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CURRENT REVIEW ON PHYTOCHEMICAL AND PHARMACOLOGICAL POTENTIAL OF *PRUNELLA VULGARIS*

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Abstract
P. vulgaris (*Prunella vulgaris*) is an important medicinal plant from Labiatae family, is widely distributed in Asia, Europe and Iran. It is traditionally used for heal wounds, ulcers, inflammation, headache, dizziness, sore throat, antibacterial, antipyretic, antiseptic, antispasmodic, and wound healing. There are some "drug like" plants remedies that their actions approach that of pharmaceuticals. *P. vulgaris* is known as selfheal; contains several active components, including oleanolic acid, botulinic acid, unsolid acid, alkaloids, flavonoids and rosmarinic acid. Some pharmacological activities such as the immunomodulatory effect, anti-viral activity against and antioxidant activity, anti-diabetic and anti-allergic action were confirmed.It can serve as a widespread, constantly renewable source of raw materials needed for phytopharmacology. Due to a wide range of PV health benefits, this article provides a comprehensive review of the composition and pharmacological activity, methods for obtaining extracts from *P. vulgaris* .

Keyword: *Prunella vulgaris*, selfheal, pharmacological, components.

Introduction

The herbal medicines contain a lot of different compounds which some of them have great complexities. Plants substances such as polysaccharides, mucilages and tannins may modulate and modify the effects of "active components". Nowadays, the reduction of pharmaceutical production costs along with increasing the efficacy, quality and safety of medicines is of great interest. The use of domestic types of medicinal plant raw materials seems to be economically viable for many researchers. The *Prunella Vulgaris* L. (PV) has a great scientific interest and practical use as well.

P. vulgaris (Labiatae), a rediscovered herb belonging to the mint family also known as self heal, was very popular in European, Asian and Chinese medicine and was used against fever, wound and throat infection. Its flowering season is from May to September (Markova *et al*., 1997). It is reported to display diverse biological activities including anti-microbial, anti-cancer, and anti-inflammation as determined by in vitro or in vivo studies. *P. vulgaris* is used in European traditional medicine since centuries. The whole plant, leaves or fruit spikes, are also commonly consumed as health-promoting food or herbal tea in China (Qu *et al*., 2017).

In Europe, *P. vulgaris* is used for the treatment of sore throat, intestinal infections, diarrhea, as healing agent and anti-hemorrhagic (Huang *et al*., 2009) while in Asia, it is consumed as herbal

tea for the treatment of health troubles such as migraine or fevers (Kalle and Soukandal., 2012). In Europe, the plant is also sometimes eaten in its whole and it has been officially approved as dietary supplement in some countries like Belgium and is evaluated at the European level.
Due to its numerous reported traditional medicinal uses and properties, the phytochemical composition and anti-oxidant activity of the aerial parts of *P. vulgaris* have been largely examined; rosmarinic acid, polysaccharides, pentacyclic triterpenes have been identified. Although the composition and properties of the areal parts are well documented in the literature, to the best of our knowledge, *P. vulgaris* seeds have never been investigated for their proximate, phytochemical composition or potential bioactivities (Gu *et al*., 2013; Golembiovska, 2014).

General health benefits of *Prunella vulgaris*: Dried fruit spikes with flowers are used for various pharmaceutical purposes, besides leaves and stems are used for olive green dye. Leaves are used as raw or cooked in salads and soups (Yeung and H.C, 1985). Fresh leaves and stem of herb are rich in protein, plant fat, carbohydrate, carotene, vitamin B and nicotinic acid (Launert, 1981). The whole plant is considered as alterative, antibacterial, antipyretic, antiseptic, antispasmodic, astringent, carminative, diuretic, febrifuge, hypotensive, stomachic, styptic, tonic, vermifuge and vulnerary (Duke *et al*., 1985). It was used to heal wounds, ulcers and sores (Chiej, 1984). It was used as a tea in treatment of fevers, diarrhoea, sore mouth and internal bleeding.It is antibiotic and hypotensive (Foster, 1990).

