8%) [72, 73] and 3,5-nonadiyne (85%) [74]. The significant variability observed in the various studies can be mainly ascribed to differences in geographic origin (related, for example, to pedoclimatic factors), phenological stage, and genetics of the samples.

Biological properties of essential oils

Antioxidant and antimicrobial activities

The essential oil obtained from the aerial parts of *P. ferulacea* growing in Semnan province, Iran (main components: *β*-phellandrene [20.4%], *α*-terpinolene [15.3%], *α*-pinene [11.6%], *δ*-3-carene [11.1%], (*E*)-*β*-ocimene [9.7%], and *α*-phellandrene [9.1%]), showed antibacterial activity against *E. coli* and *Staphylococcus saprophyticus*, with MIC values of 3.27 and 8.19 µg/mL, respectively [78], whereas the essential oils of fruits and flowers of plants growing in East Azerbaijan, Iran, both rich in *α*-pinene and

▶ **Table 2** Main constituents (> 3 %) of the essential oils of *Prangos ferulacea*.

Plant part	Origin	Compounds (%)	Ref.
aerial parts[a]	Greece, Crete	γ-terpinene (27.5), α-pinene (10.4), α-terpinolene (9.0), (*E*)-β-ocimene (8.8), *p*-cymene (6.8), apiole (5.5), myrcene (4.4)	[75]
leaves[a] (veget. stage)	Iran, E. Azerbaijan	α-pinene (57.0), 3-ethylidene-2-methyl-1-hexen-4-yne (5.3), β-pinene (4.5), (*E*)-anethole (3.9), caryophyllene oxide (3.5)	[65]
leaves[a] (flow. stage)	Iran, E. Azerbaijan	(*E*)-anethole (95.5)	[65]
fruits[a]	Iran, E. Azerbaijan	α-pinene (63.1), *cis*-ocimene (9.7), β-pinene (8.3), myrcene (4.8)	[66]
umbels[a]	Iran, E. Azerbaijan	α-pinene (42.2), *cis*-ocimene (36.3), myrcene (5.0), β-phellandrene (3.3)	[66]
roots[a]	Iran, W. Azerbaijan	β-phellandrene (32.1), *m*-tolualdehyde (26.2), δ-3-carene (25.8), α-pinene (4.7)	[72]
aerial parts	Iran, Azerbaijan	β-pinene (43.1), α-pinene (22.1), δ-3-carene (16.9), α-terpinolene (3.9)	[23]
leaves[a]	Iran, Esfahan	linalool (36.7), caryophyllene oxide (16.3), α-pinene (12.1), 1,8-cineole (8.9)	[61]
stems[a]	Iran, Esfahan	1,8-cineole (19.0), α-pinene (10.3), caryophyllene oxide (4.2), linalool (3.7)	[61]
flowers[a]	Iran, Esfahan	linalool (19.0), lavandulyl acetate (16.0), 1,8-cineole (14.5), α-pinene (12.4), geranyl isobutyrate (12.2), α-campholenal (7.0), α-cadinol (6.4)	[61]
leaves[a]	Iran, Fars	(*E*)-β-ocimene (13.6), 2,3,6-trimethylbenzaldehyde (12.7), *p*-cymene (9.7), terpinolene (8.3), (*E*)-caryophyllene (5.4), β-elemene (5.3), germacrene D (5.0), α-bisabolol (4.9), limonene (4.5), kessane (3.4), γ-terpinene (3.4), α-pinene (3.0)	[62]
leaves[b]	Iran, Fars	(*E*)-β-ocimene (23.6), limonene (13.3), *p*-cymene (12.2), 2,3,6-trimethylbenzaldehyde (7.4), terpinolene (6.7), α-pinene (3.9), (*E*)-caryophyllene (3.1)	[63]
