

A review of botanical characteristics, chemical composition, pharmacological activity and use of parsley

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Abstract

Parsley is a biennial aromatic plant from the Apiaceae family, which is characterized by an unbranched root, pinnately divided leaves, umbels and schizocarp. It contains essential oil in all parts, with phenylpropane and terpene compounds as main components. It is rich in flavonoids and other polyphenolic compounds, containing furanocoumarins, carotenoids, polyacetylenes, and its leaves are a source of vitamins and minerals. The chemical composition of parsley depends on a number of factors, so it differs not only in different parts and varieties of the plant, but also in different samples of the same parts of one variety. The most important parsley compounds are myristicin, apiol, 1-allyl-2,3,4,5-tetramethoxybenzene, β -phellandrene, 1,3,8-p-menthatriene, β -pinene, terpinolene, apiin, oxypeucedanin and falcarinol. Parsley has a long tradition of use in the treatment of urinary tract disorders, and modern *in vitro* and *in vivo* studies reveal numerous effects of various parsley preparations such as diuretic, antiurolithiasis, hypouricemic, hypolipidemic, hypoglycemic, hypotensive, antioxidant, anti-inflammatory and antiplatelet effect. Today, apart from its medical application, parsley is one of the most commonly used culinary herbs.

Key words: *Petroselinum crispum*, essential oil, flavonoids, antioxidants

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Introduction

Parsley (*Petroselinum crispum* (Mill.) Nym) is a biennial aromatic plant from the Apiaceae family. This medicinal herb has been widely used in the Mediterranean for more than 2000 years, firstly by Ancient Greeks in religious rites until Hippocrates introduced it as a diuretic. Parsley was brought to Central Europe by the Romans, and around 795 CE its cultivation in this area become obligatory by the law of Charles the Great. Today, in addition to its medical use, parsley is used as a spice around the world, mostly in omelets, salads, sauces, soups, for making herb butter but also as an accompaniment to various other dishes (1).

This paper will describe the botanical characteristics of parsley, some of which are common to all species of the Apiaceae family, as well as the chemical composition of parsley leaves, roots and fruits, including the composition of their essential oils, and variations in composition under the influence of different factors. Both *in vitro* and *in vivo* assays will be presented in order to prove the pharmacological effects of parsley fruits, roots and leaves, their various extracts, essential oils and isolated components. Toxic effects and studies of the mechanisms of action of active components will be also discussed. In addition, the use of parsley in different folk medicines, as well as the traditional and modern use, will be covered.

Taxonomy

The Umbelliflorae order includes seven families, and the most abundant is the Apiaceae family, which counts 275 genera and 2850 species growing around the world (2). Only in the Republic of Serbia, this family is represented with 53 genera and 138 species (3). This family is also commonly known as the Umbelliferae family, because of the characteristic inflorescences that look like a shield (*umbella* - shield) (4).

Petroselinum crispum (Mill.) Nym, parsley (syn. *Petroselinum sativum* Hoffm., *Petroselinum hortense* Hoffm., *Apium crispum* Mill., *Apium petroselinum* L.) is the only species of genus *Petroselinum* that grows in the Republic of Serbia (3). Parsley appears in three common cultivated varieties as *P. crispum* var. *crispum* - curly leaf parsley; *P. crispum* var. *neapolitanum* - flat leaf parsley; and *P. crispum* var. *tuberosum* - rooted parsley (5).

Botanical description

The parsley root is fusiform, up to 20 cm long, yellowish and almost fibreless, sweet to slightly astringent (1,6,7). It is a biennial plant. A leaf rosette is developed in the first year while vertical, hollow stem with opposite branches is developed during the second year. The leaves are dark green and shiny. The basal ones are 2 or 3 time pinnately divided and the upper ones are sessile with linear shaped apical lobes. The flowers are small, actinomorphic, male or hermaphroditic, with white or yellowish corolla and barely developed calyx. It flowers from June to July, in the second year (1,3,4).

The characteristic fruit for all members of the Apiaceae family is an ovate, greenish and ribbed schizocarp, which breaks into two equal mericarps when ripe (4,7). Each mericarp has a ventral, flat side and dorsal, convex side. Mericarp contains 5 main, elongated ribs (3 dorsal and 2 lateral) composed of mechanical tissue and between the main ribs, in the dents, there are secondary ribs. Secretory channels with essential oil are placed in the mesocarp of secondary ribs. Except essential oil, these channels contain simple coumarins and furanocoumarins which are responsible for characteristic smell and taste of parsley fruit (3,4).

It is important to distinguish the aerial parts of the parsley from similar poisonous species of such as *Aethusa cynapium* ("fool's parsley") and *Conium maculatum* (hemlock). Both species are characterized by lighter-colored leaves, which leave an unpleasant odor after rubbing, and white corolla leaves, while hemlock has a stem with brown-red dots. Parsley root can also be substituted for the root of *Pastinaca sativa* (parsnip), but this species is edible and also used as a culinary spice (1).