Botany

Prunella vulgaris is a perennial plant 10–50 cm high. It is green and almost glabrous, and its rhizome is creeping and oblique. The stem is erect, simple, and almost glabrous.
The leaves oblong or ovate, glabrous or sparsely pubescent, entire, sometimes obscurely serrated, 2–6 cm long.The lower leaves on the petioles are longer than the blades, the upper ones are sessile under the inflorescence. The flowers are located in false whorls, in dense capitate, ovoid or oblong terminal, sometimes lateral inflorescences. Bracts broadly ovate or almost round, about 1 cm long, sessile with a heart-shaped base, long pointed, membranous-reticulate, almost glabrous, rarely pubescent, with cilia along the edge, from red to black-violet. Its calyx is two-lipped, humpbacked above, usually hairy at the base, sessile, or on a short stalk. The upper lip is almost square and flat with three very short sharp teeth.
The corolla purple is 8–12 mm long, 1.5–2 times as long as the calyx. The corolla tube is straight; the upper lip is broadly obovate, concave, and slightly notched at the apex. The lower lip is shorter than the upper ones with an almost round, sharply dentate middle lobe and small rounded ovoid lateral. The filaments of long stamens are located under anther with a subulate, straight or slightly curved process. The nuts are ovoid and elliptical, 1.5–2 mm long, nearly 1 mm wide, trihedral, flat outside, and shiny. The flowering stage occurs between June–September (Zholdasbayev *et al*., 2023).

Figure: Appearance aerial parts of *Prunella vulgaris*

Common Names

All heal, blue curls, blue Lucy, brownwort, brunella, carpenters weed, carpenter-weed, carpenter's-weed, common self heal, common selfheal, dragonhead, heal all, heal-all, healall, heart of the earth, Hercules woundwart, hook-heal, hookweed, prunella, self heal, self-heal, selfheal, sicklewort, slough-heal, thimble-flower, thimbleweed, wild sage.

Geographical distribution

P. vulgaris is an early successional species commonly found in moist, often disturbed areas including forest edges, open woodlands, meadows, pasturelands, roadsides, clearings and lawns at elevations below 8000 ft. It grows best in full sun to partial shade and moist soil. It is native to North America and its distribution is circumboreal, including most of the Northern Hemisphere. This medicinal herb grows in grasslands and usually prefers acidic, neutral and basic soils. It grows in the semi shade or moist soil. It is widely distributed in tropical and temperate regions including Europe, North Africa, Siberia, Western Asia, India, Pakistan, Nepal, Bhutan, Japan, North Korea, and America (Chen *et al*., 2013)

Scientific classification

Kingdom: Plantae
Phylum: Anthophyta
Class: Dicotyledoneae
Order: Lamiales
Family: Lamiaceae
Genus: Prunella
Species: Vulgaris (Patel and Sharma, 2019)

Phytochemistry

Various bioactive components were identified in the extract of *P. vulgaris* (Brindley *et al*., 2009). The main active components were triterpenes (Ryu *et al*., 2000), saponins (Rasool *et al*., 2010), sterols, flavonoids (Xia *et al*., 2018), phenylpropanoids (Psotova *et al*., 2003), polysaccharides (Fang *et al*., 2005) and volatile oils.

Triterpenes and Their Saponins

A total of 28 triterpenoids were isolated from *P. vulgaris*, including 20 triterpenoid sapogenins and 8 saponins (Wang *et al*., 2000). The highest content was oleanolic acid, which was significantly correlated with the pharmacological effects of *P. vulgaris*. In nature, the compound exists in the structure of a free acid or a triterpenoid saponin glycoside ligand precursor, where it can be combined with sugar chains (Pollier and Goossens, 2012). The existence of α-l-rhamnose residues at the C-3\28 ends of oleanolic acid double-stranded glycosides is important for enhancing cytotoxicity, and the introduction of further sugar at C3-OH and C-28 carboxylic acid is an advantageous decoration to improve defense against tumor function (Liu *et al*., 2013).

Sterols

The sterol compounds in *P. vulgaris* mainly include β-sitosterol, stigmasterol and Δ7-stigmasterol. The structure of plant sterols is similar to that of cholesterol. A double bond consisting of three cyclohexane rings and one cyclopentane ring was found at the C5-6 position. It has been indicated that phytosterols can induce apoptosis in some carcinoma cell lines and exert anticancer activity (Kim *et al*., 2014).

Flavonoids

P. vulgaris also includes luteolin, iso-orientin and luteoloside. Luteolin is a tetrahydroxy flavonoid compound composed of a carbon structure and two benzene rings connected by heterocycles. It mainly exists in the form of glycoside ligands or glycosides. Luteolin has been found to have the external and internal mechanisms of apoptotic cell mortality in carcinoma. The inhibition of neoplasm cell metastasis and angiogenesis is a potential influence of luteolin and has the possibility of reversing the drug resistance of neoplasm cells (Singh *et al*., 2022).

