The *Prangos* genus: a comprehensive review on traditional use, phytochemistry, and pharmacological activities

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Abstract The members of the *Prangos* genus (Apiaceae) have been widely applied in the Iranian traditional medicine internally and externally for different purposes. The aim of this review is to summarize the ethnomedicinal and food applications of *Prangos* species and to gather the phytochemical and pharmacological data on this genus. Among the 129 constituents isolated from *Prangos* species, coumarin derivatives are the main compounds. Several papers report the compositions of essential oils obtained from different plant parts, mostly containing monoterpene and sesquiterpene hydrocarbons. Various pharmacological activities of essential oils, crude extracts or isolated compounds of the *Prangos* species have been observed, primarily in in vitro experiments. Antioxidant, antimicrobial, cytotoxic and anti-proliferative activities have been the most extensively studied. The efficacy and safety of *Prangos* plants have not been assessed in animal experiments or clinical trials. Although their furocoumarin content might be a source of adverse effects, toxic effects of *Prangos* species have not been reported. It can be concluded, that further preclinical and clinical data are necessary to assess the rationale and safety of the medicinal and food use of *Prangos* species.

Abbreviations

A2780S	Human ovarian carcinoma cell line
A375	Human melanoma cell line
A431	Human epidermoid carcinoma cell line
A549	Human lung cell line
ABTS	2,2′-SzinobisAzino-bis-(3-ethylbenzthiazoline-6-sulfonate)
ACE	Angiotensin-converting enzyme
AChE	Acetylcholinesterase enzyme
AE	Acarbose equivalent
BChE	Butyryl-cholinesterase enzyme
BHK 21	Baby hamster kidney fibroblast cell line
Caco-2	Human colon cancer cell line
CCL-221	Human colorectal cancer cell line
COX-1	Cyclooxygenase enzyme type 1
COX-2	Cyclooxygenase enzyme type 2
CUPRAC	Cupric ion reducing activity
DEET	*N,N*-Diethyl-3-methylbenzamide
DPPH	2,2-Diphenyl-1-picrylhydrazyl
EO	Essential oil
FRAP	Ferric reducing antioxidant power
GE	Galanthamine equivalent
GST	Glutathione-S-transferase

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HCT-116	Human colon cell line
HIV-1	Human immunodeficiency virus type 1
HSV	Herpes simplex virus type 1
IL-6	Interleukin 6
IL-8	Interleukin 8
IZ	Growth inhibition zone
KAE	Kojic acid equivalent
LC_{50}	Concentrations that killed 50% of the exposed insects
LC_{99}	Concentrations that killed 99% of the exposed insects
LDH	Lactate dehydrogenase
LNCaP	Human prostatic cell line
LPO	Lipid peroxidation inhibition
MED	Minimum effective dose
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
NCI-H322	Human lung cell line
NSAID	Non-steroidal anti-inflammatory drug
OE	Orlistat equivalent
ORAC	Oxygen radical absorbance capacity
PC-3	Human prostate cell line
PFU	Plaque-forming units
RC_{50}	Concentration that reduces 50% of the free radical concentration
TBA	Thiobarbituric acid
TC_{50}	Drug concentration that reduces the cell growth 50%
TE	Trolox equivalent
THP1	Human leukemia cell line
TNF-α	Tumour necrosis factor alpha

Introduction

Apiaceae (syn. Umbelliferae) is one of the largest families of Plant Kingdom: it comprises 434 genera and 3780 species. Most of these species are aromatic plants with hollow stems, and several representatives are used as vegetables or condiments (Stevens 2001). The genus *Prangos* Lindley (syn. *Cryptodiscus* Fischer & C. A. Meyer, *Koelzella* Hiroe; *Neocryptodiscus* Hedge & Lamond), distributed from Portugal to Tibet, consists of 45 species (Stevens 2001). The centre of the diversity of *Prangos* genus is the Irano-Turanian region. The main anatomical and morphological

features characteristic to Apiaceae species, can also be discovered in *Prangos* species with some specific morphological changes regarding fruits, endosperms and mesocarp. According to phylogeny studies, *Prangos* is a monophyletic taxon closely related to *Bilacunaria* and *Cachrys* (Lyskov et al. 2017) genera. Species of *Prangos* genus have been used in the traditional medicine of the Mediterranean region and the Middle East.

Prangos species possess a great importance as spices and medicinal plants in Asia, especially in Iran, Turkey, and Iraq. The above-ground part, the roots and the essential oil of different species have been applied internally and externally as well. The most popular indications of the plants are the alleviation of different gastrointestinal symptoms, but various other uses have also been reported. In the recent years, the number of papers reporting experimental data on the biological effects of *Prangos* species have been increased. However, there is no systematic review available that summarizes the current knowledge on these species.

Coumarin derivatives, particularly furocoumarins have been isolated and identified as the predominant secondary metabolites of several *Prangos* species. Considering the fact that furocoumarins may possess phototoxic and carcinogenic effects (Melough et al. 2018), the assessment of qualitative and quantitative data on the furocoumarin content of these plants is of primary importance. Furthermore, the summary of phytochemical components of the genus may be useful to understand better the described bioactivities and also to provide new directions for further research.

Our aim was to review scientific data on traditional use, bioactivity, and phytochemical profile of the *Prangos* genus, by searching for the keyword "*Prangos*" (from 1974 to 2019) on PubMed, and Web of Science databases (last search: 01. 11. 2019).

Traditional use of *Prangos* species

The ethnomedicinal applications of the *Prangos* genus are shown in Table S1. In Turkey, *Prangos* plants are used as carminative, tonic, and anthelmintic agents, in the treatment of external bleeding, gastric or digestive disorders, wounds, scars, and leuckoplakia. Moreover, *Prangos* species are also used as stimulants, aphrodisiacs and natural fertilizers (Oke Altuntas et al.

2016; Ozek et al. 2018). Some species of this genus are consumed as spices or food additives as well.

Due to its aphrodisiac, coagulant, carminative and tonic effects, different *Prangos* species are part of the traditional medicine (Razavi et al. 2010c; Abolghasemi and Piryaei 2012). The most commonly used species of this genus are *P. ferulacea* and *P. pabularia*. The leaves of these plants are traditionally used as laxative, antihypertensive, and carminative agents and are also recommended for the treatment of digestive disorders (Dokovic et al. 2004; Sagun et al. 2006; Kazerooni et al. 2006; Durmaz et al. 2006; Özek et al. 2007; Ahmed et al. 2011a; Razavi 2012b; Farooq et al. 2014a; Shokoohinia et al. 2014; Namjoyan et al. 2015; Seidi Damyeh et al. 2016; Tabanca et al. 2016; Gheisari et al. 2016; Yousefi et al. 2017; Delnavazi et al. 2017; Kiliç et al. 2017; Ozek et al. 2018; Sadeghi and Bazdar 2018; Abbas-Mohammadi et al. 2018; Numonov et al. 2018). In Western North Iran, the essential oil from roots of *P. ferulacea* has been traditionally used for wound healing (Yousefi et al. 2017).

The fresh fruits and roots of *P. pabularia* are also consumed in Tajikistan (local name: Yugan) for its putative effects in the treatment of vitiligo, and because these are considered to have tonic effects (Numonov et al. 2018). In India, only *P. pabularia* (local names: Komal, Kurangas) is native. The roots and fruits of this species are used as laxative, liver tonic, diuretic, carminative, and stimulant. Infusion from the roots is used in the treatment of flatulence, indigestion and improving of menstrual cycle in women (Farooq et al. 2014b). In Turkish folk medicine, the roots of *P. pabularia*, and *P. meliocarpoides* are eaten with honey as aphrodisiac (Ozek et al. 2018).

In Kurdish traditional medicine (eastern part of Iraq), the aerial part of *P. haussknechtii* is used for its carminative, diuretic, and sedative effects (Dissanayake et al. 2017).

Besides their medicinal use, *Prangos* species are extensively used as food additives, spices and flavouring agents (Table S1). *P. ferulacea* is used in Iran (Iranian name: Djashir) as yogurt flavouring, and animal fodder (Damyeh et al. 2016; Abbas-Mohammadi et al. 2018, Shokoohinia et al. 2014), whereas in Turkey (local names: Casir, Caksir) it is used as food ingredient, e.g. in Van herby cheese, aroma and flavour component (Sagun et al. 2006; Ozek et al. 2018) and as stimulant tea (Kiliç et al. 2017). The young stems and shoots of *P. platychlaena* Boiss. (local names: Cagsir, Caksir, Kirkor, and Korkor) are eaten freshly and used as pickle in Eastern Turkey, while it is consumed after baking in the central part of the country. Furthermore, the roots of the plant are often powdered and mixed with honey to consume as aphrodisiac (Ozek et al. 2018; Tabanca et al. 2018).

Pharmacological and biological activities

Bioactivity of extracts, essential oils, and isolated secondary metabolites of *Prangos* species have been investigated by several research groups. The most extensively studied effect of *Prangos* species have been experimented in vitro. Among them antioxidant activity is the major bioactivity evaluation. The only in vivo study is evaluation of abortifacient effect of the *P. ferulacea* leaves extracts. Antimicrobial (antibacterial, antifungal, and antiviral), anti-cancer (cytotoxic and antiproliferative), anti-inflammatory, anti-diabetic, neuroprotective and other pharmacological activities of *Prangos* species have also been assessed. Allelopathic effects including phytotoxic, insecticidal and repellent activities of EOs of *Prangos* species have also been reported. In the majority of the experiments, aerial parts were used, usually as methanolic or hydroethanolic extracts. The pharmacological studies that had been performed on *Prangos* spp. are listed in Table S2.

Antioxidant activities

Free radicals are generally synthesized as by-products in all living organisms and can result in oxidative damage to biological molecules like DNA, fatty acids, and amino acids. Free radicals and oxidative stress are proved to play an essential role in the development of certain chronic diseases (Sarma et al. 2010), hence plants possessing remarkable antioxidant activity may play role in health protection.

Many plant products (EOs, different extracts and pure constituents) obtained from different parts of *Prangos* species have been evaluated for their free radical scavenging activity, and several of these natural products possessed noteworthy antioxidant potential. Antioxidant tests, including ABTS, CUPRAC, DPPH, FRAP, LPO, ORAC and TBA

assays were carried out in vitro. Of the tested samples, the methanolic extracts of *P. ferulacea* demonstrated high antioxidant activity in various assays; and among the isolated compounds, the coumarin scopoletin (**9**) obtained from *P. uloptera* exhibited the most significant activity (Razavi et al. 2008b).

