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REVIEW ARTICLE / DERLEME MAKALE

PETROSELINUM CRISPUM (MILL.) FUSS (PARSLEY), A FOOD AND MEDICINALLY IMPORTANT PLANT: A REVIEW OF RECENT STUDIES BETWEEN 2013-2023

PETROSELINUM CRISPUM (MILL.) FUSS (MAYDANOZ), GIDA VE TIBBİ OLARAK ÖNEMLİ BİR BİTKİ: 2013-2023 ARASINDAKİ SON ÇALIŞMALARIN DERLEMESİ

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ABSTRACT

Objective: *Petroselinum crispum (Mill.) Fuss is a bright green biennial medicinal and aromatic herb that grows almost all over the world. Today, it is one of the most commonly used culinary herbs. In addition to its use as food, it has been shown to possess broad pharmacological activities in several in vivo and in vitro studies. This study aimed to comprehensively summarize the current studies on the traditional use, phytochemical composition, pharmacological activities, clinical studies, toxicity, and drug interactions of parsley.*

Result and Discussion: *According to the literature data, parsley is used as a diuretic, carminative, emmenagogue and for the prevention and treatment of kidney stone formation, the treatment of conditions such as urinary tract infections and stomach disorders. Its phytochemical composition consists of flavonoids, coumarins, phenolic compounds, organic acids, carotenoids, vitamins, minerals, fixed oil, essential oil, and other compounds. Studies on P. crispum have shown that it has a wide range of pharmacological activities, including antioxidant, antibacterial, antifungal, antidiabetic, antihypertensive, antiplatelet, analgesic, antiinflammatory, antihepatotoxic, antinephrotoxic, anticancer, antiurolithiatic, wound healing, antiobesity, estrogenic and neuroprotective effects. This review comprehensively summarizes the scientific data of the last ten years (2013-2023) on P. crispum.*

Keywords: *Parsley, Petroselinum crispum, pharmacology, phytochemistry, traditional*

ÖZ

Amaç: *Petroselinum crispum (Mill.) Fuss, neredeyse dünyanın her yerinde yetişen, iki yıllık, parlak yeşil renkli, tıbbi ve aromatik bir bitkidir. Günümüzde en çok kullanılan mutfak bitkilerinden biridir. Gıda olarak kullanımının yanı sıra çeşitli in vivo ve in vitro çalışmalarda geniş farmakolojik aktivitelere sahip olduğu gösterilmiştir. Bu çalışmada maydanozun geleneksel kullanımı, fitokimyasal bileşimi, farmakolojik aktiviteleri, klinik çalışmaları, toksisitesi ve ilaç etkileşimleri üzerine yapılan güncel çalışmaların kapsamlı bir şekilde özetlenmesi amaçlanmıştır.*

Sonuç ve Tartışma: *Literatür verilerine göre maydanoz diüretik, karminatif, emenagog olarak, böbrek taşı oluşumunun önlenmesi ve tedavisi, idrar yolu enfeksiyonları ve mide rahatsızlıkları gibi rahatsızlıkların tedavisi için kullanılmaktadır. Fitokimyasal bileşimi flavonoitler, kumarinler, fenolik bileşikler, organik asitler, karotenoitler, vitaminler, mineraller, sabit yağ, uçucu yağ ve diğer bileşiklerden oluşmaktadır. P. crispum üzerinde yapılan çalışmalar, antioksidan, antibakteriyel,*

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antifungal, antidiyabetik, antihipertansif, antiplatelet, analjezik, antiinflamatuar, antihepatotoksik, antinefrotoksik, antikanser, antiürolitiyatik, yara iyileştirici, antiobezite, östrojenik ve nöroprotektif etkiler dahil olmak üzere çok çeşitli farmakolojik aktivitelere sahip olduğunu göstermiştir. Bu derleme, P. crispum'a ilişkin son on yıla (2013-2023) ait bilimsel verileri kapsamlı bir şekilde özetlemektedir.

Anahtar Kelimeler: *Farmakoloji, fitokimya, geleneksel, maydanoz, Petroselinum crispum*

INTRODUCTION

Petroselinum crispum (Mill.) Fuss (parsley) is a shiny green biennial medicinal and aromatic herb belonging to the Apiaceae (Umbelliferae) family [1,2]. It is native to the Mediterranean region and today it has been cultivated in many parts of the world [1]. *P. crispum* is called heung choi (Chinese), peterselie (Dutch), persil (French), petersilie, petersil, peterwurz (root) (German), maintanos, makedonisi, petroselino (Greek), ajmood (Hindi), prezzemolo (Italian), salsa (Portuguese), petrushka (Russian), perejil (Spanish), and maydanoz (Turkish) [3].

It is a glabrous hairless, biennial, bright green plant. It forms a tripennate rosette and a cylindrical, corrugated, and hollow taproot in the first year. It grows with yellow to yellowish-green flowers and flat-topped umbels in the second year. The stem is erect, striated, cylindrical, and can grow up to 50-80 cm long. Leaves are triangular-ovate in outline, 3-10×2-7 cm, glabrous, straight or curled. Inflorescence paniculate-corymbose, umbels long-peduncled. Flowers opening between August and September, are 6-8 small, yellow-green, and hermaphrodite. The fruit is a schizocarp, 2-3 mm long, oval, and divided into 2 mericarps. Parsley seeds are pear-shaped, brown colored, mericarps 2.5-3×0.5 mm, slightly arcuate at maturity [4].