leaves[a]	Iran, Fars	(*E*)-β-ocimene (28.2), limonene (12.2), terpinolene (8.7), *p*-cymene (7.1), 2,3,6-trimethyl-benzaldehyde (7.0), germacrene D (5.0), (*E*)-caryophyllene (3.9), α-pinene (3.7), β-elemene (3.5), γ-terpinene (3.3)	[63]
leaves[c]	Iran, Fars	(*E*)-β-ocimene (22.1), limonene (15.2), 2,3,6-trimethylbenzaldehyde (8.6), *p*-cymene (7.6), terpinolene (6.6), (*E*)-caryophyllene (4.4), β-elemene (3.7), α-pinene (3.2), α-bisabolol (3.0)	[63]
aerial parts[a] (grow. stage), fresh	Iran, North Fars	terpinolene (56.3), (*E*)-caryophyllene (4.7), bornyl acetate (3.0)	[57]
aerial parts[a] (grow. stage), dry	Iran, North Fars	terpinolene (38.1), (*E*)-caryophyllene (3.6), bornyl acetate (1.8)	[57]
aerial parts[a] (veget. stage), fresh	Iran, North Fars	δ-3-carene (45.9), indole (11.6), terpinolene (9.6), *p*-cymen-8-ol (6.2), *n*-pentadecanol (5.5)	[58]
aerial parts[a] (veget. stage), dry	Iran, North Fars	limonene (55.1), γ-terpinene (10.7), bornyl acetate (8.5)	[58]
aerial parts[a] (flow. stage), fresh	Iran, North Fars	α-pinene (41.3), δ-3-carene (34.6), limonene (14.6), β-pinene (9.5), terpinolene (8.1), myrcene (7.4), sabinene (4.7), α-phellandrene (4.1)	[58]
aerial parts[a] (flow. stage), dry	Iran, North Fars	α-pinene (24.2), δ-3-carene (7.7), β-pinene (8.6), terpinolene (3.8), β-phellandrene (4.4)	[58]
aerial parts[a] (flow. stage)	Iran, Kermanshah	(*E*)-caryophyllene (48.2), α-humulene (10.2), spathulenol (9.3), linalool (3.5), δ-3-carene (3.4)	[58]
leaves[a]	Iran, Kurdistan	β-pinene (29.6), α-pinene (19.8), δ-3-carene (11.4), β-phellandrene (11.1), β-caryophyllene (3.7)	[67]
flowers[a]	Iran, Kordestan	β-pinene (20.6), δ-3-carene (10.4), α-pinene (8.8), β-phellandrene (8.1), germacrene D (5.8), α-humulene (5.3), *p*-cymene (3.8), δ-cadinene (3.3)	[67]
leaves[a]	Iran, Khorrasan	β-pinene (29.6), α-pinene (19.8), δ-3-carene (11.4), β-phellandrene (11.1), (*E*)-caryophyllene (3.7)	[64]
flowers[a]	Iran, Khorrasan	β-pinene (20.6), δ-3-carene (10.4), α-pinene (8.8), β-phellandrene (8.1), germacrene D (5.3), *p*-cymene (3.8), δ-cadinene (3.3)	[64]
roots[a]	Iran, Kohgiluyeh-Boirahmad	δ-3-carene (22.5), β-phellandrene (11.8), α-pinene (8.6), terpinolene (7.2), *p*-cymene (6.3), α-phellandrene (6.2), myrcene (4.5), sabinene (3.6), bornyl acetate (3.2), γ-terpinene (3.0)	[73]
aerial parts[a]	Iran, Lorestan	α-pinene (36.6), β-pinene (31.9), β-phellandrene (11.7), terpinolene (6.9), α-phellandrene (3.9), (*E*)-caryophyllene (3.1)	[76]
aerial parts[a] (pre-flow. stage)	Iran, Lorestan	β-pinene (43.0), α-pinene (40.0), β-phellandrene (6.5), α-terpinene (5.1)	[59]

cont.