Crude extracts and essential oils

In a study, various extracts of *Prangos* species have been subjected to antioxidant activity assays. Aqueous extracts of *P. denticulata* leaf (IC$_{50}$: 0.048 mg/mL) and *P. heyniae* fruit (IC$_{50}$: 0.119 mg/mL) showed the highest antioxidant activities using the DPPH test compared to α-tocopherol (IC$_{50}$: 0.011 mg/mL), BHA (IC$_{50}$: 0.003 mg/mL), and BHT (IC$_{50}$: 0.023 mg/mL) as controls. In metal chelating assay the aqueous leaf extract of *P. denticulata* (0.94 mg/mL) and methanol root extract of *P. heyniae* (0.74 mg/mL) were the most potent extracts. Aqueous extracts from leaves and fruits of *P. denticulata* were the strongest antioxidant agents with inhibition values of 69.93% and 68.98%, respectively, by using plasma lipid peroxidation method (Oke-Altuntas et al. 2015). In a comparative study, the hot water extract of *P. denticulata* leaf exerted the highest ability in scavenging free radicals (IC$_{50}$: 0.048 mg/mL), compared to various extracts of the species and the aqueous extract of *P. platychloena* was equally active (IC$_{50}$: 0.048 mg/mL) (Oke Altuntas et al. 2011).

The antioxidant activities of the EO and the hydroalcoholic extracts (particularly methanolic) of *P. ferulacea* have been extensively studied. The hydroalcoholic extract obtained from *P. ferulacea* flowers possesses the highest antioxidant capacity with IC$_{50}$ = 8.01 μL/mL in the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. The other samples derived from this species were less active: hydroalcoholic extract of flowers (IC$_{50}$: 8.01 ± 0.60 μL/mL) > hydroalcoholic extract of leaves (IC$_{50}$: 10.99 μL/mL) > aqueous extract of flowers (IC$_{50}$: 14.59 μL/mL) > aqueous extract of leaves (18.61 μL/mL) > EO of leaves (22.99 μL/mL) > EO of flowers (23.90 μL/mL) (Bazdar et al. 2018). Evaluation of free radical scavenging activity of hydroalcoholic extracts obtained from ten Iranian *P. ferulacea* samples revealed moderate activities with EC$_{50}$ values of the most potent samples of 0.013 mg/mL and 10.55 mmol Trolox equivalent (TE)/g in the DPPH and oxygen

radical absorbance capacity (ORAC) assays, respectively (Bagherifar et al. 2019). In a similar study, antioxidant activities of methanolic and aqueous extracts obtained from the roots, herbs, and flowers of four *Prangos* species (*P. ferulacea*, *P. uechtritzii*, *P. heyniae*, *P. meliocarpoides* var. *meliocarpoides*) collected in Turkey were measured by the thiobarbituric acid assay (TBA). Among the tested extracts, the methanolic extract of *P. ferulacea* and *P. uechtritzii* fruits had the highest antioxidant activities with IC$_{50}$ values of 0.047 mg/mL and 0.049 mg/mL, respectively (Ahmed et al. 2011b). In a comparative study, radical scavenging and lipid peroxidation inhibitory activities of *P. ferulacea* were compared to other Apiaceae species including *Chaerophyllum macropodum* Boiss. and *Heracleum persicum* Desf. The methanolic extract of aerial parts of *P. ferulacea* with IC$_{50}$ = 0.242 and 0.152 mg/mL for DPPH radical scavenging and lipid peroxidation inhibition (LPO), respectively, showed better antioxidant activities in comparison with the two other investigated plants (Çoruh et al. 2007). From *P. ferulacea* samples, the ethyl acetate extract of the plant had the highest antioxidant activity among the different extracts using the DPPH and the ABTS assays, showing IC$_{50}$ values of 1.4 mg/g and 5.4 mg/g, respectively (Dagdelen et al. 2014). MeOH extract of *P. ferulacea* fruit exerted a good potency in scavenging of free radicals in the DPPH assay, with 6.4% of inhibition compared with ascorbic acid (4.0%) as the positive control at a concentration of 0.01 mg/mL (Cesur et al. 2017). A methanolic extract of *P. ferulacea* (IC$_{50}$: 0.228 mg/mL) exhibited moderate antioxidant activity, evaluated by the DPPH method (Mavi et al. 2004).

The antioxidant activity of EO, *n*-hexane, dichloromethane, and methanolic extracts obtained from aerial parts of *P. gaubae* were evaluated in the DPPH, cupric ion reducing activity (CUPRAC) and ferric reducing antioxidant power (FRAP) assays. The methanolic extract was the most active extract using the DPPH (0.47 mmol TEs/g), CUPRAC (0.89 mmol TEs/g), and FRAP (0.52 mmol TEs/g) assays, whereas the EO had the highest capacity in scavenging of free radicals using the ABTS method (2.02 mmol TEs/g) (Bahadori et al. 2017a).

Yazici et al. (2013) reported that the methanolic extracts of *P. hulusii* aerial parts had stronger antioxidant activity compared to its roots analysed by different assays (Yazici et al. 2013).

The fruits of *P. meliocarpoides* were extracted with various solvents, and among the extracts the methanolic extract showed the highest DPPH radical scavenging effect (IC_{50}: 0.088 mg/mL), followed by the aqueous, acetone and ethyl acetate extracts (Oke Altuntas et al. 2016).

The dichloromethane extract of *P. pabularia* roots (collected from Iran) displayed the highest antioxidant activity using the DPPH assay with an RC_{50} (concentration of the test material that reduces 50% of the free radical concentration) value of 0.08 mg/mL followed by the methanolic and *n*-hexane extracts with RC_{50}s of 0.17 and 1.38 mg/mL, respectively (Salehi et al. 2016).

Pure compounds

8-Geranyloxy psoralen (**32**), a furocoumarin isolated from the roots and fruits of *P. uloptera* exerted weak antioxidant effect with RC_{50} of 0.262 mg/mL in the DPPH assay (Razavi et al. 2009a). Scopoletin (**9**) was the most active antioxidant compound from the five extracted coumarins (xanthotoxin (**36**), prangenin (**73**), scopoletin (**9**), deltoin (**79**) and prangolarin (syn. oxypeucedanin) (**48**)) from the aerial parts of *P. uloptera*, with an RC_{50} value of 0.0243 mg/mL (Razavi et al. 2008b). The free radical scavenging activity of oxypeucedanin (**48**), isolated from leaves of *P. uloptera* was evaluated by the DPPH assay (RC_{50} value of 51.25 mg/mL) (Razavi et al. 2010b). Aviprin (**89**), isolated from *P. uloptera* with RC_{50} of 0.54 mg/mL was more effective than aviprin-3″-*O*-D-glucopyranoside (**90**) (RC_{50}: 5 mg/mL) in the DPPH assay (Zahri et al. 2012). Among the isolated phytochemicals from aerial parts of *P. haussknechtii*, hydroxy osthol-epoxide (**4**) was the most potent antioxidant compound with IC_{50}s of 0.048 and 0.043 mM measured by MTT and LPO, respectively (Dissanayake et al. 2017).

Antimicrobial activities

Extracts, essential oils and pure compounds of *Prangos* species showed noteworthy antibacterial, antifungal, and antiviral effects. The antibacterial activities of the plant materials have been evaluated mostly by disc diffusion and microtiter broth dilution assays. Remarkably high activities were observed in case of the EO of the leaves of *P. ferulacea* against

Pseudomonas aeruginosa, *Staphylococcus epidermidis*, *S. aureus*, and *Bacillus cereus* strains. Mainly the Gram-positive bacteria (particularly *S. aureus* and *B. cereus*) were inhibited by various *Prangos* species, especially by EOs and methanolic extracts of *P. ferulacea*. *P. ferulacea, P. pabularia* and *P. platychlaena* which were active against *C. albicans*.

Antibacterial activities

Crude extracts and essential oils

The EO of the fruit of *P. asperula* was evaluated for its antibacterial activity and showed a moderate effect against *S. aureus* with a minimum inhibitory concentration (MIC) of 0.128 mg/mL (Khoury et al. 2018). *S. aureus* was the most susceptible strain against the EO obtained from the aerial parts of *P. asperula* (growth inhibition zone (IZ): 15.0 mm), the EO was less active on *Escherichia coli* (IZ: 11.8 mm) and *Salmonella enterica* (IZ: 3.8 mm). The results of the MbD assay reassured these observations (Mneimne et al. 2016).

The acetone extract of the fruit of *P. denticulata* collected from Turkey was characterized with an IZ of 11.9 mm against *Bacillus cereus* RSKK 863 (Oke-Altuntas et al. 2012).

Among EOs obtained from various organs of *P. ferulacea*, the EO obtained from the leaves was the most active one with the following MIC values: *Pseudomonas aeruginosa* (0.0000625 mg/mL), *S. epidermidis* (0.00025 mg/mL), and *S. aureus* (0.0005 mg/mL), while the EO obtained from the flowers were most active EO against *B. cereus* (0.0005 mg/mL). The EO obtained from the stem part was less active (Akbari et al. 2010). Razavi et al. (2010a) reported that *B. cereus* (IZ of 15 mm) was the most susceptible strain to the EOs of *P. ferulacea* fruits and umbels (Razavi et al. 2010a). EO of *P. ferulacea* root showed high inhibitory activity against *S. paratyphi* and *E. coli* with MIC values of 0.01 and 0.005 mg/mL, respectively (Yousefi et al. 2017).

The antimicrobial activities of some medicinal plants used in traditional Turkish cheeses were analysed in an experiment. The methanolic extract of *P. ferulacea* was active against *Enterococcus faecalis* with a MIC value of 250 mg/mL (Dagdelen et al. 2014), on other microbes the activity was even less pronounced. The methanol extract of *P. ferulacea* showed moderate antibacterial activity against *B.*

cereus, *B. subtilis*, *Micrococcus luteus*, and *S. aureus* with IZs of 12–18 mm (Durmaz et al. 2006). Gheisari et al. (2016) investigated the antibacterial activities of the methanolic extracts from the aerial parts of *P. ferulacea* by two methods. Using the disc diffusion method, *C. freundii* was the most susceptible strain with an IZ value of 12.76 mm. Furthermore, these results were supported by the microtiter broth dilution method, where the extract exerted 99% inhibition on the growth after 24 h (Gheisari et al. 2016). Methanolic and ethanolic extracts of *P. ferulacea* showed more significant activity against *Listeria monocytogenes* serotype 4ab with IZs of 13 and 11 mm, respectively, compared to its aqueous and *n*-hexane extracts having no activity (Sagun et al. 2006).

