A review on phytochemistry and pharmacological effects of *Prangos ferulacea* (L.) Lindl.

Kafash-Farkhad N (MSc)[1], Asadi-Samani M (MSc)[2*], Rafieian-Kopaei M (PhD)[2]

[1]Biology Dept, Urmia University, Urmia, I.R. Iran; [2]Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, I.R. Iran.
[*] Corresponding author Email: biology_2011@yahoo.com

Abstract: The genus of *Prangos* consists of about 30 species, 15 of which are growing wildly in many regions of Iran. *Prangos ferulacea* (L.) Lindl. with the common Persian name of "*Jashir*" is a perennial and aromatic plant from Apiaceae (Umbelliferae) family which is native to the mountains of southern Iran. *P. ferulacea* has been used in folk medicine as emulient, carminative, tonic, sedative, antiflatulent, anti-helmintic, antibacterial, antispasmodic, and antidiabetic agents. Monoterpenes, sesquiterpenes, coumarines, flavonoids, alkaloids, tannins, saponins, and terpenoids are some important compounds identified in this plant. Previous researches indicated that antioxidant properties of this plant were higher than α-tocopherole (vitamin E) and the main compounds of *P. ferulacea* in different growth stages were monoterpenes, specially α-pinene, and β-pinene. The present article aimed to examine the extensive pharmacologic active factors existing in this plant and its potential efficacy mechanisms to be used in medical and pharmacological works in the future.
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Introduction

Medicinal plants have been used in folk medicine for treatment of many diseases. The results of scientific investigations of medicinal plants for treating several diseases, including infectious diseases (Moradi et al., 2011, Khalili dehkordi et al., 2011), cancer (Shirzad et al., 2011), diabetes (Sedigheh et al., 2011), atherosclerosis (Rafieian-Kopaei et al., 2011), gastrointestinal disorders (Shahrani et al., 2007, Rahimian et al., 2010), burns (Asadi et al., 2013), and neurological difficulties (Akhlaghi et al., 2011) have been very promising. Although these plants are not completely without side effects (Jafarzadeh et al., 2010, Namjoo et al., 2013), they usually bear less side effects compared to synthetic medicines and may even lessen the toxicity of other medicines (Asadi et al., 2011, Asgary et al., 2010) thanks to the antioxidant properties (Heidarian and Rafieian-Kopaei, 2012). Nowadays, the compounds identified in medicinal plants are being used as new medicines and could be assumed as a clue to identifying inexpensive therapies with fewer side effects for treating many diseases including cancer (Asadi Samani et al., 2013). *Prangos ferulacea* (L.) Lindl. (*Jashir* in Persian, *Oppoponax* in French) is one of the valuable medicinal plants, used for treatment of many diseases in folk medicine. Various laboratory studies have demonstrated its therapeutical properties.

P. ferulacea has been used as carminative, emollient, tonic for gastrointestinal disorders, antiflatulent, sedative, anti-inflamatory, anti-viral, antihelminthic, antifuagal, and antibacterial (Ulubelen et al., 1995, Baser et al., 1996). In addition, the leaf of *P. ferulacea* is consumed for gastrointestinal diseases (Hiroshi et al., 1989), and its root is used for frigidity treatment and strengthening sexual desire (Baser et al., 2000). Among other properties of *P. ferulacea*, increasing tolerance, opening the stenosis and obstructions of the lumens, breaking the kidney and bladder stones and reducing the swelling of the spleen could be mentioned (Mavi et al., 2004). However, clinical trials are needed to use this plant for treatment of human diseases. This review article will systematically introduce morphological and biosystematic properties and herbal components of *P. ferulacea* and examine its therapeutical specifications to provide scientists with approaches to conducting clinical and pharmacological trials.