▶ **Table 2** *Continued*

Plant part	Origin	Compounds (%)	Ref.
aerial parts[a] (flow. stage)	Iran, Lorestan	α-pinene (37.1), β-pinene (33.8), δ-3-carene (6.7), α-terpinene (6.5), β-phellandrene (5.6), terpinolene (4.9)	[59]
aerial parts[a] (fruit. stage)	Iran, Lorestan	α-pinene (31.7), β-pinene (38.5), β-phellandrene (10.3), terpinolene (5.1), α-terpinene (4.9), *p*-cymene (3.2)	[59]
aerial parts[a]	Iran, Sanandaj	β-pinene (22.9), δ-3-carene (16.0), α-pinene (12.6), epi-α-bisabolol (7.7), terpinolene (3.5), limonene (3.1)	[77]
aerial parts[as]	Iran, Semnan	β-phellandrene (20.4), α-terpinolene (15.3), α-pinene (11.6), δ-3-carene (11.1), (*E*)-β-ocimene (9.7), α-phellandrene (9.1), myrcene (4.5), sabinene (4.4), γ-terpinene (3.4)	[78]
fruits[a]	Iran, Tehran	chrysanthenyl acetate (26.5), limonene (19.6), α-pinene (19.5), δ-3-carene (6.6), mesitaldehyde (6.1), germacrene B (3.5)	[69]
fruits[a]	Italy, Sardinia	α-pinene (18.2), sabinene (15.9), limonene (15.1), *cis*-chrysanthenyl acetate (14.5), 2,3,4-trimethyl benzaldehyde (13.0), γ-terpinene (3.3), *p*-cymene (3.0)	[68]
fruits[a]	Italy, Umbria	γ-terpinene (27.8), (*Z*)-β-ocimene (26.8), terpinen-4-ol (12.2), *p*-cymene (6.9), α-pinene (4.1), β-humulene (3.5)	[70]
roots[a]	Montenegro	3,5-nonadiyne (85%)	[74]
aerial parts[d]	Turkey, market	β-phellandrene (22.3), α-pinene (16.2), *p*-cymene (11.2), β-myrcene (7.2), indene (6.4)	[11]
aerial parts[a]	Turkey, East Anatolia	2,3,6-trimethylbenzaldehyde (66.6), chrysanthenyl acetate (15.1), (*E*)-β-ocimene (3.8), *p*-mentha-1,5-dien-8-ol (3.6)	[79]
fruits[a]	Turkey, Gavur Mt.	γ-terpinene (30.2), α-pinene (16.7), *p*-cymene (9.8), (*E*)-β-ocimene (7.7), (*Z*)-β-ocimene (7.1), germacrene B (6.6)	[71]

[a] Hydrodistillation, [b] Ohmic-assisted hydrodistillation, [c] Ultrasonic pretreatment, [d] SPME: Solid-phase microextraction

cis-ocimene, displayed antibacterial effects against *B. cereus* (15 mm of inhibition zone diameter) [65, 80].

It was found that the essential oil from leaves of *P. ferulacea* growing in Esfahan, Iran, rich in linalool (36.7%), caryophyllene oxide (16.3%), α-pinene (12.1%), and 1,8-cineole (9.8%), exhibited particularly strong antibacterial activity, especially against Gram-positive organisms with MIC values of 0.0625, 0.25, 0.50, and 1.00 ppm on *P. aeruginosa, S. epidermidis, S. aureus* and *B. cereus*, respectively [61]. Also, the oil from the fruits collected near Teheran, Iran, whose main components were chrysanthenyl acetate (26.53%), limonene (19.59%), and α-pinene (19.50%) presented a good activity against *S. aureus, S. epidermis*, and *E. coli*, producing inhibition zone diameters of 14, 13, and 12 mm, respectively [69].