The antibacterial activities of roots, flowers, leaves, stems, and seeds of *P. ferulacea* and *P. uloptera* were analysed using disc diffusion assay. The methanolic extracts of the roots of both species possessed high activity with MIC values of ≤ 0.25–1 mg/mL against the tested strains including *S. aureus*, *S. pyogenes*, *B. subtilis*, *E. coli*, *S. enterica*, and *Serratia marcescens* (Nosrati and Behbahani 2016). EO of *P. ferulacea* indicated a significant activity against *E. faecalis* (IZ: 23 mm) compared to gentamicin (IZ: 8 mm) as positive control (Nazemisalman et al. 2018).

In a study carried out with different extracts of *P. hulusii* roots collected in Turkey, the most potent antibacterial activity was attributed to the dichloromethane extract of the plant on *E. coli* with a MIC value of 0.156 mg/mL (Tan et al. 2017). Yazici et al. (2013) reported that *P. hulusii* possessed no activity against *S. aureus*, *E. coli*, *Klebsiella pneumoniae*, *B. cereus*, and *Proteus vulgaris* (Yazici et al. 2013).

The hydro-distilled EO of *P. pabularia* fruits demonstrated antibacterial activity against two Gram-positive [*S. epidermidis* and methicillin-resistant *S. aureus* (MRSA)], and four Gram-negative bacteria (*E. coli*, *P. aeruginosa*, *P. vulgaris*, and *Salmonella typhimurium*), and antifungal activity against *C. albicans*; while among the studied microorganisms the most susceptible was the MRSA (clinical isolate, MIC: 0.00125 mg/mL) (Özek et al. 2007).

In another study, the EO of *P. peucedanifolia* leaves was active against *S. mutans*, *S. pyogenes*, and *S. aureus* with MIC values less than 1.9 mg/mL, whereas the EO of the fruits was less active (Brusotti et al. 2013).

The evaluation of the antibacterial properties of EOs of fruits of *P. platychlaena* and *P. uechtritzii* revealed high activities against *E. coli* (MIC: 9 mg/mL) and *B. subtilis* (MIC: 36 mg/mL), respectively (Uzel et al. 2006).

Among different extracts (*n*-hexane, methanol, and dichloromethane) obtained from *P. uloptera* roots, the dichloromethane fraction demonstrated the most pronounced antibacterial effect against *S. aureus* analysed by the disc diffusion method (IZ: 15.8 mm); whereas no activity was observed against *E. coli*. Microbroth dilution assay reassured these results, where the highest and lowest activity was observed on *S. aureus* and *E. coli*, respectively (Razavi et al. 2010c).

Pure compounds

Oxypeucedanin (**48**) and imperatorin (**44**) isolated from the chloroform extract of *P. platychlaena* showed slight activity against *E. coli* (MIC of 0.048 mg/mL) (Ulubelen et al. 1995), whereas oxypeucedanin (**48**) was not active against the plant pathogen bacteria *Xanthomonas compestris* and *Erwinia cartovorum* (Razavi et al. 2010b).

Compounds isolated from *P. uloptera* were subjected to antimicrobial screening, and 8–geranyloxy psoralen (**32**) was found to be effective against *S. epidermidis* with a MIC value of 100 mg/mL (Razavi et al. 2009a). In another study, isoarnottinin 4'-glucoside (**28**) isolated from *P. uloptera* possessed high antibacterial activity (particularly against *E. carotovora* with a MIC value of 0.1 mg/mL) (Razavi et al. 2011b).

From ten isolated prenylated coumarins of *P. hulusii*, the new coumarin 4'–senecioiloxyosthol (**20**), showed the highest activity against a series of bacteria and was especially active against *B. subtilis* (MIC of 0.005 mg/mL) (Tan et al. 2017).

Osthol (**3**), isolated from *P. pabularia* exerted a remarkable effect against MRSA and *P. aeruginosa* (MIC values of 0.031 mg/mL) compared to the other tested compounds (Tada et al. 2002).

Antifungal activities

Some natural products can permanently damage fungal cell membrane by increasing permeability and fluidity. The subsequent degradation of lipids, proteins and nucleic acids along with the coagulation

of the cellular components results in the breakdown and death of fungal cells (Yoon et al. 2000). Several studies demonstrated that *Prangos* species possess antifungal activity against Gram-positive and Gram-negative fungi.

Crude extracts and essential oils

The EO of *P. asperula* fruits showed remarkable antifungal activity against *Trichophyton rubrum* and *Trichophyton tonsurans* with MICs of 0.064 mg/mL in both strains (Khoury et al. 2018). The EO obtained from the aerial parts of *P. asperula* inhibited the growth of *Trichophyton mentagrophytes*, *Aspergillus fumigatus*, and *C. albicans*, with IZ values of 7.3 mm, 9.1 mm, and 1.9 mm, respectively (Mneimne et al. 2016).

Yousefi et al. (2017) reported that the EO of the roots of *P. ferulacea* had inhibitory activity on *C. albicans* (MIC: 0.005 mg/mL) (Yousefi et al. 2017). The methanolic extract of this species did not inhibit growth of *C. albicans* (Dagdelen et al. 2014). The EO of *P. ferulacea* obtained at flowering stage significantly inhibited the growth of *Sclerotinia sclerotiorum* mycelia at doses exceeding 0.01 mg/mL; the inhibition was approximately 55% at 1.5 mg/mL concentration (Razavi 2012a). The EO obtained from fruits and umbels of *P. ferulacea* demonstrated an activity with 9–12 mm of inhibition against *C. kefyr* (Razavi et al. 2010a). By applying microbroth dilution method, the hydroalcoholic extract of *P. ferulacea* showed a weak effect (MIC: > 1000 mg/mL) against *C. albicans* (Dagdelen et al. 2014).

When assessing antifungal activity of EO of *P. pabularia* fruits, significant activity was observed against *C. albicans* (MIC: 0.0025 mg/mL) (Özek et al. 2007).

Brusotti et al. (2013) reported that the EO of *P. peucedanifolia* flowers has remarkable antifungal activity against *Trichophyton rubrum* with a MIC value of 2.4 mg/mL comparable to that of ampicillin (MIC: 0.5 mg/mL) (Brusotti et al. 2013).

The EOs yielded from fruits of *P. platychlaena* and *P. uechtritzii* had marginal activities against *C. albicans*, *C. krusei*, and *C. tropicalis* with MIC values exceeding 72 mg/mL (Uzel et al. 2006). The decoction (drug-extract ratio 1:2 w/v) of *P. uechtritzii* showed potent inhibitory activity at concentration of 80% on the growth of *Alternaria alternata*, *Aspergillus*

parasiticus, and *Penicillium digitatum* with 57, 29, and 71% inhibition, respectively; however, no inhibitory activity was found against *Aspergillus niger* (Ozcan 1999).

Furthermore, the EO of the fruit of *P. platychlaena* had no antifungal activities against three *Colletotrichum* species. Nona-(2*S*)-3,5-diyn-2-yl acetate (**134**) from the EO and its semisynthetic derivative (2*S*)-3,5-nonadiyn-2-ol were also inactive against the above-mentioned fungi (Tabanca et al. 2018).

Pure compounds

A good antifungal effect (MIC > 0.4 mg/mL) of isoarnottinin 4′-glucoside (**28**) was revealed against *S. sclerotiorum* and *C. kefyr* (Razavi et al. 2011b).

In the study of Ulubelen et al. (1995) both oxypeucedanin (**48**) and imperatorin (**44**), isolated from *P. platychlaena*, showed strong antifungal activities against *C. albicans* with MICs of 0.054 mg/mL (Ulubelen et al. 1995).

8-Geranyloxy psoralen (**32**) isolated from *P. uloptera* has been reported to possess very weak activity against *C. kruzei* and *C. kefyr*, with MIC values of 300 and 100 mg/mL, respectively (Razavi et al. 2009a).

Quercetin-3-*O*-glucoside (**98**) isolated from *P. ferulacea* had no activity against *C. kefyr* (Razavi et al. 2009c). Oxypeucedanin (**48**) isolated form leaf extract of *P. uloptera* was found to be inactive against *S. sclerotorium* (Razavi et al. 2010b).

Antiviral activities

Crude extract

Antiviral activities of the ethanolic extracts of *P. asperula* leaf and seed samples were assessed against herpes simplex virus type 1 (HSV-1) and a moderate potency was demonstrated (IC$_{50}$: 0.66 mg/mL) compared to acyclovir (IC$_{50}$: 0.00377 mM) (Saab et al. 2012).

Pure compounds

From a series of coumarins isolated from *P. tschimganica*, psoralen (**31**) was identified as the most effective compound. It inhibited the replication of human immunodeficiency virus type 1 (HIV-1) (IIIB

Strain) in H9 lymphocytes (EC_{50}: 0.0001 mg/mL) and inhibited the growth of uninfected H9 cells (IC_{50}: 0.0191 mg/mL) with IC_{50} and EC_{50} values comparable to those of the active control azidothymidine (EC_{50}: < 0.001 mg/mL; IC_{50}: 500 mg/mL) (Shikishima et al. 2001a).

Anti-herpes virus effects of the coumarins isolated from *P. ferulacea* were analysed on a confluent monolayer of Vero cells (an African green monkey kidney cell line) infected with 25 PFU (plaque-forming units) of HSV-1. None of the analysed coumarins possessed anti-HSV activity at non-toxic concentrations on Vero cells (Shokoohinia et al. 2014).

Phytotoxic activity

Phytotoxicity is the ability of plant to inhibit of plant growth, delay of seed germination or prevention of the other adverse effects caused by phytotoxins (Blok et al. 2019). The extracts, EOs, and isolated phytochemicals from three *Prangos* species including *P. ferulacea*, *P. pabularia*, and *P. uloptera* have been previously subjected to possess possible phytotoxicity by analysis of their potency in prohibition of growth of lettuce and *Trifolium resupinatum*.

Among aqueous and hydro-alcoholic extracts obtained from different plant parts (leaf, flower and shoot) of *P. ferulacea*, the hydro-alcoholic extract of the flowers showed phytotoxic effect by increasing the proline content and decreasing seedling growth and seed germination of *Trifolium resupinatum* (Bazdar and Sadeghi 2018; Sadeghi and Bazdar 2018). The EO of *P. ferulacea* obtained during the flowering period inhibited lettuce seed germination with an inhibition value of 97.0% (Razavi 2012a).

The EO extracted from *P. pabularia* showed strong phytotoxic effect with IC_{50} values of 0.14, 0.11 and 0.12 mg/mL for inhibition of the growth of the shoot, seed germination, and root of lettuce, respectively (Razavi 2012b).