There are two species belonging to the genus *Petroselinum* in the world, *P. crispum* (garden parsley) and *P. segetum* W.D.J.Koch (corn parsley). *P. crispum* is native to Algeria, Greece, Morocco, Yugoslavia and cultivated throughout Türkiye [5,6]. *P. segetum* is native to Belgium, France, Great Britain, Italy, Netherlands, Portugal, Spain [7]. There are three principal varieties of *P. crispum*: *P. crispum* var. *neapolitanum*, *P. crispum* var. *crispum*, and *P. crispum* var. *tuberosum*. The curly-leaf *P. crispum* var. *crispum* is tougher than the Italian or flat-leaved *P. crispum* var. *neapolitanum*. *P. crispum* var. *tuberosum*, Hamburg's parsley/turnip root parsley, has much thicker roots than the other species [8].

Besides being used as food, parsley has been used against diseases such as urinary tract infections, menstrual pain, diabetes, hemorrhoids and as a diuretic, to pass kidney stones and to lower blood pressure. In the literature, flavonoids, coumarins, phenolic compounds, vitamins, minerals, fixed oil, and essential oil were reported in various parts of *P. crispum*. The plant has antioxidant, antibacterial, antifungal, antidiabetic, antihypertensive, antiplatelet, analgesic, antiinflammatory, antihyperuricemic, antihepatotoxic, antinephrotoxic, anticancer, wound healing, antiobesity, estrogenic, and neuroprotective activities [4,9].

Parsley is an important culinary herb that has been used frequently since ancient times and exhibits important pharmacological activities. For this reason, the number of studies on it is increasing day by day. This review aims to summarize current studies on traditional uses, phytochemical composition, pharmacological activities, clinical studies, drug interactions and toxicity of *P. crispum*. Studies conducted on the species between 2013 and 2023 using various scientific databases were discussed. Some studies with very similar results and using the same methods were not included. As a result 106 references in English and Turkish have been included.

Traditional Uses

It is known that parsley has been cultivated as a medicinal plant in the Mediterranean region for about 2000 years [4]. It is used in traditional medicine in many parts of the World. The traditional uses of the plant in different countries are shown in Table 1. The use of the leaves, aerial parts, petioles, and roots for various purposes has been reported. It is used for menstrual pain, urinary tract infections, diuretic effect, to pass kidney stones, to lower blood pressure, diabetes, and various stomach ailments.

Table 1. Traditional use of parsley in different countries

Country	Part used	Preparations	Use	References
Algeria	Fresh aerial parts	Eat and/or add to salad daily	For bladder infection, kidney inflammation, prostate enlargement, cancers, stone disease	[10]
	Seed	Infusion	For pyelonephritis	
Bosnia and Herzegovina	Leaves	Infusion	For urinary tract infections	[11]
Brazil	Leaf	Infusion	For uterus cleansing, infection and menstrual cramps	[12]
Catalonia	Root	Ointment, liniment	For irritation; As antiecchymotic, antierythematous, external antiseptic	[13]
	Aerial parts	Ointment, bath	As antiecchymotic, cosmetic (hair)	
Morocco	Leaf	Internal, external	Food, hypertension, hair	[14]
	Whole plant, leaf, aerial parts, stem, seed, root	Infusion, maceration, decoction, oil, juice	For kidney stones, renal colic, renal detoxification	[15]
			For renal pain, diuretic, kidney inflammation, polycystic kidney disease	
Serbia	Leaves and roots	Infusion, spice	In urinary tract diseases and infections; to relieve edema	[16]
Türkiye	Aerial parts	Freshly internal	As diuretic	[17]
	Leaves and petiols	Infusion	For menstrual cramps, stomach pain, gastritis, ulcer, diabetes, cystitis, to increase breast milk production; as laxative	[18]
	Leaf, petiole	Infusion, decoction, crude, raw	For liver steatosis, cholesterol, urinary tract infection, edema, kidney stone, stomach disorder, gall bladder disorder, kidney disorder, eye diseases, inappetence; as anti-inflammatory, diuretic, expectorant	[19]
	Leaf	Decoction	For urinary tract infection, to lower cholesterol; as antiinflammatory	[20]
	Aerial parts	Fresh, crushed and mixed with lemon		

Phytochemical Composition

The most important secondary metabolites of the phytochemical composition of parsley are flavonoids. It contains especially flavones and flavonols and their glycosides [9]. In addition, coumarins (especially furanocoumarins) have been detected [21]. In some studies, coumaroyl-derived compounds whose structure was not fully determined were detected [22,23]. There are also compounds such as phenolic compounds, organic acids, carotenoids, carbohydrates, phenylpropanoids and fatty acids. The compounds that make up the phytochemical composition of parsley, plant part, extraction method and detection method of the compounds are given in Table 2. It has been determined that its leaves and roots contain vitamins (A, B, C, K, thiamine, niacin, folate) and minerals (Fe, Mg, Na, K, Zn) [24-26]. There are studies to determine the composition of the essential oil obtained from different parts of *P. crispum* and are presented in Table 3. Studies conducted to determine essential oil content have shown that essential oil yield is between 0.08-9.63%. Differences in essential oil yield and composition may have occurred depending on geographical conditions, collection season, and methods used for extraction [27].