Phenylpropanoids

Phenylpropanoids in *P. vulgaris* are cis- and trans-caffeic acids and rosmarinic acid (Psotova *et al*., 2006). Among them, rosmarinic acid has been studied more. In industry, rosmarinic acid can be manufactured via esterification concerning 3,4-dihydroxyphenyllactic acid and caffeic acid (Swamy *et al*., 2018), which has been proven to have a strong anti-tumor role (Gonzalez *et al*., 2015).

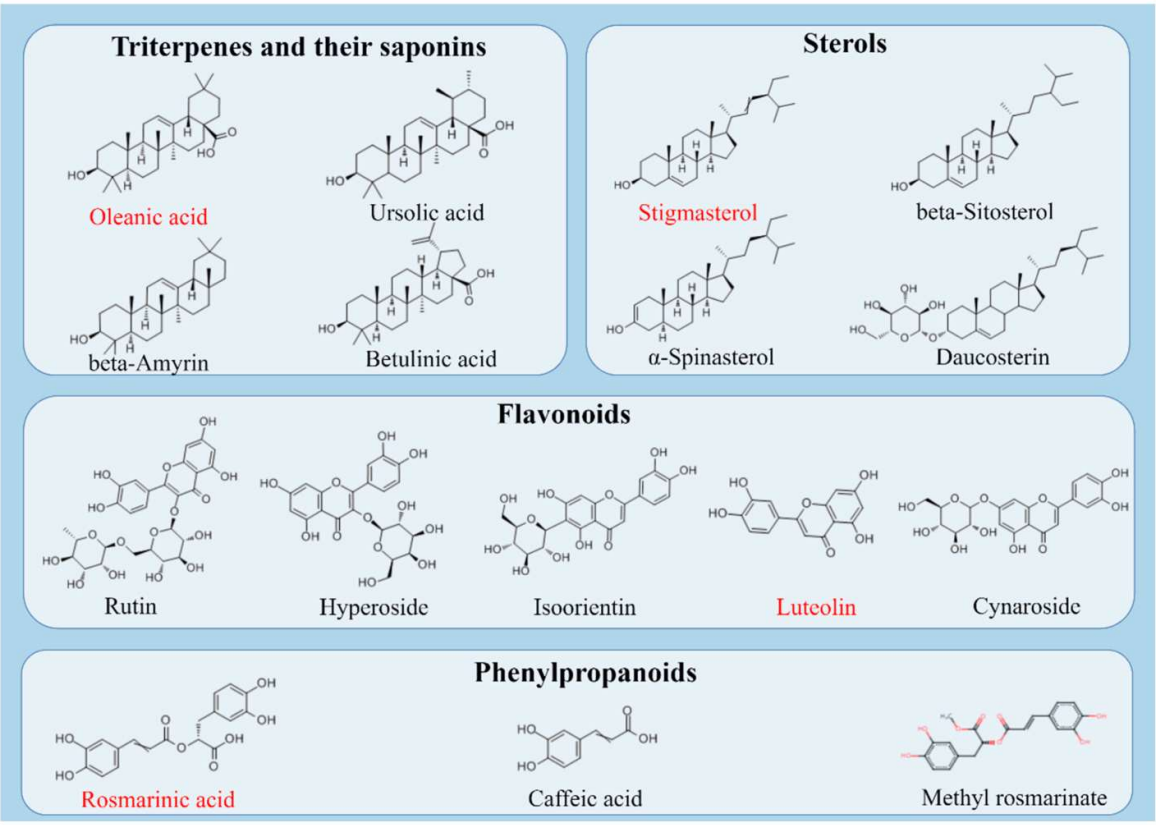

Figure: Structural formula of active components in *P. vulgaris*: the compounds highlighted in red are the four active ingredients that were the focus of the review in this study.

Fatty acids

Fatty acids are carboxylic acids often with a long unbranched aliphatic chain, which is either saturated or unsaturated. The fatty acids in *P. vulgaris* are isolated and reported as oleic acid, linoleic acid, lauric acid, palmitic acid (cetylic acid), myristic acid, stearic acid and tetracosanoic acid. Beside, another five fatty acid derivatives have been identified as ethyl palmitate, 6,9-octodecadienoic acid, 3,6,7- eicosatrienoic acid, archidic acid and behemic acid.

Volatile oils

The studies on volatile ingredients in *P. vulgaris* showed that the volatile oil has been obtained at a rate of 0.31%. By using GC-FT-IR methods, twenty-three known components have been isolated from *P. vulgaris*. The principal constituents are 1,8-eucalyptol, β-pinene, myrcene, linalylacetate, αphellandrene and linalool. The content of 1, 8- eucalyptol and β-pinene constitutes more than 60% of the total volatile oil (Pan *et al*., 2022; Lawson *et al*., 2020).