Morphological and biosystematic properties:

P. ferulacea is a member of Umbellales order, Umbelliferae (Apiaceae) family, subfamily of Smyrneae and genus Prangs. It is a perennial, perpendicular plant, which reaches 80-200 cm in length and has very thick, angular stems, and opposite branches. Leafs are green, glabrous, rarely rough, broadly ovate and mainly divided, with linear divisions. Its flowers are yellow and collected in a corymbose inflorescence with a radius of 6-12 cm. The fruits are ovate and much thinner than seeds' diameter. The flowering time is from May to July. *P. ferulacea* occurs in Elburz skirts, eastern and western

Iran (Ghahreman, 1997, Sajjadi et al., 2011, Kazerooni and Mousavizadeh, 2005).

Geographical distribution:
The genus Prangos consists of about 30 species, 15 and 5 of which, respectively, occur in and are native to Iran (Sajjadi and Mehregan, 2003, Kazerooni et al., 2006). In addition to Iran, other species of this genus are distributed in east Europe to Turkey, Caucasia, and central Asia (Coskun et al., 2004, Rechinger and Hedge, 1987). In Iran Prangos distributed in Eastern Azarbaijan, Western Azarbaijan, Kurdistan, Kermanshah, Hamedan, Semnan, Isfahan, Lorestan, Kohgilouyeh & Boyer Ahmad, and Kerman provinces, southern steep of Elburz mountains, and most mountains of Fars province (Zargari, 1997).
Climatic conditions suitable for *P. ferulacea* growth:
P. ferulacea is moisture-absorbent, needing large amount of moisture, coldness, and freezing weather to complete its life cycle. These conditions often exist in snowy regions having coldness period. The amount of its reproduction is more considerable in clay soils compared to other soils. Tissue and structure of soil contributes directly to developing main and subsidiary roots. These climatic requirements are provided in high territories and relatively specific slope directions (Hasani and shahmoradi, 2007, Rechinger and Hedge, 1987).

Growth stages of *P. ferulacea*:
P. ferulacea sends up shoots in the first half of end of March and completes its growth stage till the middle of May and then enters reproductive growth. In the late May, it produces fruits. The time for seeds is early July and simultaneously the withering is completed. In early August the plant will sleep completely with no trace on the ground (Ebrahimi et al., 2007, Keshtkar et al., 2009). Planting them for 56 to 70 days, dependent to the plants ecotype, in the 70% moist sand and 3 to 5 °C in incubator or refrigerator has been recommended to break seeds' dormancy (Safaian and Azarnivand, 2010, Razavi and Hajiboland, 2009).

Plant pests:
Pachymerus acaciae is the most important pest of *P. ferulacea* seeds in most regions of the Iran. This beetle is a polyphage insect from Bruchidae family which lays its eggs on *P. ferulacea.* The larva of this insect feeds from *P. ferulacea* seeds and hence destroys seeds (Hasani and shahmoradi, 2007).

Phytochemical compounds:
Phytochemical examinations have led to identifying and extracting some coumarines, alkaloids, flavonoids, and terpenoids in species of Prangos (Ayres et al., 1994). Examining aerial parts and the seeds of *P. ferulacea* led to identifying 33 compounds in oil of this plant (Razavi, 2012). In essential oil of this plant's fruit, 39 compounds have been detected, among which α-pinen has the highest proportion (Kuznetsova et al., 1973, Akhgara et al., 2011), and monoterpenes, sesquiterpenes, and coumarines (Sajjadi et al., 2011, Gholamzadeh et al., 2012, Ahmed et al., 2011) have been the most important compounds of the root (Razavi, 2012, Sefidkon et al., 1998, Massumi et al., 2007) (table 1).
Identifying the compounds of *P. ferulacea* essence in three stages (before flowering, during flowering, and fruition stages) has indicated that the main compounds of this plant in all stages are monoterpene compounds particularly α and β-pinen as these two compounds comprise more than 65% of essence. Among other important compounds of this essence is α-tripholence. Higher propertion of α and β-pinen before flowering compared to other stages is remarkable in terms of qualitative changes in growth stages. On the other hand, β-cariotlene was observed only in fruition stage, and γ- terpinene in flowering and fruition stages (Amiri, 2007).
Also, in different parts of the plant α-pinen (57%) and E-anethole (95.5%) were the largest compounds of the essential oil in respectively growth and flowering stages. Monoterpene hydrocarbons (72.7%) and sesquiterpenes (8.9%) are the most important compounds of aerial parts essential oils in growth stage and aromatic compounds (95.5%) comprise the largest compounds in flowering stage (Razavi, 2012, Akhgara et al., 2011).
The researches have indicated that the quantity of compounds and the proportion of extract constituents are largely affected by genotype, developmental and growth stage of the plant. Therefore, quantitative and qualitative changes of *P. ferulacea* follow this principle in different stages of growth (Akhgara et al., 2011, Marotti et al., 1994).