Table 2. Phytochemical composition of *P. crispum*

Compound	Plant part/Extract	Detection Method	References
Flavonoids			
Flavones and Flavone Glycosides			
Apigenin	Fresh plant/Ethanol:water 80:20% v/v; L./Ultrasound-Assisted Extraction	Ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS), ultra-performance liquid chromatography with quadrupole time-of-flight mass spectrometry (UPLC-QTOF-MS), high-performance liquid chromatography-photodiode array detector (HPLC-PDA)	[28,29]
Apigenin 7-glucoside (cosmosiin)	Fresh L./Ethanol:water 80:20% v/v	HPLC-electrospray ionisation tandem mass spectroscopy (HPLC-ESI-MS)	[22]
Apigenin-7-*O*-glucuronide	Fresh plant/70% ethanol	Resin, polyamide chromatography, HPLC, and antioxidant index evaluation methods	[30]
Apigenin 7-apiosylglucoside (apiin)	Fresh L./Ethanol:water 80:20% v/v; ethanol; L., St./80% methanol; L./Methanol:water 80:20% v/v; Fresh AP./By decoction using water	HPLC-ESI-MS, HPLC, LC-MS-QTof, HPLC-diode array detection (DAD)-MS/MS, HPLC-DAD-MS/MS	[22,23,25,31,32]
Apigenin-acetylapiosylglucoside (acetyl-apiin)	L./Methanol:water 80:20% v/v	HPLC-DAD-MS/MS	[25]
Apigenin-*O*-hexosyl-hexoside	L./Dry powder	UPLC/MS	[33]
Apigenin-*O*-pentosyl-hexoside	L./Dry powder	UPLC/MS	[33]
Apigenin-*O*-acetyl-pentosyl-hexoside	L./Dry powder; Fresh L./Ethanol:water 80:20% v/v	UPLC/MS, HPLC-ESI-MS	[22,33]
Apigenin-6,8-di-C-glucoside (vicenin 2)	L., St./80% methanol	LC-MS-QTof	[31]
Apigenin 7-malonylapiosylglucoside	L./Methanol:water 80:20% v/v	HPLC-DAD-MS/MS	[25]
Luteolin	L./Ultrasound-Assisted Extraction	UPLC-QTOF-MS, HPLC-PDA	[29]
Luteolin-di-glucoside	L., St./80% methanol	LC-MS-QTof	[31]
Luteolin 4'-methyl ether apiosylglucoside	Fresh AP./By decoction using water	HPLC-DAD-MS/MS	[23]
Diosmetin-7-*O*-glucoside	Fresh plant/70% ethanol	Resin, polyamide chromatography, HPLC, and antioxidant index evaluation methods	[30]
Diosmetin 7-apiosylglucoside	Fresh L./Ethanol:water 80:20% v/v; Fresh plant/Ethanol:water 80:20% v/v; L., St./80% methanol; L./Methanol:water 80:20% v/v	HPLC-ESI-MS, UHPLC-MS/MS, LC-MS-QTof, HPLC-DAD-MS/MS	[22,25,28,31]
Diosmetin-*O*-pentosyl-hexoside (isomer I)	L./Dry powder	UPLC/MS	[33]
Diosmetin-*O*-pentosyl-hexoside (isomer II)	L./Dry powder	UPLC/MS	[33]
Diosmetin-*O*-acetyl-pentosyl-hexoside (isomer I)	L./Dry powder	UPLC/MS	[33]
Diosmetin-*O*-acetyl-pentosyl-hexoside (isomer II)	L./Dry powder	UPLC/MS	[33]
Diosmetin-acetylapiosylglucoside	L./Methanol:water 80:20% v/v	HPLC-DAD-MS/MS	[25]

Table 2 (*continue*). Phytochemical composition of *P. crispum*

Compound	Plant part/Extract	Detection Method	References
Scutellarin	Fresh plant/70% ethanol	Resin, polyamide chromatography, HPLC, and antioxidant index evaluation methods	[30]
Chrysoeriol-7-*O*-malonylapiosylglucoside B	Fresh L./Ethanol:water 80:20% v/v	HPLC-ESI-MS	[22]
Flavonols and Flavonol Glycosides			
Kaempferol	L. fixed oil/Hexane	Gas chromatography-mass spectrometry (GC-MS)	[34]
Kaempferol-7-*O*-glucoside	Fresh plant/70% ethanol	Resin, polyamide chromatography, HPLC, and antioxidant index evaluation methods	[30]
Kaempferol-3-*O*-[6”-malonyl-*β*-D-apiofuranosyl-(1→2)-*β*-D-glucopiranoside]	L./Methanol:water 80:20% v/v	HPLC-DAD-MS/MS	[25]
Quercetin	AP/Ethanol:water 70:30% v/v	HPLC-DAD	[35]
Quercetin-*O*-pentosyl-hexoside	Fresh L./Ethanol:water 80:20% v/v	HPLC-ESI-MS	[22]
Quercetin-3-*O*-glucoside (isoquercitrin)	Fresh plant/Ethanol:water 80:20% v/v	UHPLC-MS/MS	[28]
3’-Methoxyquercetin dihexoside	Fresh AP./Extract prepared by decoction using water	HPLC-DAD-MS/MS	[23]
Isorhamnetin-di-*O*-hexoside	L./Dry powder; Leaves and stems/80% methanol	UPLC/MS, LC-MS-QTof	[31,33]
Isorhamnetin-3-*O*-glucoside	L., St./80% methanol	LC-MS-QTof	[31]
Isorhamnetin-3-*O*-galactoside	L., St./80% methanol	LC-MS-QTof	[31]
Isorhamnetin-3-*O*-hexoside	L., St./80% methanol	LC-MS-QTof	[31]
Isorhamnetin-di-pentosyl-rhamnoside	L., St./80% methanol	LC-MS-QTof	[31]
Myricetin	AP./Ethanol:water 70:30% v/v extract; AP./70% ethanol	HPLC-DAD, Liquid chromatography tandem mass spectrometry (LC-MS/MS)	[35,36]
Flavanols			
Catechin	L./Dry powder	UPLC/MS	[33]
Flavanones and Flavanone Glycosides			
Naringenin	AP./Ethanol:water 70:30% v/v	HPLC-DAD	[35]
Naringin	AP./70% ethanol	LC-MS/MS	[36]
Phenolic acids			
Hydroxybenzoic acid derivatives			
Gallic acid	AP./Ethanol:water 70:30% v/v	HPLC-DAD	[35]
Protocatechuic acid	Fresh plant/Ethanol:water 80:20% v/v	UHPLC-MS/MS	[28]
Vanillic acid	L. fixed oil/Hexane	GC-MS	[34]
Hydroxycinnamic acid derivatives			
p-Coumaric acid	Fresh L./Ethanol:water 80:20% v/v; Fresh plant/Ethanol:water 80:20% v/v	HPLC-ESI-MS, UHPLC-MS/MS	[22,28]
p-Coumaric acid 4-*O*-hexoside	Fresh L./Ethanol:water 80:20% v/v; Fresh plant/Ethanol:water 80:20% v/v	HPLC-ESI-MS, UHPLC-MS/MS	[22,28]
p-Coumaroyl-hexoside	L., St./80% methanol	LC-MS-QTof	[31]
o-Coumaric acid (melilotosid)	Fresh AP./Extract prepared by decoction using water	HPLC-DAD-MS/MS	[23]
Chlorogenic acid	Fresh plant/Ethanol:water 80:20% v/v	UHPLC-MS/MS	[28]