Carbohydrates

P. vulgaris contains dissoluble monosaccharides, disaccharides and polysaccharides. Dissociated glucose, galactose, fructose and sucrose have also been isolated and obtained from *P. vulgaris*.

Other components

Vitamin A, vitamin C, vitamin K, vitamin B1, vitamin PP (niacin), carotene, daucosterol, bicylic monoterpenoids (dcamphor, d-fenchone), tannic acid, resin, bitter substance, fatty oil, alkaloid (1120 mg%), proteins (441.6 mg%) and lipids (2403.8 mg%) are contained in *P. vulgaris*. Apart from these above compounds, *P. vulgaris* also contains 3.5% water-soluble inorganic salts, in which potassium chloride constitutes 68%.

Pharmacology Actions

P. vulgaris is a plant source of a variety of medicinal active ingredients, and its wide range of uses can treat various diseases, including cancer. It has anti-inflammatory effect. The wound-healing effect of the chemical compound of *P. vulgaris* in rats and mice was studied via wound models. The experimentation studies have indicated its remarkable ability to heal a wound and its anti-inflammatory efficacy (Akkol *et al*., 2022); antibacterial effect studies have shown that *P. vulgaris* extract has antibacterial activity against Escherichia coli in patients with urinary tract infection (Komal *et al*., 2018), as *P. vulgaris* extract is a natural antioxidant that restores the level of the oxidation index and has significant antioxidant and hepatoprotective activities (Li *et al*., 2021); and studies of anti-hypertensive effects have shown that these effects can significantly reduce systolic blood pressure and blood pressure in rats, with the anti-hypertensive effect having a dose–effect relationship. The acute and chronic hypoglycemic effects of *P. vulgaris* in type I diabetes were evaluated in a mouse model, and studies showed that serum insulin in mice increased and α-amylase and α-glucosidase decreased under the intervention of *P. vulgaris*; therefore, the active ingredients in *P. vulgaris* may be potential drugs to improve type I diabetes and related complications (Raafat *et al*., 2016).

P. vulgaris is a commonly used Chinese medicinal material in clinical practice. It has a wide range of pharmacological activities due to its rich chemical composition. In this section, we refer to "General Requirements for developing, conducting and researching medicinal plants and natural products (phytopharmacology)" (Heinrich *et al*., 2020).

Anti-allergic: The effect of aqueous extract of herb on immediate-type allergic reactions was studied which showed that extract (0.005 to 1 g kg^{-1}) inhibited systemic anaphylactic shock in rats. When extract was given at concentrations ranging from 0.005 to 1 g kg^{-1}, the serum histamine levels were also reduced (Shin *et al*., 2001). Again the effect of aqueous extract of *P. vulgaris* on the mast cell-mediated allergy model was investigated and it was found that extract (0.001 to 0.1 g kg^{-1}) dose dependently inhibited systemic anaphylaxis and serum histamine release in mice (Kim *et al*., 2007).

Anti-diabetic: *P. vulgaris* extract at dose of 100 mg kg^{-1} significantly suppressed the rise in blood glucose after 30 min in the acute glucose tolerance test. It enhanced the antihyperglycemic effects of exogenous insulin without stimulating insulin secretion in streptozotocin-induced diabetic mice (Zheng *et al*., 2007). Extract also has a protective effect on IL-1β-induced INS-1 cell apoptosis. It attenuates IL-1β-increased NF-κB binding activity and inflammatory cytokine expression in INS-1 pancreatic β-cells. PVAE may have a benefit for type I diabetic patients (Wu *et al*., 2012).

Anti-stress: The ability of ethanolic extract of leaves of *P. vulgaris* to prolong the swimming time and ameliorate the stress induced changes in animal stress models was reported, therefore suggested its adaptogenic property (Mrudula *et al*., 2010).

Anti-Tumor: Early on, Chen et al. carried out a series of cell experiments *in vitro*, found that PVL extract could induce Jurkat cell apoptosis by down-regulating Bcl-2 protein and up-regulating Bax protein, thereby inhibiting the growth of Jurkat human T lymphoma cell (Chen *et al*., 2009). Some researchers found that the 60% ethanol extract of PVL had a chemopreventive effect on non-small cell lung cancer, and its mechanism of action may be related to promoting apoptosis and regulating cell cycle (Feng *et al*., 2010a). Thereafter, PVL aqueous extract was found to inhibit the invasion and migration of human liver carcinoma HepG2, Huh-7 and Hep3B cells via attenuating matrix metalloproteinases (Kim, 2012).