The dichloromethane extract of *P. uloptera* exhibited higher stunting effect compared to the *n*-hexane, and methanolic fractions against root growth, seed germination, and shoot elongation of lettuce (*Lactuca sativa* L. CV. Varamin), with IC_{50}s of 1.85, 2.00, and 2.08 mg/mL, respectively (Razavi et al. 2010c). Oxypeucedanin (48), isolated from *P. uloptera* exhibited phytotoxic effect by inhibiting the growth of

lettuce shoots with an IC_{50} value of 0.21 mg/mL (Razavi et al. 2010b). Isoarnottinin 4′-glucoside (28) possessed considerable phytotoxic activity against root elongation of lettuce; whereas the length of the root was decreased from 38.72 to 5.84 mm at concentrations 0 to 1 mg/mL of isoarnottinin 4′-glucoside (28), respectively (Razavi et al. 2011b).

Insecticidal and repellent activity

In general, the insecticidal and repellent activities of EOs extracted from *P. ferulacea*, *P. heyniae*, and *P. platychlaena* have been evaluated. They showed a moderate activity comparing to the applied controls.

The EO of *P. ferulacea* was active against the egg stage of *Trichogramma embryophagum* with an LC_{50} value of 0.0021 mL/L (Sumer Ercan et al. 2013).

P. heyniae EO obtained from four different regions of Turkey possessed moderate larvicidal activity at 0.03125 and 0.062 mg/mL against *Aedes aegypti* compared to permethrin (0.000025 mg/mL) as positive control (Ozek et al. 2018).

The EO gained from *P. platychlaena* collected in Eastern part of Turkey showed repellent activity against female *A. aegypti* L. mosquito with a minimum effective dosage (MED) value of 0.156 mg/cm^2 (Tabanca et al. 2018).

Suberosin (6), a coumarin from *P. pabularia* demonstrated moderate mosquito repellent effect compared to *N*,*N*-diethyl-3-methylbenzamide (DEET) as the positive control. This compound also showed a remarkable larvicidal activity with an LC_{50} value of 0.008 mg/mL at 24-h post treatment (Tabanca et al. 2016).

Cytotoxic and antiproliferative activities

The secondary metabolites isolated form plants have been demonstrated promising approach to discover potential drugs to be considered as a complementation of chemotherapeutics treatment (Newman and Cragg 2012). Nowadays, some of the phytochemicals are known for their strong potency as anti-tumour agents. The plants in the genus of *Prangos* have been subjected to evaluate their effects on various cancer cell lines possessing cytotoxicity and antiproliferation activities.

Crude extracts and essential oil

The ethanolic extract of aerial parts of *P. asperula* were investigated for cytotoxic effects on Vero cell line (ATCC: CCL 81) using the MTT assay, and it showed moderated activity with TC_{50} values higher than 1 mg/mL (Saab et al. 2012). The antiproliferative activity of the EO obtained from the leaves of *P. asperula* was investigated by the sulphorhodamine B assay, and an IC_{50} of 0.139 mg/mL was observed against renal cell adenocarcinoma (Loizzo et al. 2008b).

Rostami et al. (2012) studied the in vitro antiproliferative activity of aqueous extracts of *P. platychloena* by the Trypan Blue exclusion test. The extract was active at concentration of 1 mg/mL with maximum inhibitions 72% and 59% in colorectal cancer cell line (CCL-221) and colon cancer cell line (Caco-2), respectively (Rostami et al. 2012).

The dichloromethane extract of *P. uloptera* roots reduced the viability of HeLa cells after 24 h with an IC_{50} 0.10 mg/mL; 100% cytotoxicity was recorded at concentrations exceeding 1 mg/mL (Razavi et al. 2010c).

Remarkable cytotoxic activity was reported for the dichloromethane extract of *P. pabularia* on HeLa cell line (IC_{50}: 0.52 mg/mL at 24 h) in the MTT assay (Salehi et al. 2016).

Yazici et al. (2013) investigated the cytotoxic activity of various extracts of *P. hulusii* obtained from aerial parts and roots using the MTT and lactate dehydrogenase (LDH) assays. In the MTT assay, the extracts had no effects at the tested concentrations; however, petroleum ether extracts demonstrated low activity in the LDH assay on the rat kidney epithelial cell line (Yazici et al. 2013).

Using the MTT assay, the extracts of *P. meliocarpoides* were not toxic to baby hamster kidney fibroblast cell line (BHK 21) in concentrations of 0.01–0.1 mg/mL (Altuntas et al. 2011).

Pure compounds

Compounds isolated from *P. ferulacea* were tested on human ovarian carcinoma cell line (A2780S) using the MTT assay, and osthol (**3**) had an IC_{50} value of (0.38 mM, viability of 9.41%), while isoimperatorin (**45**) was less active (IC_{50}: 1.1 mM) (Shokoohinia et al. 2014). From the EO of the root part of *P. ferulacea*

3,5-nonadiyne (**133**) was isolated, and this compound exhibited no activity against Thymic T lymphocytes rat cell line (Dokovic et al. 2004). The isolated quercetin 3-*O*-glucoside (**98**) from *P. ferulacea* showed no activity against McCoy cell line evaluated by MTT assay (Razavi et al. 2009c).

In a further experiment, osthol (**3**) was found to be the most active compound against lung (NCI-H322 and A549), melanoma (A375), prostate (PC-3), colon (HCT-116), and epidermoid carcinoma (A431) cell lines compared to other compounds from *P. pabularia*. Osthol (**3**) had IC_{50} values of 0.0145, 0.0032, and 0.0302 mM, for lung (A549), epidermoid carcinoma (A431), and colon (HCT-116) cell lines, respectively (Farooq et al. 2014a). Farooq et al. (2018) measured the cytotoxicity of the semi-synthesized analogues of osthol (**3**) using the MTT method. Among all the tested compounds, *N*-(2-methylpropyl)-3-{4 methoxy-3-(3-methylbut-2-enyl)-2-(prop-2-en-1-oxy)phenyl} prop-2-en-1-amide exhibited the best results against leukaemia cell line (THP1) with an IC_{50} of 0.005 mM (Farooq et al. 2018). Numonov et al. (2018) reported that the coumarin yuganin A (**22**), isolated for the first time from *P. pabularia* improved the proliferation of B16 melanoma cells; while the cell viability was 127.90% at concentration of 0.05 mM and the intracellular melanin content was significantly increased (Numonov et al. 2018).

In a study carried out by Razavi et al. (2009a), 8-geranyloxy psoralen (**32**) isolated from *P. uloptera* showed a good potency in reducing the viability of HeLa and Mc-Coy cell lines with IC_{50} values of 0.792 and 0.835 mM, respectively, determined by the MTT assay, and IC_{50} of 1.26 mM for Mc-Coy cell line evaluated by Tripan blue assay (Razavi et al. 2009b). Oxypeucedanin (**48**) and isoarnottinin 4'-glucoside (**28**) isolated from *P. uloptera* exhibited strong to moderate cytotoxic effects against HeLa cells with IC_{50} values of 0.314 mg/mL and 0.84 mg/mL, respectively (Razavi et al. 2010b, 2011b).

An MTT assay revealed that aviprin (**89**) inhibited HeLa and prostate cancer (LNCaP) cells with IC_{50} values of 0.265 and 0.411 mg/mL, respectively; whilst aviprin-3''-*O*-D-glucopyranoside (**90**) showed mild effects on the above-mentioned cell lines, with IC_{50} values of 0.335 and 6.632 mg/mL, respectively (Zahri et al. 2012).

Anti-inflammatory effect

Inflammation is defined as the body response to defend against allergens and/or injury of the tissues, while they can cause various disorders (e.g. allergies, cardiovascular dysfunctions, metabolic syndrome, cancer, and autoimmune diseases) (Ghasemian et al. 2016). In order to decrease the adverse effects of the available anti-inflammatory drugs, the natural drugs can be promoted to replace. The plants are rich sources of natural products, considering they have been used in traditional medicine as natural anti-inflammatory agents. Among the *Prangos* species, the extracts of *P. platychloena* and isolated coumarins from *P. haussknechtii* have been assessed for their anti-inflammatory effects.

Aqueous extract of *P. platychloena* decreased the secretion of interleukin 8 (IL-8) in colorectal cancer cell line (CCL-221) from 519.07 to 28.3 pg/mL, while the methanolic extract reduced its secretion to 92.73 pg/mL; and the secretion of interleukin 6 (IL-6) was decreased from 63 to 1 and 4 pg/mL using the aqueous and methanolic extract, respectively (Rostami et al. 2012).

Coumarins isolated from *P. haussknechtii* inhibited cyclooxygenase enzymes (COX-1 and COX-2) with IC_{50} values ranging from 0.0368 to 0.0564 mM comparable to NSAIDs including aspirin (IC_{50} of 0.6 mM for COX-1), naproxen (IC_{50} of 0.0522 mM for COX-1, and -2), and ibuprofen (IC_{50} of 0.0728 mM for COX-1) (Dissanayake et al. 2017).

Anti-hypertensive effect

The angiotensin converting enzyme (ACE) inhibitory activity of different *P. asperula* extracts was tested in vitro, and only the *n*-hexane fraction was found to be active with an IC_{50} of 0.150 mg/mL (Loizzo et al. 2008a). The hydroalcoholic extract of *P. ferulacea* exhibited a weak inhibition of ACE with IC_{50} value of 4.057 mg/mL (Namjoyan et al. 2015).

Antidiabetic effects

The methanolic extract of *P. asperula* had no effects on α-amylase and α-glucosidase enzymes (Loizzo et al. 2008a). In the same assay, the EO of *P. gaubae* possessed the higher inhibitory activity against α-amylase (1.35 mmol acarbose equivalent (AE)/g oil),

and α-glucosidase (38.84 mmol AEs/g oil) in comparison with its dichloromethane, methanol, and *n*-hexane extracts (Bahadori et al. 2017b).

Neuroprotective effect

The EO and dichloromethane extract of *P. gaubae* possessed the highest neuroprotective effects when compared to *n*-hexane, and methanolic soluble-extracts against acetylcholinesterase (AChE) and butyryl-cholinesterase (BChE) enzymes with inhibition values of 2.97 and 3.51 mg galanthamine equivalent (GE)/g, respectively (Bahadori et al. 2017a). In a similar work, various extracts of *P. ferulacea* were tested and the *n*-hexane fraction had the highest AChE inhibitory activity (75.6% at IC_{50}: 0.05 mg/mL). The furocoumarin heraclenin (**60**) isolated from the above-mentioned *n*-hexane fraction showed the highest activity among the studied compounds with an IC_{50} value of 0.0568 mg/mL (Abbas-Mohammadi et al. 2018).