Table 2 (*continue*). Phytochemical composition of *P. crispum*

Compound	Plant part/Extract	Detection Method	References
Caffeic acid	Fresh plant/Ethanol:water 80:20% v/v; L./Ultrasound-Assisted Extraction	UHPLC-MS/MS, UPLC-QTOF-MS, HPLC-PDA	[28,29]
Ferulic acid	AP./Ethanol:water 70:30% v/v	HPLC-DAD	[35]
Phenolic compounds			
Cinnamic acid	AP./Ethanol:water 70:30% v/v	HPLC-DAD	[35]
trans-Cinnamic acid	L. fixed oil/Hexane	GC-MS	[34]
Hydroxytyrosol	AP./Ethanol:water 70:30% v/v	HPLC-DAD	[35]
Arbutin	AP./70% ethanol	LC-MS/MS	[36]
Furocoumarins			
Oxypeucedanin	L./Dichlorometan subfraction	Column chromatography (normal phase silica gel, Sephadex LH-20), preparative thin layer chromatography (TLC)	[21]
Oxypeucedanin hydrate	L./Dichlorometan subfraction	Column chromatography (normal phase silica gel, Sephadex LH-20), preparative TLC	[21]
Pabulenol	L./Dichlorometan subfraction	Column chromatography (normal phase silica gel, Sephadex LH-20), preparative TLC, HPLC	[21]
Organic acids			
Citric acid	Fresh L./Ethanol:water 80:20% v/v; Fresh AP./By decoction using water	HPLC-ESI-MS HPLC-DAD-MS/MS	[22,23]
Malic acid	Fresh L./Ethanol:water 80:20% v/v; AP./70% ethanol	HPLC-ESI-MS LC-MS/MS	[22,36]
Carotenoids			
All-*trans*-lutein	L./Aceton, transferred to petroleum ether/diethyl ether mixture (1:1 v/v), saponified with 10% (w/v) methanolic KOH	HPLC-DAD-MS/MS	[25]
All-*trans*-*β*-carotene	L./Aceton, transferred to petroleum ether/diethyl ether mixture (1:1 v/v), saponified with 10% (w/v) methanolic KOH	HPLC-DAD-MS/MS	[25]
Carbohydrates			
D-Glucose	AP./70% ethanol	LC-MS/MS	[36]
D-Mannitol	AP./70% ethanol	LC-MS/MS	[36]
Talose	AP./70% ethanol	LC-MS/MS	[36]
Saccarose	Fresh AP./By decoction using water	HPLC-DAD-MS/MS	[23]
Monoterpenes			
Limonene	Fresh L./Ethanol	HPLC	[32]
Phenylpropanoids			
Eugenol	Fresh L./Ethanol	HPLC	[32]
Apiol, myristicin, elemicin, 3-methoxy-γ-asarone	Seed-Fixed oil/Petroleum ether	GC	[37]
Fatty Acids			
13-docosenoic acid methyl ester, (*Z*), *cis*-13-docosenoic acid, *cis*-11-eicosenoic acid methyl ester, 11-octadecenoic acid (stearate), methyl ester, hexadecanoic acid (palmitate) methyl ester, 15-tetracosenoic acid methyl ester (*Z*), cyclopentanone, 3,4-bis(methylene) and stigmastan-3-ol, 5-chloro-acetate	Fresh L./Cold maceration with methanol	GC-MS	[38]