Habitat and cultivation

Parsley originates from Southwestern Europe and Western Asia. Although parsley grows widely upon old walls and fields, it is cultivated around the world as a culinary spice (1,3). Parsley is usually sown at the end of winter (in March or April), less often in autumn, on moist, light, humus soil. The leaves can be harvested in June, and the roots in October or November. Parsley can also be grown as a potted plant. Interestingly, it cannot be sown for more than one season in the same location due to auto-incompatibility (1). Despite being commonly known as an aromatic plant, in addition to essential oil, parsley contains numerous components of various pharmacological activities (6). The root (*Petroselinia radix*), aerial parts (*Petroselinia herba*) and fruit (*Petroselinia fructus*) are used as herbal drugs. The essential oil of parsley (*Petroselinia aetheroleum*) is derived from the fruit (1,6,8). Parsley essential oil is used in the food industry as a flavoring agent for various foods (8).

Chemical composition of parsley essential oil

Parsley essential oil is obtained by steam distillation of parsley fruit (fresh, ripe and pulverized). Although the fruit contains most of the oil, it is also present in leaves and roots. Parsley essential oil is pale yellow or colorless (6). This essential oil is a mixture of different metabolites such as phenylpropanoids, monoterpenes, sesquiterpenes, alcohols, aldehydes, ketones and aromatic compounds (1,9). Parsley essential oil is best known for its use in food, pharmaceutical, cosmetic and chemical industries (10). The major components of essential oil from parsley leaf, herb, root and fruit are presented in Table I.

Table I Major components of parsley leaf, herb, root and fruit essential oils.**Tabela I** Glavne komponente etarskog ulja listova, herbe, korena i plodova peršuna.

Part of the plant		Leaf (1, 5, 7, 9)	Herb (7, 11)	Root (1, 7, 8)	Fruit (7, 8, 9)
Phenylpropanoids	apiol	+	+	+	+
	myristicin	+	+	+	+
	elemicin	+	-	+	+
	1-allyl-2,3,4,5-tetramethoxybenzene	-	+	-	+
	eugenol	-	-	-	+
Monoterpenes	β -phellandrene	+	+	+	+
	<i>p</i> -mentha-1,3,8-triene	+	+	-	-
	4-isopropenyl-1-methylbenzene	+	-	-	-
	myrcene	+	+	-	+
	α -pinene	+	+	+	+
	β -pinene	+	+	+	+
	α -phellandrene	+	+	-	-
	<i>p</i> -cymene	+	-	-	+
	terpinolene	+	+	+	-
	α -terpinene	+	-	-	-
	myrtenyl acetate	+	-	-	-
	limonene	+	+	+	+
	α , <i>p</i> - dimethylstyrene	-	+	-	-
	sabinene	+	-	-	+
γ -terpinene	+	-	-	+	
Sesquiterpenes	(<i>E</i>)- β -farnesene	+			
	germacrene D	+			
	angelic acid esters	+			
	α -copaene	+			
	α and β -cubebene	+		-	
	γ -elemene	+			-
	α -humulene	+	-		
	γ -amorphene	+			
	α -, γ - and δ -cadinene	+			
	germacrene A	-		+	
	β - bisabolene	+		+	
	carotol	-		-	+

Leaf essential oil

Parsley leaf contains 0.02-0.9% of essential oil with phenylpropanoids (up to 80%) and monoterpenes as main compounds. Sesquiterpenes are present in smaller amounts, up to 4%. Phenylpropanoids and monoterpenes contribute to the odor (1). Odor-contributing substances, found in small amounts, are also: methyl-2-methylbutanoate, oct-1-en-3-one, (*Z*)-1,5-octadiene-3-one, 2-(*p*-tolyl)propan-2-ol, 2-isopropyl-3-methoxypyrazine, 2-*sec*-butyl-3-methoxypyrazine, (*Z*)-6-decenal, (*E,E*)-2,4-decadienal, myrcene, linalool, citronellol and β -ionone (1). Other substances found in parsley essential oil are: aldehydes (phenylacetaldehyde, hexanal, benzaldehyde), aromatic compounds (toluene, *m*- and/or *p*-xylene), ethers (2-pentylfuran), alcohols ((*Z*)-hex-3-en-1-ol) and ketones (cryptone) (9). A hay-like odor develops through leaf drying processes as a result of 3-methyl-2,4-nonanedione forming. Parsley leaf taste is similar to cabbage, due to presence of dimethyl sulfide, methylpropane and 2- and 3-methylbutanal (1).

Essential oils of different chemical composition can be the consequence of seasonal variation (plant and harvest time), stage of growth („age“ of parsley) and geographic location. As a consequence of seasonal variation, higher concentrations of apiol were detected in parsley planted in December and harvested in April than in parsley planted in September and harvested in January. The aging of flat leaf parsley caused a decrease in the concentration of β -phellandrene (58.3%→0%) and myristicin (12%→0%), and an increase in the concentration of 1,3,8-*p*-menthatriene (0.4%→79.9%) (5). The amount of individual components varies in different parts of the plant and varieties (9). For example, the variable chemical composition of parsley essential oil was confirmed by testing the composition of essential oil obtained by hydrodistillation from 4 commercial samples – 2 samples of flat leaf parsley and 2 samples of curly leaf parsley. Apiol (52.9% and 33.0%) and β -phellandrene (10.0 and 17.0%) were the two most abundant compounds in flat leaf samples, while the third most represented compound in first sample was 1, 3, 8-*p*-menthatriene with 23.4% (1.5% in the second sample) and *p*-cymene in the second sample with 17.3% (0.3% in the first sample). Myristicin was not detected in flat leaf parsley, but in curly leaf samples it was the most represented compound (39.4% and 43.2%) followed by β -phellandrene (31.7% and 35.0%) and 1,3,8-*p*-menthatriene (14.9% and 7.9%) (5).