Abortifacient effect

In an in vivo study, the hydroalcoholic and aqueous extracts of *P. ferulacea* leaves were administered orally to 60 pregnant rats at different doses (25, 50, 100, 300, 500, and 1000 mg/g per day). No significant effect on abortion frequency was detected; however, the abortion rate was slightly and dose-independently increased by taking the hydroalcoholic extract (Kazerooni and Mousavizadeh 2005; Kazerooni et al. 2006).

Miscellaneous bioactivities

The EO of *P. gaubae* inhibited lipase enzyme activity [1.59 mmol orlistat equivalent (OE)/g] which might indicate an anti-obesity effect. The *n*-hexane extract of *P. gaubae* was more active than the dichloromethane and methanolic extracts against tyrosinase enzyme activity [36.33 mg kojic acid equivalent (KAE)/g], therefore, it seems to be worth for further testing as a natural skin-care agent (Bahadori et al. 2017a).

Regarding the glutathione-S-transferase (GST) activity, the methanolic extract obtained from the aerial parts of *P. ferulacea* was the most effective inhibitor from the studied plants (*Chaerophyllum macropodum* Boiss. and *Heracleum persicum* Desf.)

with an IC_{50} value of 0.079 mg/mL (Çoruh et al. 2007).

Several compounds, including coumarins and γ-pyrone derivatives isolated from *P. pabularia* inhibited the release of cytokines interleukin (IL-2, IL-4, and IL-1β) and tumour necrosis factor (TNF-α) which indicates potential anti-inflammatory effects (Tada et al. 2002).

3,5-Nonadiyne (**133**) isolated from the EO of the root part of *P. ferulacea* exhibited a concentration-dependent inhibition on endogenous nitric oxide release on rat peritoneal macrophages with an IC_{50} of 0.0067 mM (Dokovic et al. 2004).

Phytochemistry

Phytochemicals are produced in higher plants as secondary metabolites, considering their crucial roles in plants (e.g. defending against herbivores, preserving under stress conditions, attracting of pollinators, etc.), their bioactivities for human are also considerable. In order to discover the potent natural drugs, isolation and identification of phytoconstituents are vital.

16 species of the *Prangos* genus have been studied for their secondary metabolites. Various coumarin derivatives have been isolated and identified as the major secondary metabolites of this genus. Overall, 30 simple coumarins (**1–30**), 66 linear and angular furocoumarins (**31–96**), six flavonoids (**97–102**), 16 terpenoids (**103–118**), seven γ-pyrones (**119–125**), three phytosterols (**129–131**), and eight other compounds (**126, 127, 128, 132–136**) have been isolated from different products of the *Prangos* genus. Totally 131 non-volatile natural products have been reported. These secondary metabolites along with the applied plant parts and plant products are listed in Table S3 and their chemical structures are shown in Fig. 1.

Coumarins

Coumarins have been isolated from hundreds of plants species distributed in more than 40 different families with diversity of 1300 types. Families with occurrence numbers of > 100 are identified as Apiaceae (Umbelliferae), Rutaceae, Asteraceae (Compositae), Fabaceae (Leguminosae), Oleaceae, Moraceae, and Thymelaeaceae, respectively (Ribeiro and Kaplan 2002). Apiaceae is the major and most diverse source of coumarins, containing five major types of coumarin derivatives including simple coumarins, linear and angular furocoumarins, linear and angular pyranocoumarins (Ribeiro and Kaplan 2002; Kontogiorgis and Hadjipavlou-Litina 2003). So far, from the *Prangos* genus simple coumarins, linear and angular, glycosylated, and condensed furocoumarins, along with linear dihydro-furocoumarin derivatives have been identified.

Simple coumarins

Farooq et al. (2014a) isolated the simple coumarins umbelliferon (**1**), 6-hydroxycoumarin (**2**), osthol (**3**), and meranzin (**11**) from *P. pabularia* (Farooq et al. 2014a). Suberosin (**6**) (Tabanca et al. 2016), uloperol (**8**), auraptenol (**10**), panicular (**14**), tamarin (**25**) (Tada et al. 2002), and a new coumarin yuganin A (**22**) (Numonov et al. 2018) were also isolated and identified from this species.

A new coumarin 4′-senecioiloxyosthol (**20**), along with hydroxyl-osthol-epoxide (**4**), murraol (**15**), and macrocarpin (**22**) were isolated from *P. hulusii* roots (Tan et al. 2017).

From *P. tschimganica*, osthenol (**5**), demethyl-7 suberosin (**7**), scopoletin (**9**), isomeranzin (**13**), peucedanol (**18**), yuehgesin-B (**19**), and a new coumarin glycoside tschimganic ester A (**30**) have been isolated (Shikishima et al. 2001b).

Two novel prenylated coumarins 2-oxo-2H-1-benzopyran-8-yl-2-methyl-2-buten-1-yl ester (**23**) and butanoic acid, 3-methyl,(2E)-4-(7-methoxy-2-oxo-2H-1-benzopyran-8-yl)-2-methyl-2-buten-1-yl ester (**24**) were also isolated from aerial portions of *P. haussknechtii* (Dissanayake et al. 2017).

In a study performed by Abyshev (1974), ferudenol (**16**), ferudiol (**17**), and prangone (**26**) were isolated from the root part of *P. ferulacea* (Abyshev 1974).

A new coumarin glycoside 6-*O*-[β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranosyl]-prenyletin (**27**), and two known coumarin glycosides [tortuoside (**27**), and isoarnottinin 4′-glucoside (**28**)] were obtained from the methanolic extract of *P. uloptera* roots (Razavi et al. 2008a, 2011b).
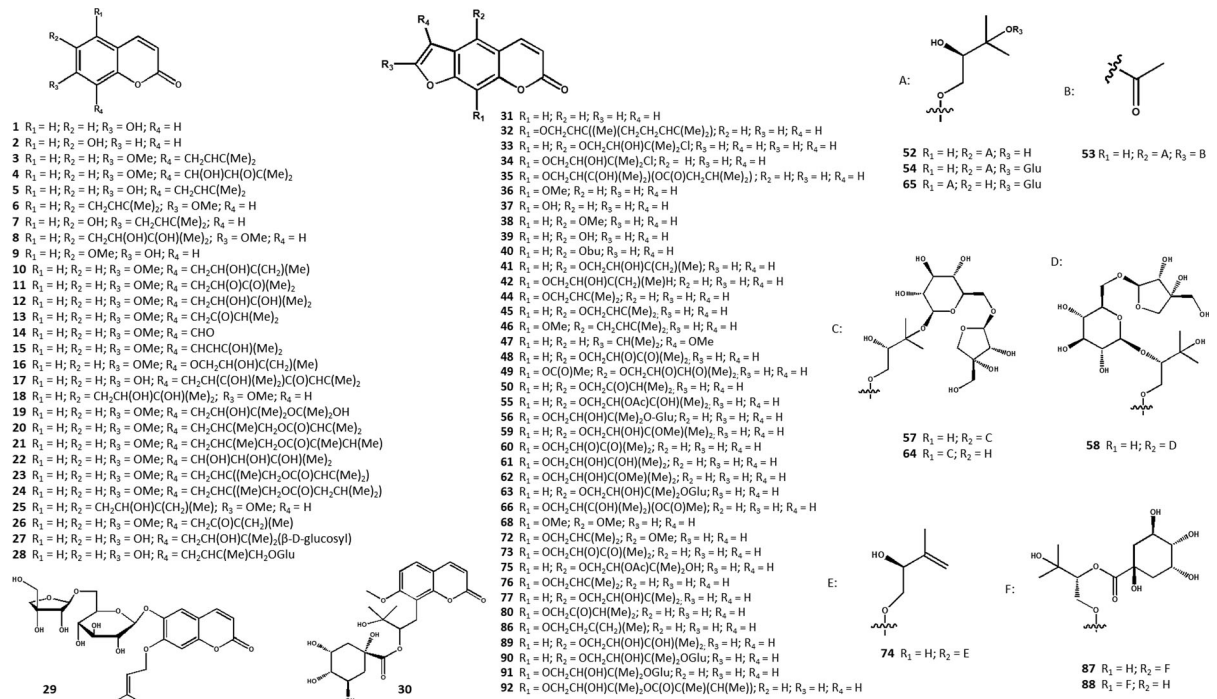
1 R₁ = H; R₂ = H; R₃ = OH; R₄ = H
2 R₁ = H; R₂ = OH; R₃ = H; R₄ = H
3 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CH₂CHC(Me)₂
4 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CH(OH)CH₂C(O)C(Me)₂
5 R₁ = H; R₂ = H; R₃ = OH; R₄ = CH₂CHC(Me)₂
6 R₁ = H; R₂ = H; R₃ = CH₂CHC(Me)₂; R₃ = OMe; R₄ = H
7 R₃ = H; R₂ = OH; R₃ = CH₂CHC(Me)₂; R₄ = H
8 R₁ = H; R₂ = CH₂CH(OH)C(OH)(Me)₂; R₃ = OMe; R₄ = H
9 R₁ = H; R₂ = OMe; R₃ = Obu; R₄ = H
10 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CH₂CH(OH)C(CH₂)(Me)
11 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CH₂CH(O)C(O)(Me)₂
12 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CH₂CHC(OH)(Me)₂
13 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CH₂C(O)CH(Me)₂
14 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CHO
15 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CHCHC(OH)(Me)₂
16 R₁ = H; R₂ = H; R₃ = OMe; R₄ = OCH₂CH(OH)C(CH₂)(Me)
17 R₁ = H; R₂ = H; R₃ = OH; R₄ = CH₂CH(C(OH)(Me)₂)C(O)CHC(Me)₂
18 R₁ = H; R₂ = CH₂CH(OH)C(OH)(Me)₂; R₃ = OMe; R₄ = H
19 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CH₂CH(OH)C(Me)₂OC(O)CHC(Me)₂
20 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CH₂CHC(Me)CH₂OC(O)C(Me)₂
21 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CH₂CHC(Me)CH₂OC(O)C(Me)CH(Me)
22 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CH(OH)CH(OH)C(OH)(Me)₂
23 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CH₂CHC((Me)CH₂OC(O)CHC(Me)₂)
24 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CH₂CHC(Me)CH₂OC(O)CH₂CH(Me)₂
25 R₁ = H; R₂ = CH₂CH(OH)C(CH₂)(Me); R₃ = OMe; R₄ = H
26 R₁ = H; R₂ = H; R₃ = OMe; R₄ = CH₂C(O)C(CH₂)(Me)
27 R₁ = H; R₂ = H; R₃ = OH; R₄ = CH₂CH(OH)C(Me)₂(β-D-glucosyl)
28 R₁ = H; R₂ = H; R₃ = OH; R₄ = CH₂CHC(Me)CH₂OGlu