Table 2 (*continue*). Phytochemical composition of *P. crispum*

Compound	Plant part/Extract	Detection Method	References
Palmitic acid, oleic acid, stearic acid	Seed-Fixed oil/Petroleum ether	GC	[37]
Palmitic acid, linoleic acid, *α*-linolenic acid, stearic acid, oleic acid	L. fixed oil/Hexane	GC-MS	[34]
Petroselinic acid, linoleic acid, lauric acid, myristic acid, palmitic acid	S./Methanol	GC-MS	[39]
Tocopherols			
(β+γ)-Tocopherol	L. fixed oil/Hexane	GC-MS	[34]
γ-tocopherol, *α*-tocopherol, *α*-tocotrienol, *γ*-tocotrienol	S./Methanol	GC-MS	[39]
Sterols			
Stigmasterol+campesterol, *β*-sitosterol	L. fixed oil/Hexane	GC-MS	[34]
β-sitosterol, Δ-5-stigmasterol, Δ-7-stigmasterol, compesterol	S./Methanol	GC-MS	[39]
Other Compounds			
Oleuropein	AP./70% ethanol	LC-MS/MS	[36]
N-(2'-phenylethyl)-hexanamide	L./Dichlorometan subfraction	Column chromatography (normal phase silica gel, Sephadex LH-20), Preparative TLC	[21]

L.: Leaves; AP.: Aerial parts; S.: Seed, St.: Stem

Table 3. Some studies on the components of essential oil obtained from *P. crispum*

	Part used / place of assembly	Essential oil extraction method	Essential oil yield (%)	Main ingredient(s) (%)	References
1	Seed/ Hatay, Türkiye	Hydrodistillation	2.52 (w/w)	3-Methoxy-*γ*-asarone (34.2), apiol (27.5), myristicine (23.8), *α*-pinene (2.5), *β*-pinene (2.4), *β*-Phellandrene (1.3)	[37]
2	Aerial parts/ Parana, Brazil	Hydrodistillation	0.2 v/w	Apiol (50.3), myristicine (14), *β*-phellandrene (14.6)	[40]
	Dried leaf/ Estonia		2.9 mg/g	*p*-Menta-1,3,8-triene (40), *β*-phellandrene (15.1), myristicine (13.1), myrcene (6.5)	
	Fresh root/ Estonia		0.42 mg/g	Apiol (34.5), myristicine (28.8), terpinolene (13.2), *β*-phellandrene (4.6)	
3	Fresh leaf/ Giza, Egypt	Hydrodistillation	-	*α*-Pinene (26.6), myristicin (20.3), apiol (13.2), 1-allyl-2,3,4,5-tetramethoxybenzene (11.6), *β*-pinene (10.5)	[41]
4	Seed/ Draa-Tafilalet, Morocco	Hydrodistillation	2.01 v/w	Apiol (23.5), *α*-pinene (19.0), myristicine (17.2), allyltetramethoxybenzene (4.3)	[42]
5	Leaves/ Al-Kharj, Kingdom of Saudi Arabia	Hydrodistillation	0.08 w/w	Myristicin (41.2), sabinene (9.3), *β*-myrcene (6.0), benzene, (2-methyl-1-propenyl) (5.3), *p*-mentha-1,5,8-triene (4.2), *β*-Caryophyllene (4.0)	[43]
6	Chopped fruit, seed/ Serbia	Hydrodistillation	9.63 w/w	Myristicin (35.8), apiol (24.4), 6-methoxyelemicin (17.4), *α*-pinene (8.2), *β*-pinene (6.0), elemicin (5.5)	[44]
7	Fresh aerial parts/ Mauritius	Hydrodistillation	0.09 w/w	Myristicin (40.3), 1,3,8-*p*-dimenthatriene (17.9), *β*-phellandrene (15.0), myrcene (4.2) *α,p*-dimethylstyrene (3.7), terpinolene (2.6), limonene (2.5)	[45]
8	Leaf/ New Delhi, India	Hydrodistillation	-	Carvacrol (48.5), *d*-limonene (20.8), cuminaldehyde (15.8)	[46]

Table 3 (*continue*). Some studies on the components of essential oil obtained from *P. crispum*

	Part used / place of assembly	Essential oil extraction method	Essential oil yield (%)	Main ingredient(s) (%)	References
9	Aerial parts/ Mauritius	Hydrodistillation	-	Myristicin (40.3), 1,3,8-*p*-dimenthatriene (17.9), *β*-phellandrene (15.0), myrcene (4.2), *α,p*-dimethylstyrene (3.7), terpinolene (2.6), limonene (2.5)	[47]
10	Seeds/ Peru	Steam distillation	0.106	1,3,8-*ρ*-Menthatriene (22.6), apiole (22.4), *β*-phellandrene (15.0), 6-methoxy-elemicin (7.0), myrcene (5.9)	[48]
11	Aerial parts/ Milan, Italy	Steam distillation	-	*α*-pinene (30.8), *β*-pinene (19.4), Limonene+*β*-phellandrene (13.3), myristicin (9.5), terpinolene (5.4), *p*-cymenene (4.9)	[49]