Nutritional properties of *P. ferulacea*:
In many parts of Iran, this plant is one of the main plants supplying fodder in winter. Some people prefer *P. ferulacea* over alfalfa for feeding cattle (Azarfard, 2008, Eilami, 2008). Green *P. ferulacea* is not consumed by cattle; rather, it is cut and dried to be used as fodder in winter (Hasani and shahmoradi, 2007). Studies have indicated that different cattle (cows, sheep and goats) do not graze *P. ferulacea* in any growth stage (Ebrahimi et al., 2007, Farid, 1991).The existence of coumarines in large quantities in green limbs of *P. ferulacea* (Ahmed et al., 2011) and its unpleasant odor probably prevents *P. ferulacea* from being grazed in different growth stages. However, In a study in Turkey, chemical

decomposition of *P. ferulacea* indicated that this plant can be used as energetic fodder (Coskun et al., 2004). In addition, in another study, aluminum, calcium, iron, potassium, magnesium, sodium, phosphorus, and zinc were found as the most important minerals of *P. ferulacea* (Ozcan et al., 2007).

Therapeutical properties:

Antioxidant properties:

P. ferulacea is a rich source of antioxidants. In a study, the protective and antioxidant effects of *P. ferulacea* are reported to be higher compared to α-tocopherol (vitamin E) and the effect of glutathione-S- transferase (GST) has been demonstrated (Coruh et al., 2007). The existence of this property is directly related to coumarines, alkaloids, flavonoids, and terpenoids, which was repeatedly reported in previous research (Sajjadi and Mehregan, 2003). In addition phenolic compounds of *P. ferulacea* confirm this plant's antioxidant properties (Coruh et al., 2007). However, Razavi et al.'s study indicated that one of the recently identified flavonoids in the extract of aerial parts called quercetin-3-0-glucoside was found to had no effect in the expression of *P. ferulacea*'s antioxidant properties (Razavi et al., 2009).

Anti diabetic properties:

In previous investigations, the antidiabetic properties of *P. ferulacea* were examined for the first time, indicating that diabetized rats treatment with hydroalcoholic extract of the root in 100 mg/kg dose helped blood glucose, total cholesterol (TC), trygliuride (TG), glycosilated hemoglobin (HbA1C), and low-density-lipoprotein (LDL) decrease significantly. It also causes significant increase in high-density lipoprotein (HDL) and regulation of white blood cells (WBC) to a normal level (Kafash-Farkhad et al., 2012, Soltani band et al., 2011). In addition, histologic examinations showed that the extract of *P. ferulacea* could recover many tissue lesions, including necrotic focuses, tissue atrophies, lymphocytic infiltrations increase in some regions, and glomerosclerosis renal lesions to a large extent and mostly cause an increase in the treated rats' weight (Kafash-Farkhad et al., 2012, Farokhi et al., 2013). In other research, the effect of *P. ferulacea* on diabetes-associated renal and hepatic lesions recovery was shown to be effective, leading to a significant increase in blood indices of liver function such as creatinine, alanine amino-transferase (ALT), and aspartat-amino-transferase (AST) (Mokhtari and Mohammadi, 2012). The existence of a compound called umbelliferone and the coumarines extracted from *P. ferulacea* root, and the flavonoid compounds that have antioxidant properties, with helpful effects on recovery of hepatic enzymes' serum levels and renal disorders, could explain the effectiveness of the plant's root extract on diabetes-associated biochemical and histologic complications recovery (Soltani band et al., 2011, Mokhtari and Mohammadi, 2012, Ramesh and Pugalendi, 2005, Farokhi et al., 2012).