29

30

31 R₁ = H; R₂ = H; R₃ = H; R₄ = H
32 R₁ =OCH₂CHC((Me)(CH₂CH₂CHC(Me)₂); R₂ = H; R₃ = H; R₄ = H
33 R₁ = H; R₂ = OCH₂CH(OH)C(Me)₂Cl; R₃ = H; R₄ = H; R₃ = H; R₄ = H
34 R₁ = OCH₂CH(OH)C(Me)₂Cl; R₂ = H; R₃ = H; R₄ = H
35 R₁ = OCH₂CH(C(OH)(Me)₂)(OC(O)CH₂CH(Me)₂) ; R₂ = H; R₃ = H; R₄ = H
36 R₁ = OMe; R₂ = H; R₃ = H; R₄ = H
37 R₁ = OH; R₂ = H; R₃ = H; R₄ = H
38 R₁ = H; R₂ = OMe; R₃ = H; R₄ = H
39 R₁ = H; R₂ = OH; R₃ = H; R₄ = H
40 R₁ = H; R₂ = Obu; R₃ = H; R₄ = H
41 R₁ = H; R₂ = OCH₃CH(OH)C(CH₂)(Me); R₃ = H; R₄ = H
42 R₁ = OCH₂CH(OH)C(CH₃)(Me)H; R₂ = H; R₃ = H; R₄ = H
44 R₁ = OCH₂CHC(Me)₂; R₂ = H; R₃ = H; R₄ = H
45 R₁ = H; R₂ = OCH₂CHC(Me)₂; R₃ = H; R₄ = H
46 R₁ = OMe; R₂ = CH₂CHC(Me)₂; R₃ = H; R₄ = H
47 R₁ = H; R₂ = H; R₃ = CH(Me)₂; R₄ = OMe
48 R₁ = H; R₂ = OCH₂CH(O)C(O)(Me)₂; R₃ = H; R₄ = H
49 R₁ = OC(O)Me; R₂ = OCH₂CH(O)C(H)(O)(Me)₂; R₃ = H; R₄ = H
50 R₁ = H; R₂ = OCH₂C(O)CH(Me)₂; R₃ = H; R₄ = H
55 R₁ = H; R₂ = OCH₂CH(OAc)C(OH)(Me)₂; R₃ = H; R₄ = H
56 R₁ = OCH₂CH(OH)C(Me)₂O-Glu; R₂ = H; R₃ = H; R₄ = H
59 R₁ = H; R₂ = OCH₂CH(OH)(OMe)(Me)₂; R₃ = H; R₄ = H
60 R₁ = OCH₂CH(O)C(O)(Me)₂; R₂ = H; R₃ = H; R₄ = H
61 R₁ = OCH₂CH(OH)C(OH)(Me)₂; R₂ = H; R₃ = H; R₄ = H
62 R₁ = OCH₂CH(OH)(OMe)(Me)₂; R₂ = H; R₃ = H; R₄ = H
63 R₁ = H; R₃ = OCH₂CH(OH)C(Me)₂OGlu; R₃ = H; R₄ = H
66 R₁ = OCH₂CH(C(H)(OH)₃)(OC(O)(Me); R₂ = H; R₃ = H; R₄ = H
68 R₁ = OMe; R₂ = OMe; R₃ = H; R₄ = H
72 R₁ = OCH₂CHC(Me)₂; R₂ = OMe; R₃ = H; R₄ = H
73 R₁ = OCH₂CH(O)C(O)(Me)₂; R₂ = H; R₃ = H; R₄ = H
75 R₁ = H; R₂ = OCH₂CH(OAc)C(Me)₂OH; R₃ = H; R₄ = H
76 R₁ = OCH₂CHC(Me)₂; R₂ = H; R₃ = H; R₄ = H
77 R₁ = H; R₂ = OCH₂CH(OH)C(Me)₂; R₃ = H; R₄ = H
80 R₁ = OCH₂C(O)C(Me)₂; R₂ = H; R₃ = H; R₄ = H
86 R₁ = OCH₂C₂(CH₂)(Me); R₂ = H; R₃ = H; R₄ = H
89 R₁ = H; R₂ = OCH₂CH(OH)(OH)(Me)₂; R₃ = H; R₄ = H
90 R₁ = H; R₂ = OCH₂CH(OH)C(Me)₂OGlu; R₃ = H; R₄ = H
91 R₁ = OCH₂CH(OH)C(Me)₂OGlu; R₂ = H; R₃ = H; R₄ = H
92 R₁ = OCH₂CH(OH)C(Me)₂OC(O)C(Me)(CH(Me)); R₂ = H; R₃ = H; R₄ = H

A:
52 R₁ = H; R₂ = A; R₃ = H
54 R₁ = H; R₂ = A; R₃ = Glu
65 R₁ = A; R₂ = H; R₃ = Glu

B:
53 R₁ = H; R₂ = A; R₃ = B

C:
57 R₁ = H; R₂ = C
64 R₁ = C; R₂ = H

D:
58 R₁ = H; R₂ = D

E:
74 R₁ = H; R₂ = E

F:
87 R₁ = H; R₂ = F
88 R₁ = F; R₂ = H

Fig. 1 Chemical structures of the compounds of *Prangos* spp.

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94 R = C(CH₂)(Me)
95 R = C(Me)₂OH
96 R = C(Me)₂OGlc

93

43 R = C(Me)₂OC(O)C(Me)(OH)CH(OH)(Me)
67 R = C(Me)₂OC(O)CH(Me)
69 R = C(Me)₂OH
70 R = C(Me)₂OGlu
71 R = C(Me)(OH)CH₂OH
78 R = CH(Me)CH₂OC(O)CHC(Me)₂
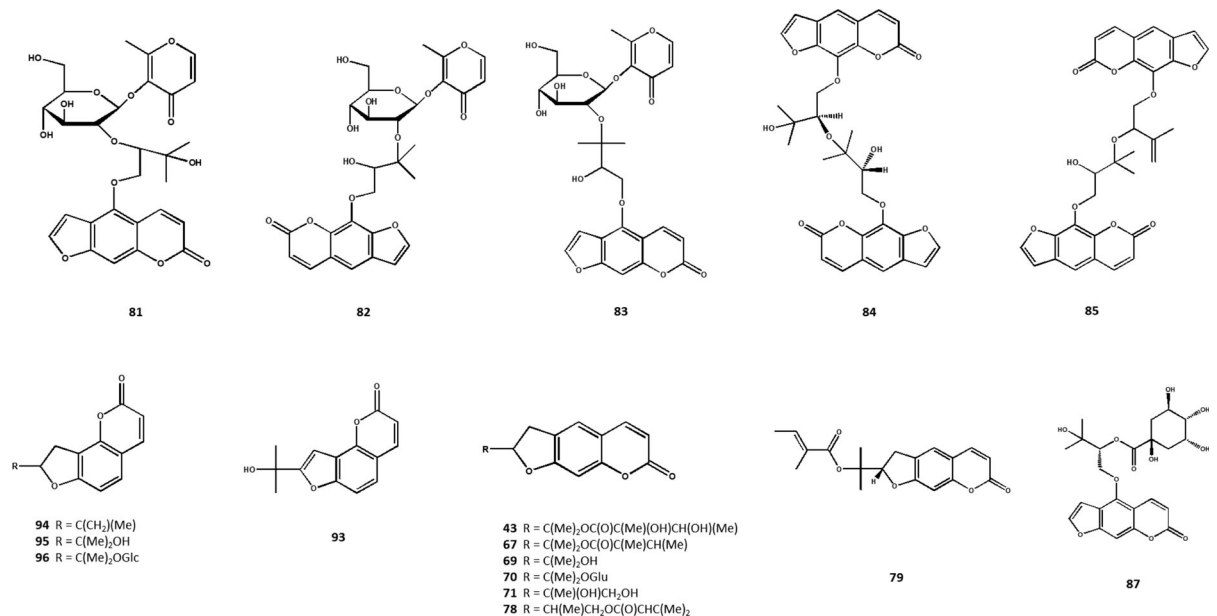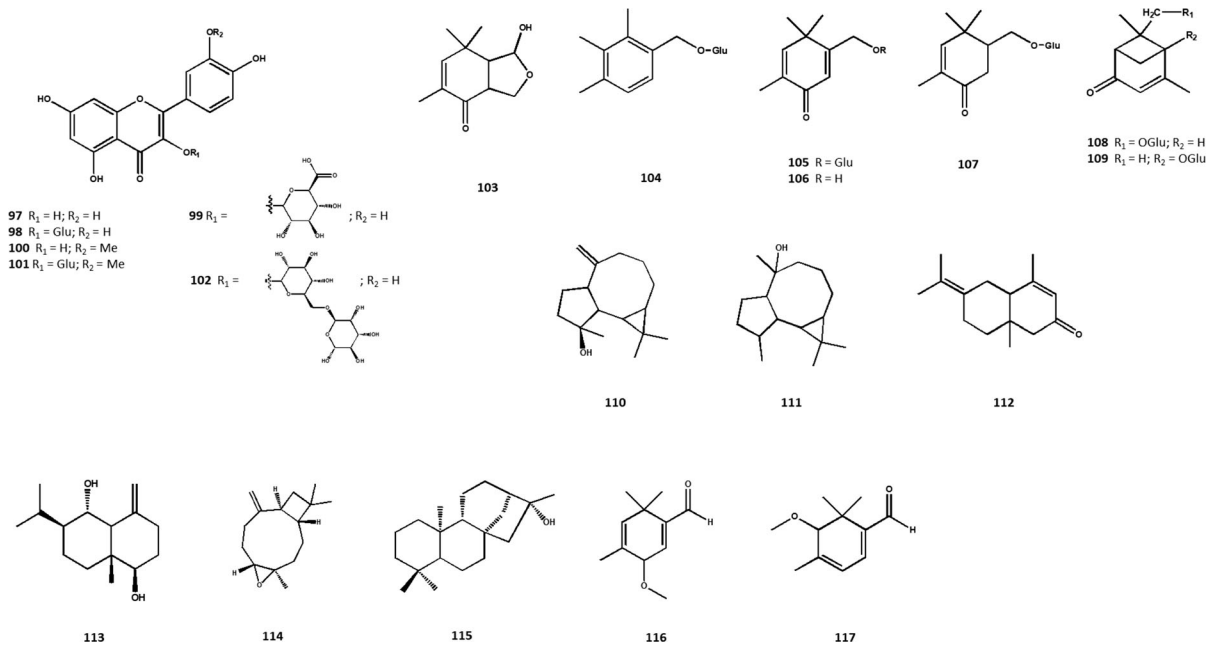
79