Due to large differences in the content of individual components, parsley leaf essential oils can be divided into three classes: a myristicin-rich oil (most of the samples that originated from curly leaf); a 1,3,8-*p*-menthatriene-rich oil (most of the samples that originated from flat leaf); and an apiole-rich oil (can be found in both sample varieties). All three of the classes contain high levels of β -phellandrene (5).

Root essential oil

P. crispum ssp. *foliosum* and *P. crispum* ssp. *tuberosum* roots have different amounts of essential oil and a slightly different composition. *P. crispum* ssp. *tuberosum* roots consist of 0.1 to 0.3% of essential oil. The quantity of essential oil in *P. crispum* ssp. *foliosum* roots is 0.20-0.75% (1). If oil is acquired by using hydrodistillation, the

main components are phenylpropanoids and monoterpenes, but if the oil is obtained by using diethyl ether, the main compounds are polyacetylenes: falcarinol (30%) and falcarinidiol (9%) (1,8).

Fruit essential oil

Parsley fruit contains 1-6% of essential oil; *P. crispum* ssp. *tuberosum* has 1-4% and *P. crispum* ssp. *foliosum* 2-6% of essential oil. Phenylpropanoid contents differ between various fruit types: *P. crispum* ssp. *tuberosum* fruit contains the highest levels of apiole; *P. crispum* ssp. *foliosum* contains the highest levels of myristicin and *P. crispum* ssp. *foliosum* contains similar levels of apiol and myristicin and high level of 1-allyl-2,3,4,5-tetramethoxybenzene (8). Ethanol fruit extract contains sesquiterpenes crispane and crispanone (9).

Other constituents of parsley leaf, root and fruit

Flavonoids are major ingredients of parsley, followed by polyacetylenes (9,12). Parsley contains several important nutrients such as vitamin C, A and B vitamin complex, vitamin K, tocopherols, ergosterol (precursor of vitamin D). It is also rich in minerals (Fe, Zn, Ca, Mg, Na, K, P), fatty acids (linolenic and palmitic acid), carotenoids and furanocoumarins (13,14,15,16). Major furanocoumarins and flavonoids are presented in Table II.

Table II Major flavonoids and furanocoumarins in parsley leaf, root and fruit.

Tabela II Glavni flavonoidi i furanokumarini u listu, korenu i plodu peršuna.

	Parsley leaf (1, 13)	Parsley roots (1, 13)	Parsley fruit (7, 8)
Total flavonoid content	1.9-6.6%	0.2-1.6%	2%
Apiin	+	+	+
Total furanocoumarins content	0.2%	0.1%	/
Oxypeucedanin	+	+	+
Xanthotoxin	+	+	+
Bergaptene	+	+	+
Psoralen	+	-	+
Isopimpinellin	+	+	+
Imperatorin	+	+	+
Angelicin	+	+	-
Trioxsalen	+	+	-

Parsley leaf

Flavonoids are the predominant compounds of parsley leaf. Besides apigenin, which is also found in roots and fruit, other flavonoid compounds found only in parsley leaf are glycosides such as luteolin 7-apiosylglucoside, apigenin 7-glucoside, isorhamnetin 3,7-diglucoside and 6''-acetylapiin and aglycones quercetin and kaempferol (1,9,13,15). In parsley aqueous extract naringin, naringenin, hesperidin, rutin and also glycosides of luteolin and apigenin with arabinose, rhamnose and glucose are identified, along with glycosides of isorhamnetin, kaempferol and chrysoeriol (9,15,17).

Parsley leaves also contain 0.2% of furanocoumarins (oxypeucetanin, bergaptene, psoralen and others) (1,13).

Vitamin C can be found in fresh parsley leaf in quantities between 0.12-0.4 % (1). Cultivated flat leaf form of *P. crispum* ssp. *foliosum* contains the highest content of ascorbic acid, followed by α - and γ -tocopherol. The content of γ -tocopherol and total tocopherols is the highest in flat leaf parsley form. Variations in α -tocopherol (main form of vitamin E) content can be significant in relation to antioxidative activity of this plant (13). Parsley leaf also contains carbohydrates such as apiose, which are mostly part of flavonoid glycosides (9). Sucrose, glucose, rhamnose, mannose, arabinose and mannitol were identified in parsley leaf aqueous extract (15). Carotenoids, β -carotene, lutein, violaxanthin and neoxanthin are also found (9,13). Falcarinol, falcarindiol, falcarinone and falcarinolone are identified among polyacetylenes (12).

Parsley roots

Furanocoumarins (oxypeucetanin, bergaptene, xanthotoxin and others) are the main constituents of roots (1,13). Phtalides such as (*Z*)-ligustilide, senkyunolide and butylphtalide are also present in lower concentrations in parsley roots and they are shown to contribute to odor (1,8). The majority of polyacetylenes are detected in parsley root: falcarinol, falcarindiol, falcarinone and falcarinolone (1,7,8).

Parsley fruit

The main components of parsley fruit, besides furanocoumarins, are fatty oils in the content of 25% (8). The main fatty acid is petroselinic acid (60-80%) in the form of glycerides (7). Carbohydrate apiose (as a part of flavonoid glycosides) is also detected (9).