Antibacterial properties:

The antibacterial effects of four extracts (ethanolic, methanolic, acqeous, an n-hexne) of *P. ferulacea* against several positive gram bacteria such as *Bacillus cereus*, *Bacillus subtilis*, *Micrococcus luteus*, *Staphylococcus aureus*, and negative gram including *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Salmonella enteritidis* were examined which indicated that the highest antibacterial properties were associated with ethanolic and methanolic extracts with significantly strong antibacterial effects (Durmaz et al., 2006). In another research, the antibacterial properties of the fruit extract against positive and negative gram bacteria like *Eschrechia coli*, *Staphylococus aureus*, *S. epidermis*, and *Pseudomonas aeroginosa* have been demonstrated. In these investigations, the presence of some compounds such as limonene, a-pinen, and humulene have been offered as the reason for exhibiting antibacterial porperties by this plant (Massumi et al., 2007, Razavi et al., 2009).

Antiviral properties:

Recently, some reports on inhibitory effect of cytokines' release and anti HIV virus effects exhibited by different species of *P. ferulacea* have appeared. In a research in 2012, several important coumarines obtained from *P. ferulacea* root expressed cytotoxic and anti HIV properties (Gholamzadeh et al., 2012).

The effect of *P. ferulacea* on abortion:

The study of abortifacient effects of *P. ferulacea* in rats indicated that plant's leaf extract in *only* some doses increased the number of abortions in pregnant rats. However, this increase was not significant and no association was observed between the dose and kind of the extract and the number of abortions. Obviously, examinations of other doses are needed in the future to find out this property in *P. ferulacea* (Kazerooni and Mousavizadeh, 2005, Kazerooni et al., 2006).

Analgesic effect of *P. ferulacea*:

In folk medicine, *P. ferulacea* is used as a sedative for decreasing many kinds of pain including toothache, the pain due to bone breaking, the pain of joints, bruises, headache, muscle pain, etc. In a study in Shiraz, the analgesic effects of aqueous and

alcoholic extracts of *P. ferulacea* on formalin-induced pain in female rats were examined. The prescription of aqueous extract in 100 mg/kg could decrease the pain in the second phase of formalin test and 300, 900, and 1350 kg/mg doses led to decrease in the first and second phase of this test. In addition, methanolic extract in 200mg/kg decreased the pain in the second phase and 400 and 800 mg/kg doses resulted in decrease in pain in the first and second phases. In this work, the existence of some compounds such as saponin, antrakinon, tannin, and flavonoids in *P. ferulacea* extract was offered as potential reasons for analgesic effects (Emamghoreishi et al., 2012).

Anti spasm effects of *P. ferulacea*:

In Sadrai et al.'s study, loosening and contraction-removing effects of *P. ferulacea*'s root and aerial parts on smooth muscles of uterine in rats were examined, and the results indicated dose-dependent anti-spasmodic effects of *P. ferulacea* on the contraction especially induced by exitoxin. This property possibly is derived from one of the most important coumarines of this plant called osthole which expresses these properties in *P. ferulacea* through blocking calcium channels and its important role in child bearing process (Sadraei et al., 2012, Sadraei et al., 2013).

Potential Mechanisms:

According to the literature, some potential mechanisms of the plant's effects have been shown in table 2.

Dose and side effects:

This plant like some other plants is toxic. Therefore, the amount and duration of consumption and therapeutical time should be determined by a physician. This plant is usually eaten accompanied with *Oryganum vulgar* because *O. vulgar* regulates or decreases the complications possibly caused by *P. ferulacea* (27).