The essential oil of the aerial parts of *P. ferulacea* collected in the Broujerd mountains of Lorestan province, Iran, showed good antibacterial activity against several Gram-positive and Gram-negative bacteria, especially *S. aureus*. The inhibition of bacterial growth was attributed to the large content of monoterpenes such as α-pinene (36.6%) and β-pinene (31.1%) [76].

The essential oil from the flowering aerial parts of *P. ferulacea* collected in East Azerbaijan, Iran, characterized by a large content of (*E*)-anethole, exhibited significant phytotoxic activity (IC_{50} = 244.19 µg/mL) on lettuce and fungitoxic effects (0.01 mg/mL) against *Sclerotinia sclerotiorum* [65].

It was seen that ultrasonic pre-treatment of sample had no adverse effects on the biological properties of *P. ferulacea* essential oils and particularly improved the antioxidant activity [63].

The roots of *P. ferulacea* are traditionally used as an effective wound healing agent especially for pus-filled wounds both in human and livestock in the northwest of Iran. The antimicrobial properties of the root essential oil (major constituents: β-phellandrene [32.1%], *m*-tolualdehyde [26.2%], and δ-3-carene [25.8%]) were evaluated against *Staphylococcus aureus, S. epidermidis, Escherichia coli, Pseudomonas aeruginosa, Salmonella paratyphi* and *Candida albicans* using the agar dilution method. Very good growth inhibition of *S. aureus* and *P. aeruginosa* with a MIC value of 20 µg/mL, for both pathogens, was shown. In addition, the oil, at concentrations of 4 and 16 µg/mL, significantly enhanced the migration rate of L929 cells (63% and 87%, respectively, after 2 d), with a significant increase of collagen production [72].

Other properties

3,5-Nonadiyne, isolated from the root essential oil of *P. ferulacea* collected in Montenegro, selectively inhibited the endogenous nitric oxide release in rat peritoneal macrophages (IC_{50} = 6.7 µM) without inhibiting T cell proliferation [74].

Essential oil obtained from *P. ferulacea*, containing mainly 2,3,6-trimethylbenzaldehyde (66.6%) and chrysanthenyl acetate (15.1%), was tested on different stages of *Ephestia kuehniella* Zeller (Lepidoptera: Pyralidae) and against the egg parasite *Trichogramma embryophagum* Hartig (Hymenoptera: Trichogrammatidae). The essential oil was toxic to the adult stages of both pests with 100% mortality obtained after 24 h at 1.0 and 0.25 µL/L air, respectively. The LC_{50} and LC_{99} values of the essential oil against the egg stages of *E. kuehniella* and *T. embryophagum* were 320.372–486.839 and 2.121–5.662 µL/L air, respectively. The results of this study indicated that essential oil of *P. ferulacea* should be used as a control agent against these pests for integrated pest management programs [79].

Conclusions and Perspectives

This review summarized the main phytochemicals and biological properties of *P. ferulacea*, a species traditionally used in different countries for its antispasmodic, sedative, analgesic, anti-inflammatory, antiseptic, anti-viral, and antimicrobial properties. In several cases, scientific evidence has supported and validated its traditional uses. The most investigated characteristic of this species has been its antimicrobial activity, and both extracts and essential oils have been shown to possess promising effects, thus confirming the ethno-traditional uses. Coumarins are the main class of constituents isolated to date, although a few flavonoids have also been detected. These secondary metabolites, including mainly prenyl-coumarins and furano-coumarins, showed notable cytotoxic activity that is worthy of further investigation. Despite the large number of investigations reported, other studies should be carried out in order to increase our knowledge about this species. Most of the phytochemical studies examined the less polar fractions; consequently, a complete metabolic profile that also includes polar compounds is lacking. Furthermore, the biological activities of the extracts, essential oils, and pure compounds were mainly investigated using *in vitro* tests. Given that the potential health risks of *P. ferulacea*-derived products have not been investigated in depth, more detailed studies will be needed before they can be used for future pharmacological and commercial purposes.

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Conflict of Interest

The authors declare no conflicts of interest.

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