Pharmacological activities

In addition to the well-known diuretic and antispasmodic effect, the active ingredients of parsley are responsible for a very wide range of positive effects: hepatoprotective, antidiabetic, analgesic effects. Anti-inflammatory, antianemic, antihyperlipidemic, antitumor, antihypertensive, anticoagulant and immunosuppressive effects are more related to the active components of parsley leaves (13). Various preparations of parsley also have antimicrobial, hypouricemic, antioxidant, and estrogenic effects (18).

Diuretic effect

It has been proven *in vivo*, on mice and rats, that parsley fruit has a diuretic effect, due to the irritating effect of the essential oil and flavonoids on renal parenchyma (1,6,8). Moreover, *in vivo* experiments show that aqueous extract of parsley fruit increases urine volume and water intake, and consequently increases urine flow while inhibiting kidney Na^+/K^+ -ATPase activity, with stronger inhibition observed against cortex ATPase (94.7% compared to 55% inhibition of medullary ATPase). This inhibition results in decreased reabsorption of K^+ and Na^+ from the tubular lumen; water follows these ions, which leads to a diuretic effect (19). Additionally, flavonoids, such as quercetin, kaempferol and naringenin found in parsley leaves, have an antagonistic activity at adenosine A1 receptors, which leads to a diuretic effect. It should be noted that conventional diuretics often cause hypokalemia, while parsley, as a rich source of potassium, does not express this side effect (14,20). The parsley root also has a diuretic effect, but it is less intense than the effect of the fruit (8).

Spasmolytic effect

Preparations of the fruit, root and herb of parsley have a spasmolytic effect. Essential oil constituents apiol and myristicin act primarily on the uterus (8). Ethanol extract of *P. crispum* fruit reduces KCl and CaCl_2 -induced contractions of isolated rat ileum by blocking voltage-dependent Ca^{2+} channels. Aqueous and ethanol extracts of the aerial parts also show a spasmolytic effect on contracted isolated rat ileum induced both spontaneously and by acetylcholine. Both these effects are dose-dependent (21,22). Parsley root also acts as a mild antispasmodic (6).

Anti-urolithiasis effect

The anti-urolithiasis effect of parsley has been the subject of several *in vivo* studies on rats with induced urolithiasis and similar results were obtained. In ethylene glycol (EG) - induced urolithiasis, the aqueous extract of *P. crispum* aerial parts and roots reduced serum urea and uric acid levels and increased serum Mg^{2+} levels. In rats fed with EG, the aqueous extract of the roots and aerial parts of *P. crispum* led to a decrease in the number of calcium oxalate deposits (16). In EG and NH_4Cl -induced urolithiasis on male albino rats, ethanol extract of *P. crispum* fruit contributed to a decrease in urinary Ca^{2+} , protein excretion and urine pH, and a decrease in the number, size and precipitation of calcium oxalate crystals. Some studies suggest that the potential mechanisms by which parsley exerts its anti-urolithiasis effect may be related to the high chlorophyll content (inhibits the calcium oxalate dehydrate formation, which consequently prevents the occurrence of kidney stones) and Mg^{2+} content (binds intestinal oxalates and reduces their availability for calcium to form calcium oxalate stones) (14,16). Active compounds with antioxidant activity (rutin, quercetin, hyperoside and diosmin) are probably the most responsible for the anti-urolithiasis effect (16).

Hypouricemic effect

In an *in vivo* investigation performed on mice with oxonate-induced hyperuricemia, the effect of aqueous parsley leaf extract was demonstrated by various mechanisms. The use of this extract leads to a significant reduction of uric acid levels, blood urea nitrogen (BUN), aspartate transaminase (AST) and alanine transaminase (ALT), and a reduction of the activity of serum and hepatic xanthine oxidase (an enzyme responsible for uric acid synthesis). Also, it acts against oxidative stress that occurs in hyperuricemic mice by: lowering the level of interleukin 1 beta (IL-1 β) and tumor necrosis factor alpha (TNF- α) (inflammatory cytokines) and increasing the level of interleukin 10 (IL-10) in the serum (anti-inflammatory cytokines), lowering the level of malondialdehyde (MDA) that causes tissue damage and enhancing antioxidant capacity by increasing catalase enzyme levels, glutathione peroxidase, as well as reduced glutathione levels. In addition, it promotes the regeneration of normal kidney structure (23).

Antioxidant effect

Phenolic compounds and especially flavonoids can be H-donors to free radicals and can prevent cell damage and inhibit numerous biochemical processes in the human body, thus having a positive effect on chronic degenerative and neurodegenerative changes, atherosclerosis and the consequences of aging (17). The highest content of flavonoids was found in parsley extracts made from leaves (8). Numerous *in vitro* models have proven the high antioxidant capacity of different polarity extracts of leaves, aerial parts and roots, as well as the essential oil of the fruit. Parsley extracts (mostly methanol and aqueous), with apigenin as active compound, show a high capacity to neutralize 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals, high chelating capacity of Fe²⁺ ions, high ability to "capture" hydroxyl radicals and significant lipid peroxidation inhibition capacity *in vitro*. All these effects were higher than tested standards and are dose-dependent (9,10). The essential oil of the fruit, with myristicin and apiol as main compounds, also expresses antioxidant activity, but it is lower than the activity of the mentioned extracts and tested standard substances (24). Additionally, it is believed that sesquiterpenes play a potentially important role in the antioxidant effect of parsley essential oil (10). Various leaf extracts have shown antioxidative activity on isolated rat brain, liver and blood by increasing the activity of enzymes, such as glutathione peroxidase, xanthine oxidase and catalase, or by decreasing lipid peroxidation (25,26).