87

Fig. 1 continued
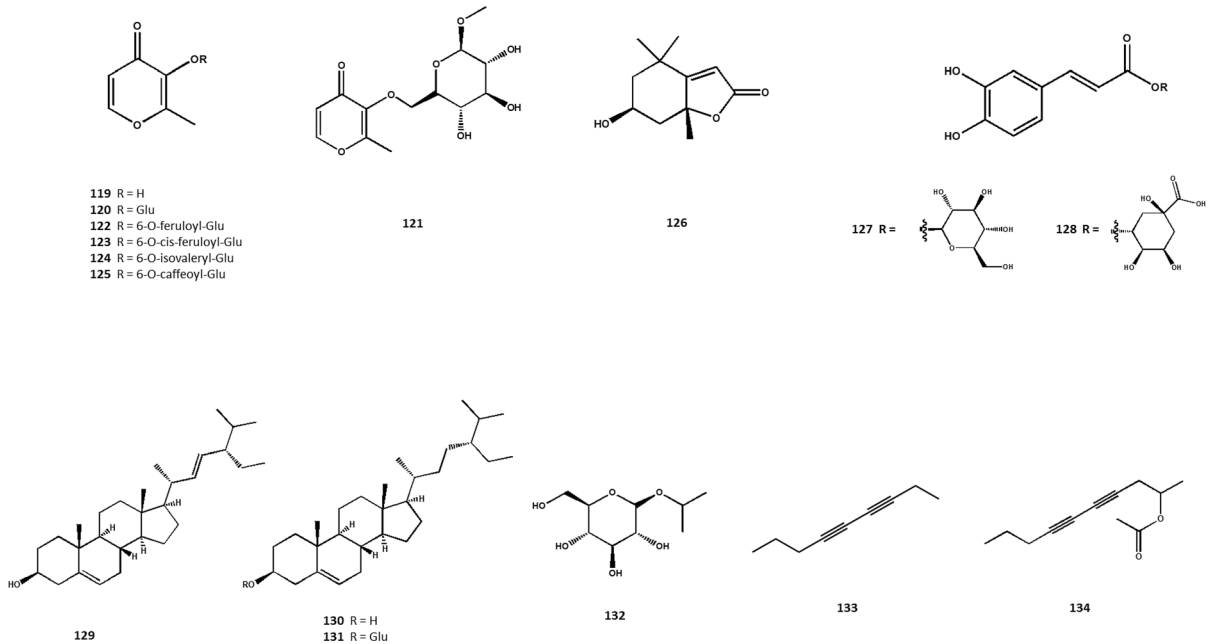
Fig. 1 continued

Fig. 1 continued

Linear furocoumarins

Psoralen (**31**) was isolated and identified from various extracts of *P. lipskyi* (Danchul et al. 1975a), *P. acaulis*

(Kuznetsova et al. 1979), *P. quasiperforata* (Danchul et al. 1975b), *P. tschimganica* (Shikishima et al. 2001b), *P. ferulacea* (Shokoohinia et al. 2014), and *P. hulusii* (Tan et al. 2017). A psoralen derivative called

8-geranyloxy psoralen (**32**) was also isolated from *n*-hexane extract of the root part of *P. uloptera* (Razavi et al. [2009a](#)).

In a study carried out by Shikishima et al. ([2001a](#)), the *n*-butanol extract from the aerial parts of *P. tschimganica* was fractionated to yield saxalin (**33**), (±)-8-(3-chloro-2-hydroxyl-3-methylbutoxy)-psoralen (syn. isosaxalin) (**34**), xanthotoxin (**36**), xanthotoxol (**37**), bergapten (**38**), isogosferol (**42**), imperatorin (**44**), isoimperatorin (**45**), oxypeucedanin hydrate (**52**), heraclenol (**61**), tert-*O*-methyl heraclenol (**62**), pabulenol (**74**), and pabularinone (**80**) (Shikishima et al. [2001b](#)).

Different parts including aerial parts and roots of *P. ferulacea* have been studied for their phytochemical contents. From various extracts (chloroform, methanolic, acetone) 8-[2-(3-methylbutyroxy)-3-hydroxyl-3-methylbutoxylpsoralen (**35**), gosferol (**41**), oxypeucedanin (**48**), oxypeucedanin methanolate (**59**), heraclenin (**60**), isopimpinellin (**68**), phellopterin (**72**), pranferol (**77**), feruliden (**86**), and [3-hydroxy-2-methyl-4-(7-oxofuro[3,2 g]chromen-9-yl) oxybutan-2-yl] (Z)-2-methylbut-2-enoate (**92**) were isolated (Kuznetsova et al. [1966](#); Abyshev [1974](#); Shokoohinia et al. [2014](#); Gholivand et al. [2015](#); Abbas-Mohammadi et al. [2018](#)).

Ulubelen et al. ([1995](#)) isolated bergaptol (**39**), *n*-butyl bergaptol (**40**), 8-acetyloxypeucedanin (**49**), and prangenin (**73**) from chloroform extract of *P. platychlaena* (Ulubelen et al. [1995](#)).

Furthermore, various researchers have been investigated the secondary metabolite profile of *P. pabularia*. The linear furocoumarins allo-imperatorin methyl ether (**46**), oxypeucedanin hydrate 2′-*O*-monoacetate (**53**), oxypeucedanin hydrate monoacetate (**55**), heraclenol 3′-methyl ester (**66**), 8-((3,3-dimethyloxiran-2-yl) methyl)-7-methoxy-2H-chromen-2-one (syn. merangin) (**75**), and 4-((2-hydroxy-3-methylbut-3-en-1-yl) oxy)-7H-furo[3,2-g] chromen-7-one (**76**) were isolated from the plant (Koul et al. [1979](#); Tada et al. [2002](#); Farooq et al. [2014a](#)).

Peucedanin (**47**) and isooxypeucedanin (**50**) were isolated and identified from *P. biebersteinii*, whereas aviprin (**89**) from *P. uloptera* (Abyshev and Brodskii [1974](#); Geidarov and Serkerov [2016](#); Heydarov and Serkerov [2017](#)).

Linear dihydro-furocoumarins

From the methanolic extract of *P. ferulacea* roots, a new natural product, lindiol (**43**) have been isolated (Abyshev [1974](#)). Sprengelianin (**67**) was isolated as a dihydro-furocoumarin derivative from *n*-hexane extract of aerial parts of *P. ferulacea* (Abbas-Mohammadi et al. [2018](#)). Furthermore, marmesine (**69**) and its dehydrated glycosylated form marmesinine (**70**) were found in several *Prangos* species: *P. ferulacea* (Abbas-Mohammadi et al. [2018](#)), *P. latiloba* (Serkerov et al. [1976](#)), *P. quasiperforata* (Danchul et al. [1975a](#)), *P. tschimganica* (Shikishima et al. [2001b](#)), *P. lipskyi* (Danchul et al. [1975a](#)) and *P. biebersteinii* (Geidarov and Serkerov [2016](#)).

Prandiol (**71**) was isolated for the first time from methanolic extract of the roots of *P. biebersteinii* (Abyshev and Brodskii [1974](#)). Diverse separation techniques were utilized to isolate pranchimgin (**78**) and deltoin (**79**) from different *Prangos* species as dihydro-furocoumarin compounds (Danchul et al. [1975a](#); Serkerov et al. [1976](#); Kuznetsova et al. [1979](#); Eshbakova et al. [2006](#); Razavi et al. [2008b](#)).

Glycosylated furocoumarins

Several glycosylated furocoumarins were detected in three *Prangos* species. From *P. pabularia*, oxypeucedanin hydrate 3′-*O*-β-D-glucopyranoside (**54**), oxypeucedanin hydrate 3′-*O*-β-D-glucopyranoside (**56**), heraclenol 3′-*O*-β-D-glucopyranoside (**63**), 3″-*O*-(β-D-glucopyranosyl)-heraclenol (**65**), aviprin-3″-*O*-D-glucopyranoside (**90**), and (-)9-[3-(β-D-glucopyranosyloxy)-2 hydroxy-3-methyl butoxy]-7H furo [3,2-g] [1]benzopyran-7-one (syn. komaline 2′-β-D-glucopyranoside) (**91**) were isolated (Koul et al. [1979](#); Tada et al. [2002](#); Farooq et al. [2014a](#); Numonov et al. [2018](#)).

Two new compounds 3″-*O*-[β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranosyl]-oxypeucedanin hydrate (**57**) and 2″-*O*-[β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranosyl]-oxypeucedanin hydrate (**58**), along with 3″-*O*-[β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranosyl]-heraclenol (**64**) and aviprin-3″-*O*-D-glucopyranoside (**90**) were isolated as glycosylated linear furocoumarins from the methanolic extract of *P. uloptera* roots (Razavi et al. [2008a](#); Zahri et al. [2012](#)).

Shikishima et al. ([2001a](#)) isolated two new glycosylated furocoumarins, tschimganic ester B (**87**) and

tschimganic ester C (**88**) from methanolic extract of *P. tschimganica* aerial parts (Shikishima et al. 2001b).

Angular furocoumarins

From the *n*-hexane extract of *P. ferulacea*, oroselol (**93**) was obtained (Abbas-Mohammadi et al. 2018). Majurin (**94**) was isolated from the *n*-hexane extract of *P. pabularia* stems (Tada et al. 2002). Columbianetin (**95**) and columbianetin-*O*-β-D-glucopyranoside (**96**) were isolated and identified from *P. tschimganica* (Shikishima et al. 2001b).

Condensed furocoumarin derivatives

The new furocoumarin derivatives pabularin A (**81**), pabularin B (**82**), and pabularin C (**83**) were obtained from the EtOAc extract of *P. pabularia* stems. A known compound rivurobirin E (**84**) was also isolated from the same plant extract (Tada et al. 2002). Rivulobirin A (**85**) was isolated from *n*-hexane extract of *P. ferulacea* (Abbas-Mohammadi et al. 2018).