Pharmacological Activities

Antioxidant Activity

It has been observed that research on *P. crispum* is mostly focused on its antioxidant activity. Different extracts of leaves and stems of parsley (hexane, dichloromethane, ethyl acetate, methanol and water) were prepared. The antioxidant activity of dichloromethane extract, which had the highest phenolic content, was evaluated. It was found that the extract showed antioxidant activity for the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method (IC_{50}= 3310.0±80.5 µg/ml). In mouse fibroblasts (3T3-L1) applied with 400 µg/ml extract, the extract was determined to have a protective activity against cancer by exhibiting 50.9% protection against H_2O_2-induced DNA damage detected by the Comet assay. In addition, the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was found to inhibit H_2O_2-induced MCF-7 (estrogen-sensitive breast cancer cell line) cell migration (41%±4%) [50]. The antioxidant activity of the hydroethanolic extract and polyphenolic fraction prepared from the aerial parts of *P. sativum* was evaluated by DPPH, Ferric ion reducing antioxidant power (FRAP), and total antioxidant capacity (TAC) methods. While the DPPH radical scavenging activity of the hydroethanolic extract was higher than that of the polyphenol extract, the polyphenol extract was found to be more effective in the FRAP assay. The activities are lower than standard compounds. In the TAC assay, hydro-ethanolic extract (175.2±6.360 mg ascorbic acid equivalent (AAE)/g) showed higher antioxidant capacity than polyphenolic extract (148.2±13.86 mg AAE/g) [36].

The results of the analyzes performed to determine the antioxidant activity of the hydroalcoholic extract of fresh leaves are as follows: total phenolic content (TPC)= 5.12±0.03 mg GAE/g, total flavonoid content (TFC)= 14.73±1.01 mg quercetin equivalent/g, 13.07±0.64 %, oxygen radical antioxidant capacity (ORAC)= 54.76±1.12 µM trolox equivalent (TE)/g, *β*-carotene/linoleic acid assay= 12.14±2.89% [22]. The antioxidant activity of fixed oil obtained from *P. crispum* leaves was examined by different methods. It was determined as TPC= 40.81±0.7 mg gallic acid equivalent (GAE)/100 g, DPPH= 13.31±1.29 mg AAE/100 g, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS)= 788.39±42.61 mM TE/100 g, FRAP= 2104.38±109.64 mM TE/100 g [34]. Apiin was isolated as the main component of the aqueous extract from the leaves of curly leaf parsley. The extract was determined to contain great phenolic (12.49±1.70 mg/g GAE) and also TFC (15.05±2.20 mg quercetin equivalent). The extract showed high antioxidant activity by the FRAP assay (189.8 mM Fe(II) per mg dry extract of the plant) and DPPH (EC_{50}= 15.50 mg/ml) methods. With the *in vitro* analysis performed on the *Saccharomyces cerevisiae* cells, extract had low toxicity. It has been reported that apiin has a more potent antioxidant effect and lipid peroxidation (0.01 and 0.1 mM) than apigenin under oxidative stress in a cell viability assay (0.1 mM) in yeast cells. It was concluded that the extract and apiin showed antioxidant activity in the eukaryotic cellular model [51].

The antioxidant activity of the ethanol extract of green parts and seeds of *P. crispum* was investigated by *in vitro* methods. The TPC was determined to be in parsley green parts (0.92±0.4) and seeds (0.62±0.01 g GAE/100 g). In the primary oxidation of sunflower oil experiment, the peroxide

value was measured at 7-day intervals for 28 days and it was observed that parsley seed significantly reduced the peroxide value than butylated hydroxytoluene (BHT), more than its leaves. In the P-anisidine experiment, it was determined that parsley green parts and seeds had a significant inhibitory effect on 2-alkene formation in sunflower oil after 7 days. It has been determined that the thiobarbituric acid (TBA) method reduces malondialdehyde (MDA) formation in sunflower oil better than BHT with parsley seeds and green parsley. DPPH radical scavenging activity was found to be high in parsley seeds (91.97±4.38%) (BHT= 90.73±2.69%) and green parts of parsley (88.91±1.41%), respectively, at a concentration of 1000 µg/ml. It is possible to consider parsley as a food additive owing to its antioxidant activity [52]. The TPC of the methanol extract of *P. crispum* seeds was found to be 11.59±0.20 mg GAE/g DW, DPPH and ABTS radical scavenging activity, IC_{50}= 368.78±5.69 and 439.35±2.91 µg/ml, respectively [39]. *P. crispum* samples were exposed to processes such as roasting (150-180°C), baking (200°C) or boiling (100°C) for 10, 20, and 30 min, or no treatment was applied. The TPC and antioxidant activity (DPPH and total reducing power) of the samples were compared. It was determined that the samples had higher phenolic content after heating and the highest reduction potential was found in the samples heated for 10 minutes. It has been reported that the TPC and DPPH results show a strong correlation [53]. 40, 60, and 80% ethanol extracts were prepared from *P. crispum* by microwave-assisted extraction method, and total phenolic content and antioxidant activity were investigated. It was shown that the TPC determined by the Folin-Ciocalteu method was 600.33 mg GAE/100 g dry weight (DW), and the 40% ethanol extract had the highest content (747.73±21.32 mg GAE/100 g DW) compared to other extracts. It was revealed that the antioxidant activity determined by the DPPH method was 7.60 mM TE/100 g DW, and the 40% ethanol extract was higher (5.51% 8.42±1.11 mM TE/100 g DW) [54].