The introduction of parsley leaves into the diet of 14 people (7 males and 7 females) for one week caused a significant increase in the levels of antioxidant enzymes, erythrocyte glutathione reductase and superoxide dismutase compared to the control group of people with a normal diet. Apigenin is the most responsible for this effect (27).

Anti-inflammatory effect

An *in vitro* study of the anti-inflammatory effect of water-methanol extract of the parsley herb, rich in flavonoids and other polyphenols, was performed. All the effects of parsley extract correlated with the content of flavonoids, but not with the content of total polyphenols, which indicates the important role of flavonoids in the anti-inflammatory action. Parsley extracts have a high potential for removing nitric oxide (NO) free radicals, a strong antidenaturation effect on proteins, and a high potential for membrane stabilization, compared to diclofenac-sodium as a standard. There is evidence (experiments with *p*-lactoglobulin, bovine serum albumin and soybean glycine) that the interaction between flavonoids and protein increases the thermal stability of the protein and has a great influence on its secondary structure, which explains the antidenaturation effect. Flavonoids can build hydrogen bonds with the hydrophilic heads of the lipid bilayer of the membrane and thus reduce the fluidity and increase the rigidity of the membrane, which ensures its integrity and stabilization (28).

Antibacterial effect

Freeze-dried parsley leaves (in the quantities of 0.12 to 8%) inhibit the growth of *Escherichia coli*, *Listeria monocytogenes*, *L. innocua* and *Erwinia carotovora*, while they are inefficient against *Pseudomonas fragi*. This effect can be related to the presence of furanocoumarins (1). Methanol and aqueous leaf and stem extracts have an antibacterial effect against *Bacillus subtilis* and *E. coli*. This effect is also due to the presence of furanocoumarins. Leaf extracts are more effective in terms of cell damage of both bacteria, while stem extracts have a stronger inhibitory effect on the growth of both bacteria (29). Methanol leaf extract also has *in vitro* antimicrobial activity against *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *S. aureus* and *Saccharomyces cerevisiae* (30). Ethanol leaf extract inhibits the growth of *Lactobacillus plantarum* and *Leuconostoc mesenteroides* (9).

Essential oils have a greater *in vitro* and *in vivo* antibacterial potential than extracts, and they are generally more effective against G⁺ bacteria, since G⁻ bacteria are less sensitive due to the specific composition of the cell membrane, which represents a barrier to hydrophobic substances such as essential oils (10,11). Due to their complex composition, they probably act through several mechanisms of action simultaneously, such as cell wall lysis, increase of membrane permeability, consequent loss of ions, decrease of membrane potential, proton pump dysfunction and decrease of ATP reserves. Several studies have confirmed the effectiveness of essential oils against bacteria resistant to numerous antibiotics, and they are also effective in dermatological infections. Parsley essential oil from aerial parts demonstrated a moderate antibacterial effect, and was bactericidal against *E. coli* (minimal inhibitory concentration, MIC 32 mg/mL) and *Bacillus spizizeciaela* (MIC 16 mg/mL), and bacteriostatic against *S. epidermidis* (MIC 4 mg/mL), *S. aureus* (MIC 16 mg/mL), *Enterococcus faecalis* (MIC 16 mg/mL) and *Klebsiella pneumonia* (MIC 32 mg/mL), except against *P. aeruginosa* (11).

High antibacterial activity of the essential oil phenolic components has been linked to the alkyl substitution of the phenolic nucleus, which rarely occurs with stable oil constituents such as myristicin, one of the main components of parsley essential oil. Monoterpene components have practically no antibacterial effect due to low solubility in water. It is important to note that several studies have shown that essential oil usually has a stronger antibacterial effect than a mixture of its main components, which indicates the importance of compounds present in smaller quantities (11).

Hypolipidemic effect

The hypolipidemic effect of 20% methanol extract of parsley fruit was proven *in vivo* in rats fed with a diet rich in fat and cholesterol. The 8-week administration of the mentioned parsley extract in hypercholesterolemic rats significantly decreased the total cholesterol, triglycerides, low density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) cholesterol and increased the level of high density lipoprotein (HDL) cholesterol in the blood. Also, biomarkers of heart and liver tissues were monitored in the study as well: the use of this extract decreases the levels of all enzymes: lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), ALT, AST and alkaline phosphatase (ALP). The examination of organs (liver, heart and blood vessels) with extract-treated rats showed an almost normal tissue structure with significantly milder damage compared to the organs of rats with hyperlipidemia. The hypolipidemic effect of parsley can be caused by the presence of plant proteins, betalaine, glucosinolates and antioxidant components, while the organoprotective effect is most likely due to the action of antioxidant ingredients such as flavonoids, carotenoids and phenolic compounds (18).