Anti-Viral: As early as 1986, the powerful inhibitory effect of PVL polysaccharide on HIV *in vitro* has been proved by Tabba et al. (Tabba *et al*., 1989), although its mechanism has not been elucidated. Later, Yao et al. found that the PVL extract inhibited HlV-1 replication in the lymphoid cell line MT-4, monocytoid cell line U937, and peripheral blood mononuclear cells, it antagonized HV-1 infection of susceptible cells by preventing infection attachment to the CD4 receptor (Yao *et al*., 1992).

Anti-Bacterial: The emergence and spread of bacterial resistance have made the infection caused by multidrug-resistant bacteria a serious problem (Jiang S. *et al*., 2020). *In vitro* experiments showed that PVL had certain inhibitory effects on *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Penicillium* sp., *Aspergillus niger* and *Pseudomonas aeruginosa* (Wang *et al*., 2004). Lin et al. took the bacterial vaginitis model of rats and discussed the antibacterial effect of PVL aqueous extract *in vivo* for the first time. The results showed that PVL could significantly resist bacterial vaginitis in rats caused by mixed infection of *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* in a dose-dependent manner (Lin *et al*., 2011).

Anti-Oxidant: Many studies have shown that PVL has an obvious antioxidant capacity *in vitro*, which makes it possible to increase its application as a natural antioxidant in the food and drug industries (Lugasi *et al*., 2006). Zhang et al. found that flavonoids in PVL had obvious antioxidant activity *in vitro* and could significantly scavenge DPPH and OH radicals (Zhang *et al*., 2011). Song et al. found that different extracts of PVL had certain antioxidant activity. Among them, 70% ethanol extract had relatively high DPPH, OH scavenging activity and lipid peroxidation inhibition activity, aqueous extract had the highest O_2^-·scavenging activity (Song *et al*., 2016).

Anti-Inflammatory and Immunoregulation: Previous studies have shown that polysaccharide fraction of PVL exhibits both immune stimulatory and anti-inflammatory effects against microbial invasion (Fang *et al*., 2005b). Zdařilová et al. found that rosmarinic acid (RA) in PVL inhibited up-regulation of IL-1β, IL-6, TNF-α and suppressed expression of iNOS on LPS-induced inflammation in human gingival fibroblasts. They speculated that the

effect was presumably linked to anti-inflammatory activitity and use of RA may be relevant in modulating the inflammation process (Zdarilova *et al*., 2009). Xie et al. found that total triterpenoids from PVL (TTP) could inhibit the secretion of PGE2, TNF-α and IL-6 in LPS-stimulated RAW264.7 cells, and significantly inhibit the gene expression of Jak2 and Stat3. The results indicated that TTP had a certain anti-inflammatory effect, and the production of this effect might be related to the Jak/Stat pathway (Xie *et al*., 2013).

Hepatoprotective: In the past few decades, studies have shown that complex prescription PVL exhibits a protective effect on acute liver injury induced by CCl_4 in mice. It could significantly reduce the increase of serum ALT and AST in mice with acute liver injury induced by CCl_4, and alleviate the damage of CCl_4 on liver cells (Feng *et al*., 2011c). Soon afterwards, some scholars found that total triterpenoids from PVL could reduce the activities of ALT and AST in serum of rats with acute liver injury, reduce the level of MDA in liver homogenate, increase the levels of SOD and GSH-Px, and inhibit the expression of CYP2E1 in liver tissue, and its mechanism might be related to the inhibition of lipid peroxidation and CYP2E1 expression (Zhang *et al*., 2012).

Conclusion

The present comprehensive etheno- medicinal or etheno- pharmaceutical review reveals that *P. vulgaris* is a very important medicinal plant with its large number of phytochemical and pharmacological properties as well as medicinally important chemicals like Triterpenes, Saponins, Sterols, Flavonoids, Phenylpropanoids, Fatty acids, Volatile oils and Carbohydrates. From the point of view a number of investigations of pharmacological activity have been observed. *P. vulgaris* is to be very useful in anti-bacterial, anti-viral, anti-mutagenic, anti-inflammatory and wound healing activities. While some of the other reported uses include anti-allergic, anti-pyretic, anti-diabetic, anti-oxidant, gastric and reproductive activity. The most exciting aspects of the medicinal plant of *P. vulgaris* was treatment of diabetics, fevers, diarrhoea, sore mouth and internal bleeding. This compendium literature are supported various potential medicinal characteristics of *P. vulgaris*.

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