The antioxidant activity of the essential oil obtained from fresh leaves of *P. crispum* was investigated with DPPH and Ferric Chloride Assay. Although the activity is lower than ascorbic acid, it was determined that it showed 68.42%±0.27% inhibition and 0.517±0.01 absorbance at 5 mg/ml, respectively. Myristicin, the main component of the essential oil, was found to interact with antioxidant (PDB: 3NM8 and 1HD2) receptors *in silico* [43]. The antioxidant activity of the essential oil obtained by hydrodistillation from chopped fruits and seeds of *P. crispum* was examined with DPPH and ABTS radical scavenging activity. The antioxidant activity of the essential oil was found to be 1.52±0.9029 µM TE/g in the DPPH experiment at a concentration of 20 mg/ml and 24.95±0.3825 µM TE/g at 10 mg/ml in the ABTS assay [44]. The activity of essential oil obtained from *P. crispum* by hydrodistillation was measured by different methods. DPPH (53.91±1.19 mg TE/g EO), ABTS (75.58±1.76 mg TE/g EO), radical scavenging activity, cupric ion reducing antioxidant capacity (CUPRAC) (147.48±4.08 mg TE/g EO), FRAP (110.64±1.44 mg TE/g EO) and the TPC were found to be 18.46±0.55 mg GAE/g EO [55].

Antimicrobial Activity

There are studies on the antimicrobial activity of different extracts and essential oils obtained from the different parts of *P. crispum*. In a study conducted the inhibition of the leaves of *P. crispum* on bacteria isolated from patients with burning infection were investigated using the agar well diffusion method. 250 mg/ml of hot aqueous extract shows an efficient inhibition against *Pseudomonas aeruginosa* reproduction. Inhibition zone diameter (29.667 mm) was significantly different compared to nitrofurantoin (positive control) ($p<0.05$). Based on the results of this study, *P. crispum* has a good antibacterial against *P. aeruginosa, Staphylococcus aureus* and *Staphylococcus pyogenes* associated with skin infections [56]. In another study, the antibacterial activity of silver nanoparticles and the extract prepared from the aqueous extract of *P. crispum* leaves using different methods (autoclave or heater) was examined according to the well diffusion method. As a result, it was determined that the clean area created by the nanoparticles prepared with autoclave and heater against *Escherichia coli* and *S. aureus* was 16±1, 17±1 and 12±1, 14±1 mm, respectively. It was determined that the particle prepared by autoclave showed the highest antibacterial activity, and the extract alone was not effective [57]. It has been determined that the cold methanol maceration extract of *P. crispum* leaves, which contains carbohydrates, steroids, and saponins shows low-spectrum antibacterial effects against some pathogenic bacteria and is more effective against gram-negative bacteria than gram-positive bacteria [38]. The effect of apiin detected in the ethanol extract prepared from the leaves of *P. crispum* on SARS-CoV-2 was

evaluated *in silico*. It has been shown that the binding affinity of apiin to the nucleocapsid N-terminal RNA binding domain of SARS-CoV-2 is better than remdesivir [32].

The antibacterial effect of the essential oil obtained from the aerial parts of parsley was evaluated by determining the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values. It was determined that the essential oil inhibited the growth of all bacteria with MIC values between 0.04 and 1.00 mg/ml, and killed all bacteria with MBC values between 0.15 and 10.00 mg/ml. According to results the most resistant bacteria were found to be *Enterobacter cloacae* and *E. coli* (MBC values of 10.00 mg/ml). The most sensitive bacteria were *P. aeruginosa, Salmonella enterica*, and *S. aureus*. The MBC value of essential oil against *S. aureus* was close to ampicillin and 1.7 times lower than streptomycin ($p \leq 0.05$) [40]. The antifungal activity of the essential oil obtained by hydrodistillation from the aerial parts of *P. crispum* was examined. In experiments using the Microdilution Broth Susceptibility Assay, it was found to show MIC values of 4 mg/ml (fungistatic) against *Candida albicans* and 2 mg/ml (fungicidal) against *C. tropicalis* [45]. The antimicrobial activity of the essential oil obtained from the aerial part of *P. crispum* was determined by the agar disc diffusion method. Its effect against *Aspergillus flavus* (MIC= 0.25%, MBC= 0.5%), *A. ochraceus* (MIC= 0.125%, MBC= 0.5%), *Geotrichum candidum* (MIC= 0.25%, MBC= 0.5%), *Mucor circinelloides* (MIC= 2%, MBC= 4%) and *Penicillium roqueforti* (MIC= 1%, MBC= 2%) has been detected [49]. The antifungal activity of the essential oil extracted from the aerial parts of parsley was evaluated by determining the minimum fungicidal concentration (MFC) values. *P. ochrochloron* and *Trichoderma viride* were found to have low concentrations of MICs compared to ketoconazole. As a fungicide, parsley essential oil was efficient for all fungi, especially *P. funiculosum* (MFC= 1.25 mg/ml) and *T. viride* (MFC= 2.50 mg/ml). However, in general, the fungicide amounts of the essential oil against fungi (*A. niger, A. fumigatus, A. ochraceus, A. versicolor, P. ochrochloron, P. funiculosum, P. verrucosum, T. viride*) were 5-62.5 times higher than those of the positive controls ($p \leq 0.05$) [40]. The antimicrobial activity of the essential oil obtained from the fresh leaves of *P. crispum* was determined by the agar diffusion method. At 20 mg/ml, the inhibition zone and MIC values were found to be *C. albicans* (19.4±0.08 mm, 1.25 mg/ml), *S. aureus* (17.86±0.09 mm, 2.5 mg/ml), *Bacillus subtilis* (15.73±0.04 mm, 2.5 mg/ml), *Klebsiella pneumoniae* (9.43±0.09 mm, 5 mg/ml) and *E. coli* (8.67±0.12 mm, <5 mg/ml), respectively. The interaction of myristicin, the main component of the essential oil, with antibacterial receptors (PDB: 1AJ6 and 1JIJ) *in silico* experiments has been shown to support *in vitro* study and has been reported to be responsible for the activity [43]. It was determined that the nanoemulsion carrying the essential oil obtained by hydrodistillation from *P. crispum* leaves completely inhibited the growth of *A. flavus* and some other storage fungi at 1.0 µl/ml and the production of Aflatoxin B1 at 0.75 µl/ml. The mechanism of antifungal action has been reported to be by reducing cellular ergosterol and subsequent release of cellular components [46].