Conclusion:

P. ferulacea is one of Iran's medicinal plants which possess many medical properties because of coumarines, flavonoids, alkaloids, umbelliferon, monoterpenes, etc. and has been used in traditional medicine in several cases. The existence of these compound and medicinal properties necessitates further examinations of helpful and unknown effects of this plant in the future to be used as a medicine for treating human diseases. Some clues that can be resorted to in these investigations are anti-inflammatory, analgesic, antifungal, anti-diabetic, and therapeutic properties of *P. ferulacea* for gastrointestinal diseases including gastric disorders which have been less studied.

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Corresponding author:

Vice Chancellery for Research and Technology, Shahrekord University of Medical Sciences, Shahrekord, I.R. Iran. Tel: 00983813349509, E-mail: biology_2011@yahoo.com

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Table 1: The main compounds of roots oil aerial parts, seeds and fruit of *P. ferulacea*.

Plant parts	Root	Shoot	Fruit
Important compounds	δ-3-carene	δ-3-carene	δ-3-carene
	α-Pinene	α-Pinene	α-Pinene
	β-Pinene	β-Pinene	β-Pinene
	Gosferol	Limonene	Limonene
	Myrcene	β-Ocimene	Myrcene
	Osthole	3-Ethylidene-2-methyl-1-hexen-4-yne	Mesitaldehyde
	Oxypeucedanin methnolate	α- Camphene aldehyde	Sabinene
	Psoralen	E-anethole	3-n-butyl phthalide
	Isoimperatorin	Caryophyllen oxide	α-Humulene
	Oxypeucedanin	Epi-α-bisabolol	Chrysanthenyl acetate
	Terpinolene	Sabinene	Camphene
	Oxypeucedanin hydrate	Pinocarvone	Terpinolene
	A-phellandrene	Kessane	-
	p-cymene	Spathulenol	-
	-	E-β-Farnesene	-
	-	p- Cymene	-

Table 2: The potential mechanisms of efficacy of some pharmacologic properties of *P.ferulacea*.

Effects	Mechanisms	References
Antioxidant	Inhibition of enzymatic activity of GST, decrease in lipid peroxidation because of inhibition of malonaldehyde activity, and decomposition of detrimental androgen compounds such as DNA hydroperoxidase because of high content of poly-phenolic compounds existing in this plant.	(Durmaz et al., 2006, Massumi et al., 2007)
Antidiabetic	Increase in insulin release resulting from remaking up of β-pancreas cells due to compounds like umbelliferon in its root Flavonoild compounds existing in this plant and capable of counteracting DPPH free radical and hence decreasing its destructive effects. Decrease in oxidative stress and increase in glucose absorption by kidney, lipid, and muscle cells.	(Kafash-Farkhad et al., 2012, Soltani band et al., 2011, Farokhi et al., 2012, Farokhi et al., 2013, Mokhtari and Mohammadi, 2012)
Antibacterial	Existence of compounds such as limonene, α-pinen, and α-humulen potentially through enzymatic inhibition of oxidized compounds, or reaction with solfidryle groups is the reason for antibacterial properties of this plant.	(Durmaz et al., 2006, Massumi et al., 2007)
Antiviral	Existence of isoimperatorin،oxypeucedanin, psoralen, oxypeucedanin hydrate, gosferol, oxypeucedanin methnolate is the reason for cytotoxic properties and anti HSV virus effect potentially via deactivating viral DNA polymerase.	(Sajjadi and Mehregan, 2003)
Analgesic	Existence of compounds such as saponin, antrakinon, and flavonoids in its metanolic extract, and saponin, nitrogenic groups, and tannin in its aqueous extract which exert analgesic effects centrally and peripherally and possibly through inhibiting prostaglandins. It seems that aqueous extract in small doses functions peripherally and in larger doses through which larger amounts of effective compounds enter central nervous system the effect of the extract on the first phase magnifies; in other words, the analgesic effects, when the dose increases, are exhibited through central mechanisms	(Emamghoreishi et al., 2012)
Anti-spasm	Existence of a coumarine called osthole with anticoagulant property, loosening muscles, and blocking calcium channels.	(Sadraei et al., 2012, Sadraei et al., 2013)