Antihypertensive effect

Examination of the antihypertensive effect of parsley aerial part aqueous extract was performed *in vivo* on rats with normal blood pressure and N-nitro-L-arginine methyl ether (L-NAME) induced hypertension, after a single application of parsley extract (acute treatment) and after repeated application of the same extract (sub-chronic treatment). After one dose of the aqueous extract, a decrease in systolic, diastolic and mean blood pressure was noted in hypertensive rats, while the effect was absent in normotensive rats. With repeated administration, there was a decrease in arterial blood pressure in both groups, with a stronger hypotensive effect in hypertensive individuals. In order to determine the mechanism of action, an *in vitro* study was performed on an isolated rat aorta. A pronounced dose-dependent vasodilatory effect on contractions induced by KCl and epinephrine was demonstrated, by blocking the entry of extracellular Ca^{2+} into smooth muscle cells of the aortic wall, through voltage-gated and receptor-operated Ca^{2+} channels. Parsley extract-induced vasorelaxant effect was endothelium-independent and was not mediated through the potassium channels, β -adrenergic receptors, vascular cyclooxygenase or NO-cGMP pathways. The diuretic effect of parsley the most likely contributed to the antihypertensive effect. Interestingly, the potentiating effect of L-NAME (NO synthase inhibitor) on the vasodilatory effect of low-dose parsley extract was

observed in this study and requires further consideration (31). Aqueous and ethanol parsley leaf extract lowered blood pressure measured in the carotid artery of anesthetized rats; ethanol extract showed a stronger hypotensive effect. Reduced pulse strength and heart rate were observed in the subsequently isolated rat heart chamber, and this effect was more pronounced with ethanol extract. These results indicate antihypertensive and negative inotropic and chronotropic effects of parsley leaf extracts (9).

Antidiabetic activity

Antidiabetic effect of aqueous parsley leaf extract has been examined in several studies. It has been demonstrated that the extract lowers blood glucose levels and serum ALP and ALT, and has hepatoprotective and cardioprotective effects in rats with streptozotocin-induced diabetes. The antihyperglycemic effect is not due to the regeneration of pancreatic β -cells, since no morphological changes have been observed in the pancreas due to treatment with parsley leaf extract, but due to the presence of flavonoids, phenolic components and ascorbic acid and their antioxidant action (9).

Effects on the gastrointestinal tract

The ingredients of parsley essential oil stimulate the secretion of bile and gastric juices and thus contribute to better digestion (1). Ethanol leaf extract has beneficial effects on peptic ulcer in rats due to its antisecretory and cytoprotective effect; tannins, flavonoids and triterpenes are responsible for the effects (32). The aqueous extract from parsley seeds exhibited laxative activity *in vivo* by the inhibition of sodium and water absorption via colon Na^+/K^+ - ATPase (33).

Estrogenic activity

In estrogen-dependent breast tumor cell line, methanol extract of the parsley aerial parts shows proliferative activity (estrogenic effect), similar to soybean isoflavone glycoside. This effect is primarily attributed to flavonoid glycoside 6"-acetylapiin, and aglycones apigenin, diosmetin and kaempferol. Additionally, oral administration of the extract can significantly restore uterine mass that is reduced after an ovariectomy performed in mice, and the effect is derived from apiin and apigenin (1,15,34).

Antiplatelet effect

Aqueous parsley leaf extract *in vitro* shows a strong antiplatelet effect, with apigenin and cosmosin being responsible for this activity (35). Kaempferol and apigenin aglycones, previously incorporated into human platelets, reduce their adhesion to the collagen-coated surface and inhibit dose-dependent aggregation in various *in vitro* models (aggregation induced by ADP, collagen, thrombin) (36). In rats, aqueous extract administered orally inhibits platelet aggregation *in vivo* and significantly delays bleeding time *ex vivo* (37).

Other pharmacological and non-pharmacological effects

In vitro studies have demonstrated the neuritogenic effect of falcarinol on paraneurons and the neuroprotective effect on induced neuronal apoptosis. In experiments on mice, scopolamine-induced memory deficits improved, which was thought to be a consequence of the aforementioned effects on neurons. Furthermore, falcarinol isolated from the root of *Angelica sinensis* acts by serotonin 5-HT₇ receptors, which implies a potential serotonergic effect. Additional *in vivo* studies are necessary to determine whether falcarinol is a candidate for Alzheimer's disease treatment or for improvement in mood and behavior (12).

Isolated oil of parsley fruit showed a protective effect on the reproductive system in zearalenone-caused toxicity in *in vivo* studies. An increased level of testosterone, number and motility of sperm was determined. Moreover, inhibition of chromosomal aberrations of germ cells caused by zearalenone was detected (38). The hydroalcoholic extract of parsley fruit showed significant analgesic effects in some studies conducted on mice (e.g. a test based on formalin-induced paw licking; on the other hand, there was no significant results in a test based on acetic acid-induced cramping) (39). Parsley root deodorant effect is becoming more frequently recognized, especially in the context of neutralizing the odor of garlic (8).

Myristicin caused the inhibition of benz[a]pyrene-induced tumor development in studies on mice, possibly due to the stimulation of glutathione-S-transferase synthesis in liver and small intestine mucosa (1). Myristicin demonstrated hepatoprotective and anxiolytic effects in rats, and also insecticidal and anti-inflammatory activity. Additionally, myristicin metabolite named MMDA (3-methoxy-4,5-methylenedioxyamphetamine) acts as a monoamine oxidase inhibitor and agonist of serotonin receptor. It was reported that apiol can cause antipyretic, insecticidal, diuretic and antitumor effects (5). Essential oil acted as an immunosuppressant in *in vivo* studies. It caused the inhibition of splenocyte and macrophage (as major congenital immune cells) function, which led to a decrease in humoral and cellular immune response. Also, in higher concentrations, parsley essential oil suppressed the production of NO (40). An *in vitro* study on hamster lung fibroblasts, thyroid epithelial cells of rats and astrocytes isolated from neonatal mice has been conducted. In this study, geraldol (isolated from parsley) inhibited binding of NMO-IgG autoantibodies, which are present at 80% of NMO (*neuromyelitis optica*) patients, for aquaporin-4 (AQP4 – the most common water transport channel in astrocytes membrane) without affecting the physiological function of these channels (41).