Flavonoids

Two flavonoid aglycones: quercetin (**97**) and isorhamnetin (**100**) were isolated from *P. ferulacea*. Their glycosydes, quercetin-3-*O*-glucoside (**98**), and isorhamnetin-3-*O*-β-D-glucopyranoside (**101**), along with querciturone (**99**) were obtained from *P. ferulacea* (Razavi et al. 2009c; Mouri et al. 2014; Delnavazi et al. 2017; Abbas-Mohammadi et al. 2018). Rutin (**102**) was also reported as one of the components of *P. denticulata* and *P. heyniae* (Oke-Altuntas et al. 2015).

Terpenoids

From the methanolic extract of the aerial parts of *P. tschimganica*, two new monoterpenes, tschimganical A (**103**) and 1,1,5-trimethyl-2-hydroxymethyl-(2,5)-cyclohexadien-(4)-one (**106**), two known monoterpenes 1,1,5-trimethyl-2-formyl-4-methoxyl-(2,5)-cyclohexadiene (**118**) and 1,1,5-trimethyl-2-formyl-6-methoxyl-(2,4)-cyclohexadiene (**119**), along with five new monoterpene glycosides including 2,3,4-trimethylbenzylalcohol-*O*-β-D-glucopyranoside (**106**), 1,1,5-trimethyl-2-hydroxymethyl-(2,5)-cyclohexadien-(4)-one-*O*-β-D-glucopyranoside (**105**), 1,1,5-trimethyl-2-

hydroxymethyl-5-cyclohexadien-(4)-one-7-*O*-β-D-glucopyranoside (**107**), vervenone-8-*O*-β-D-glucopyranoside (**108**), and vervenone-5-*O*-β-D-glucopyranoside (**109**) were isolated (Shikishima et al. 2001a). In this study, the presence of further terpenoids, namely spathulenol (**110**), globulol (**111**), 1β,6α-dihydroxyyeudesm-4(15)-ene (syn. voleneol) (**113**), and (-)-caryophyllene-β-oxide (**114**) was detected (Shikishima et al. 2001a).

From the EO of *P. heyniae* a new eudesmane type sesquiterpene, 3,7(11)-eudesmadien-2-one (**110**) was isolated (Ozek et al. 2018).

The diterpenoid kauranol (**115**) was obtained and identified from *P. pabularia* (Tada et al. 2002).

A new terpenoid (**118**) was also isolated from *P. haussknechtii* aerial parts by using diverse range of chromatographic techniques (Dissanayake et al. 2017).

γ-Pyrones

From *P. tschimganica* the γ-pyrone aglycone maltol (**119**), and five glycosides including maltol-β-D-glucopyranoside (**120**), 3-hydroxyl-2-methyl-4-H-pyran-4-one-3-*O*-(6)-β-D-glucopyranoside (**122**), 3-hydroxyl-2-methyl-4-H-pyran-4-one-3-*O*-(6-*O*-cis-feruloyl)-β-D-glucopyranoside (**123**), 3-hydroxyl-2-methyl-4-H-pyran-4-one-3-*O*-(6-*O*-cis-isovaleryl)-β-D-glucopyranoside (**124**), and 3-hydroxyl-2-methyl-4-H-pyran-4-one-3-*O*-(6-*O*-cis-caffeoyl)-β-D-glucopyranoside (**125**) were isolated and identified (Shikishima et al. 2001a).

A new γ-pyrone derivative, maltol-(6-*O*-acetyl)-β-D-glucopyranoside (**121**) was also isolated for the first time from EtOAc extract of *P. pabularia* stem (Tada et al. 2002).

Other compounds

Beside the above-listed main constituents of the *Prangos* genus, a carotenoid named loliolide (**126**) from *P. pabularia*, caffeic acid glucosyl ester (**127**) from *P. ferulacea*, and chlorogenic acid (**128**) from *P. denticulata* and *P. heyniae* were reported (Tada et al. 2002; Oke-Altuntas et al. 2015; Delnavazi et al. 2017). The ubiquitous phytosterols stigmasterol (**129**) and β-sitosterol (**130**) were identified from *P. hulusii* roots, and β-sitosterol-β-D-glucopyranoside (**131**) from *P. pabularia* stems (Tada et al. 2002; Tan et al. 2017).
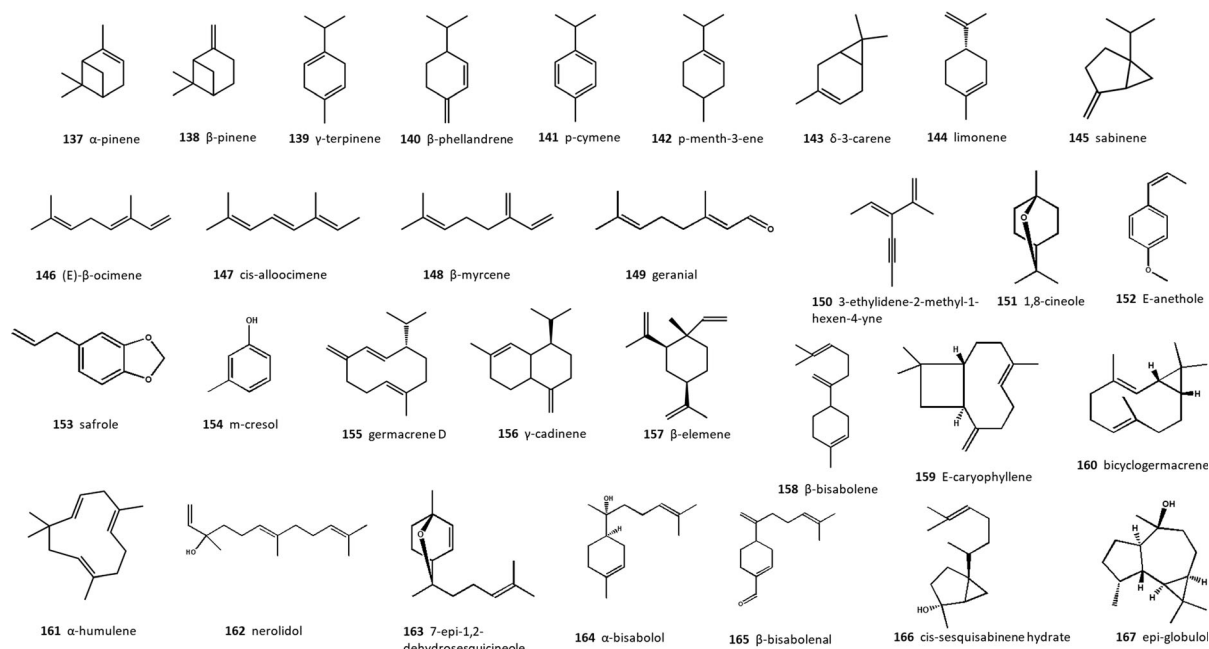
Fig. 2 Major essential oil constituents of *Prangos* spp.

Three polyacetylene compounds were also identified from the genus, namely: 1-*O*-isopropyl-β-D-glucopyranoside (**132**) from *P. pabularia*, 3,5-nonadiyne (**133**) from *P. ferulacea*, and nona-(2S)-3,5-diyn-2-yl acetate (**134**) from *P. platychlaena* (Tada et al. 2002; Dokovic et al. 2004; Tabanca et al. 2018).

2-(4-Hydroxyphenyl) ethyl triacontanoate (**135**) was also isolated from *n*-hexane extract of aerial parts of *P. ferulacea* (Abbas-Mohammadi et al. 2018). An amino acid derivative (**136**) was isolated from the methanolic extract obtained from the aerial parts of *P. haussknechtii* (Dissanayake et al. 2017).

Essential oils

Various parts of *Prangos* genus including fruits, seeds, and flowers at different growth stages were subjected to analyse the compositions of their EOs (Table S4). The roots of *P. denticulata* and immature seeds of *P. ferulacea* at flowering stage possessed the highest EO contents with 3.2% (v/w) and 3.0% (w/w), respectively (Kilic et al. 2010; Bagherifar et al. 2019). The chemical structures of the main EO components are given in Fig. 2. As demonstrated in Table S4, monoterpene hydrocarbons were the major EO constituents. Among them, α-pinene (**137**), β-pinene

(**138**), γ-terpinene (**139**), β-phellandrene (**140**), and *p*-cymene (**141**) were characterized as the main terpenoids.

Although monoterpenes were the most abundant volatile constituents, sesquiterpene hydrocarbons were further detected as significant fragrance components of the *Prangos* genus. In this terpenoid class, the genus was rich in germacrene D (**155**), γ-cadinene (**156**), β-elemene (**157**), and β-bisabolene (**158**) (Fig. 2).

Conclusions and prospective

Prangos species have been extensively used as food and medicine in Asia. *Prangos* species have been the subject of intense phytochemical examination in the past few decades. From the 30 *Prangos* species existing worldwide, 15 and 17 species have been investigated for non-volatile components and EO compositions, respectively. Furthermore, biological activities of 14 plant species have been evaluated. In these studies, crude extracts, EOs, and pure compounds isolated from *Prangos* species have been tested.

Phytochemical investigations of the genus revealed that coumarins, flavonoids and terpenoids are the major components of the plants. Coumarin derivatives, including aglycones and glycosylated simple coumarins, aglycones and glycosylated linear and angular furocoumarins, and condensed furocoumarins are the main constituents of this genus. There are no quantitative data on the non-volatile secondary metabolites, and their occurrence in different plant parts has not been studied extensively. Different plant parts of this genus are fragrant and produce EO with remarkable yield. Monoterpene hydrocarbons, especially α- and β-pinenes, γ-terpinene, (E)-β-ocimene, and δ-3-carene have been identified as the major volatile oil components.

Since coumarins have a wide range of pharmacological effects (e.g. anti-neurodegenerative, antiviral, antimicrobial, antioxidant, antidiabetic, anti-inflammatory, and anticancer activities), the genus is a promising source of new bioactive compounds. However, considering the toxic effects of certain furocoumarins, including their cytotoxic and carcinogenic effects (Mullen et al. 1984), there is a need for further studies to support the safe use of *Prangos* species or their extracts. All the phytochemical studies reporting furocoumarins were preparative experiments and there are no quantitative data on the occurrence of furocoumarins in different species and plant parts. Moreover, the toxicological profiles of *Prangos* species is unknown, since no scientific studies focused on this aspect. The majority of the studies reported antimicrobial and antioxidant effects, and with one exception all the experiments were carried out in vitro.

Further pharmacological studies, including in vivo studies would be indispensable in determining and assessing the pharmacological potential of the isolated compounds and the species of the genus. The available experimental evidence does not support the rationale folk medicinal use of *Prangos* species. Although the antimicrobial activities may explain some of the uses, no human studies were carried out to assess efficacy and safety. The application as spice might be related to the essential oil and coumarin content of the species; however, the safety of these food is yet to be studied.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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