Toxicity and side effects

After the ingestion of a regular amount of parsley leaf and root (as a spice), acute and chronic poisoning was not observed. Parsley fruit has never been used as a spice, because of phenylpropane derivatives which are toxic in high levels (1). Side effects were not detected after medical use of therapeutic dosages of parsley herb and root (7). Parsley

has a low potential of sensitization, but allergic reactions are possible and could be the consequence of contact with fresh plant, herbal drug or essential oil (1,6,7). Most frequently, they occur among people who are allergic to other plants from the Apiaceae family (e.g. celery, carrots and caraway) and among light-skinned people. Additionally, photodermatitis occurs in commonly exposed people (e.g. garden workers) after intensive contact with the fresh plant (1,7). Furanocoumarins (such as oxypeucedanin) and polyacetylenes (such as falcarinol) are responsible for this effect, but their levels in parsley are low, and desensitization may also occur after oral ingestion (1,6,9,12,42).

The application of higher doses of the essential oil or products that contain high concentrations of the essential oil can cause poisoning. Symptoms include increased smooth muscle contractility, specifically in the bladder, intestine and uterus, also anuria, blood in the stool, general weakness, steatosis, hemolysis, methaemoglobinuria and bleeding of mucous membranes (7). Myristicin (0.01-0.05 mL/L), apiol (50-100 mg/L) and fruit essential oil abortifacient effect has been shown in some previous studies. This effect appears as a result of increased tonus and contractions in isolated guinea pig uterus. Essential oil leads to acute toxicity in high abortus-used doses by causing gastroenteritis, headache, kidney and liver damage, coma and death (1). Pure apiol in higher doses has abortifacient effect. Based on the available evidence, damage of liver parenchyma and heart arrhythmias were detected after an apiol overdose. However, it should be noted that all these effects were observed after the use of high doses of the essential oil (concentrated plant isolate) or pure isolated compounds, while there is no danger of intoxication after common use of parsley (8). Myristicin poses a hallucinogenic effect (contributed to his metabolite MMDA). Consequently, after ingestion of larger amounts of the essential oil, central excitation was noticed; drunkenness, strong irritations of gastrointestinal and urinary tract are also possible (5,8). Apiol and myristicin demonstrated hepatocarcinogenic effects (6).

The use of parsley in folk medicine

Parsley roots are useful for dysmenorrhea, nocturia in kids and as a stomachic (6,8). Parsley roots and herb are used for gastrointestinal problems, jaundice, kidney inflammation, as a diuretic and emmenagogues in treatment of menstrual problems and flatulence (1,7). The spasmolytic effect of parsley fruit can help with dysmenorrhea and menstrual cramps. Additionally, parsley fruit acts as an emmenagogues, galactagogue, stomachic and digestive, and it has also proven useful in relation to the disrupted function of kidneys and lower urinary tract (7,8).

The use of parsley in folk medicine differs across the countries (9). In Serbia, parsley leaf is used as a diuretic, in the treatment of infections and diseases of the urinary system and in the treatment of fluid retention in the organism (43,44). In Iranian folk medicine, parsley is used as a carminative, astringent, gastrotonic, antidote, as well as for kidney stones, inflammation, amenorrhoea, halitosis and for improvement of digestion. Parsley leaf is known as a spice, diuretic and antitussive; additionally, the leaf can be significant in the treatment of dermatitis, vision problems, otitis etc. (9). In different

countries such as Spain, Italy, Turkey, China, Iraq, Morocco and Peru, parsley is used for various purposes. It is thought that the leaf acts as a disinfectant, anticoagulant, antihypertensive, antihyperlipidemic, abortifacient. Also, the leaf showed beneficial effects in diabetes, cardiac and renal diseases, kidney stones, abdominal aches, hyperuricaemia, skin disease, lumbago, eczema, problems with appetite, nose bleeding, insect bites, anaemia, constipation, baldness, odontalgia, amenorrhea and dysmenorrhea (5,9). Aerial parts of parsley are used as abortifacients, while seeds are used as a carminative and in the treatment of gastritis (9).

Traditional use of parsley

Parsley roots and essential oil are used as a diuretic in urinary tract disease, as well as for irrigation for prevention or treatment of urinary stones. Contrary to herbal teas or herbal medicinal products, the essential oil is rarely used for therapeutic purposes (6). Parsley roots and herb are used for infections of the urinary tract and for kidney stones. Homeopathic preparations of parsley roots and herb are used for inflammation of the urinary tract and for sensitive bladder (7).

Modern-day use of parsley

Parsley is known as an antioxidant and anti-inflammatory agent-rich plant (the leaves contain significant levels of polyphenols and flavonoids). Various possible therapeutic indications for parsley use could be based on these effects (23,28). Parsley represent a natural safe remedy which could be used as an anti-inflammatory (reduces inflammation, especially in joints), antihyperglycemic (decreases glucose level in blood of diabetes induced rats), antihyperlipidemic (by enhancing serum lipid profile), antihypertensive (diuretic effect also contributes to blood pressure lowering), hypouricemic (high level of antioxidative substances contributes to the reduction of hyperuricemia and gout effect on liver, kidney and other tissues) and antimicrobial agent (18,19,23,31). Additionally, hepatoprotective and cardioprotective effect, reduction of allergy symptoms, chronic bronchitis, skin diseases, cystitis, thrombosis, stroke and Alzheimer`s disease are promising, but human studies are still missing (9,13,18,23).

Contraindications

Parsley herbal drug-based preparations are contraindicated when used by people allergic to parsley or apiol. People with renal inflammatory disease may not use the herb and roots of parsley, as well as people with edema caused by insufficient heart or renal function when used as irrigation treatment. Also, in pregnant women, the use of herb, roots and fruit is contraindicated because of the abortive effect of parsley (1,7,8).

Conclusion

Parsley is an edible plant with positive effects on human health. Based on morphological characteristics, parsley is a classic representative of Apiaceae family, with fruit schizocarp rich in essential oil. *Petroselinum crispum* ssp. *foliosum* is generally

richer in essential oil in comparison to *P. crispum* ssp. *tuberosum*. In the parsley fruit, the most common essential oil substances are phenylpropanoids. Apiol, myristicin and 1-allyl-2,3,4,5-tetramethoxybenzene were detected in the highest level. The chemical composition of essential oil differs between parsley parts and varieties, geographical location of cultivation, development stage of plant, seasonal variations, climatic conditions, genetic and other factors. In most cases, the main compound of the flat leaf form of parsley is apiol, and of the curly leaf form - myristicin. The essential oil of parsley roots is rich in monoterpenes, in essential oil of *P. crispum* ssp. *foliosum* roots terpinolene dominates, and in *P. crispum* ssp. *radicosum* β -pinene. Polyacetylenes are the main ingredients of *P. crispum* ssp. *tuberosum* roots. Flavonoids are the predominant compounds of parsley leaves (up to 3 times more in comparison to parsley fruit and roots). Apiin is considered the most important flavonoid detected. Oxypeucedanin, psoralen, bergaptene, xanthotoxin, imperatorin and isopimpinellin are relevant representatives of furanocoumarins. Parsley leaf is a significant source of minerals and vitamins.

Parsley fruit, root, leaf and essential oil showed diuretic, spasmolytic and antiurolytic activity. Parsley leaf-based preparations demonstrated hypouricemic and, also antioxidative, anti-inflammatory, antibacterial, estrogenic, hypoglycemic, hypotensive and antiagregative effects in experiments, while fruit extract acted as a hypolipidemic, laxative and analgesic. Studies have indicated the importance of sesquiterpenes, as well as other substances that were present in lower concentrations, for the antioxidative effect of essential oil, while the weakening of antibacterial effect was also in correlation with the increased content of myristicin in the essential oil.

Apiol and myristicin showed insecticidal and antitumor effects, while flavonoids were the carriers of antioxidative and anti-inflammatory activity of parsley. Falcarinol could be characterized as a cardio protective and a candidate for treatment of Alzheimer's disease, mood and behavior disorders, but further *in vivo* research is needed.

Allergic reactions manifested as photodermatitis are very rare. Adverse effects after the ingestion of therapeutic doses were not recorded, which qualifies this plant and its pharmacologically active compounds for further *in vivo* research and research on human subjects, in order to fulfill its therapeutic potential.

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Pregled botaničkih karakteristika, hemijskog sastava, farmakološke aktivnosti i primene peršuna

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Kratak sadržaj

Peršun je dvogodišnja aromatična biljka iz familije Apiaceae koju karakterišu nerazgranat koren, perasto deljeni listovi, štitaste cvasti i plod šizokarpium. U svim delovima sadrži etarsko ulje, čije su glavne komponente fenilpropanska i terpenska jedinjenja. Bogat je flavonoidima i drugim polifenolnim jedinjenjima, sadrži furanokumarine, karotenoide, poliacetilene, a listovi su izvor vitamina i minerala. Hemijski sastav peršuna zavisi od brojnih faktora, pa tako postoje razlike u sastavu između ne samo različitih delova i varijeteta biljke, već i različitih uzoraka istih delova jednog varijeteta. Najzastupljenija jedinjenja peršuna su miristicin, apiol, 1-alil-2,3,4,5-tetrametoksibenzen, β -felandren, 1,3,8-*p*-mentatrien, β -pinen, terpinolen, apiin, oksipeucedanin i falkarinol. Peršun ima dugu tradiciju upotrebe u tretmanu poremećaja funkcije urinarnog trakta, a savremena *in vitro* i *in vivo* ispitivanja otkrivaju i brojne efekte koje poseduju različiti preparati peršuna kao što su diuretički, antiurolitijazni, hipourikemijski, hipolipidemijski, hipoglikemijski, hipotenzivni, antioksidativni, antiinflamatorni, antimikrobni i antiagregacioni. Danas, pored medicinske primene, peršun je jedna od najkorišćenijih začinskih biljaka.

Ključne reči: *Petroselinum crispum*, etarsko ulje, flavonoidi, antioksidansi