The antimicrobial activity of the hydroethanolic extract and polyphenolic fraction prepared from the aerial parts of *P. sativum* against *P. aeruginosa, S. aureus*, and *C. albicans* was determined by agar well diffusion and broth dilution methods. It was found that the polyphenolic fraction (inhibition diameters and MIC values: *P. aeruginosa*: 14.00±0.33 mm, 6.25 mg/ml, *S. aureus*: 9±0.16 mm, 3.125 mg/ml and *C. albicans*: 13±0.57 mm, 6.25 mg/ml) showed better activity than the hydroethanol extract (inhibition diameters and MIC values: *P. aeruginosa*: 14.00±0.33 mm, 6.25 mg/ml, *S. aureus*: 9±0.16 mm, 3.125 mg/ml and *C. albicans*: 13±0.57 mm, 6.25 mg/ml), being lower than the standard substances [36].

The antimicrobial activity of 40, 60, and 80% ethanol extracts prepared from *P. crispum* by microwave-assisted extraction method was examined by disc-diffusion method. The 60% ethanol extract was found to show higher activity against *E. coli* (3.00±1.41 mm) and *C. albicans* (2.00±0.00 mm) than other extracts [54]. The activity of aqueous and ethanol extracts of parsley against bacteria isolated from children with urinary tract infection was examined by disc diffusion method. It was observed that the inhibition zones of the ethanol extract for the bacteria studied except *Miroccoccus* were between 2-22 mm. It was determined that the aqueous extract was not effective against *Micrococcus, P. aeruginosa, K. oxytoca*, and others it created an inhibition zone between 2-21 mm [58]. The antimicrobial activity of the ethanol extract of green parts and seeds of *P. crispum* against pathogenic bacteria, yeast and food-born fungi was determined by the agar well diffusion method. It

was observed that the seeds formed more inhibition zones than the green parts. The inhibitions of seeds and green parts were determined as *C. tropicalis* (25, 22 mm), *S. typhi* (23, 20 mm), *S. aureus, A. flavus* (18, 16 mm), *Mucor* sp. (19, 19 mm) and *Emericella nidulais* (17, 15 mm), respectively [52]. *P. crispum* samples were exposed to processes such as roasting (150-180 °C), baking (200 °C) or boiling (100 °C) for 10, 20, and 30 min, or no treatment was applied. The antibacterial effect of the samples was examined against *E. faecalis*, *B. subtilis*, *E. coli,* and *K. pneumoniae*. Fresh samples heated for 10 minutes were found to be effective against *K. pneumoniae*. It was observed that the processed sample heated for 10 minutes was effective against *B. subtilis* [53].

Antiinflammatory Activity

The antiinflammatory activity of the hydroethanolic extract and polyphenolic fraction of the aerial parts of *P. sativum* was examined *in vivo* by the paw edema method. Rats were administered indomethacin (positive control), 500 and 1000 mg/kg *P. sativum* hydroethanolic extract, or 220 mg/kg polyphenolic fraction. At the end of 3 and 6 hours, it was determined that 25%, 65.33%, and 38% inhibition occurred with 500 and 1000 mg/kg extract, 74%, 48% and 81% inhibition occurred with the fraction. Indomethacin exhibited 50% and 86.67% inhibition, respectively [35].

In another study, the antiinflammatory activity of the essential oil obtained from fresh leaves of *P. crispum* was examined by albumin and trypsin analysis. It was determined that inhibition with egg albumin provided 22.2-90.4% inhibition at 5-1000 ppm, while ibuprofen varied between 32.8-91.7%. It has been reported that inflammation caused by trypsin is inhibited by 8.4-74.7% with essential oil at 5-200 ppm and by 74.7-76.5% with ibuprofen. The interaction of the main component of the essential oil, myristicin, with anti-inflammatory (3N8Y and 3LN1) receptors was examined *in silico* and it was suggested that it may be responsible for the activity [43]. Thangavelu et al. [59] examined the cytotoxicity of methanol, petroleum ether, and aqueous extracts (500 µg/ml) prepared from *P. crispum* leaves on A549 cells by MTT assay. The IC_{50} value of the methanol extract was found to be 1521.4 mg/ml. It was determined that cell migration was significantly accelerated after application and the extract had a high antiinflammatory effect.

Antidiabetic Activity

The antidiabetic activity of *P. crispum* was determined by evaluating its effect on enzymes such as α-amylase and α-glucosidase. In a screening study, it was determined that the methanol extract of *P. crispum* inhibited α-amylase significantly (37.48±0.33%) at a dose of 2 mg/ml. It has been found that the correlation of this activity with the free radical scavenging effect of the extract is relatively weak [60]. *P. crispum* samples were exposed to processes such as roasting (150-180 °C), baking (200 °C) or boiling (100 °C) for 10, 20, and 30 min, or no treatment was applied. α-amylase enzyme inhibition of the samples was examined and it was noted that fresh (83.8%) and processed (75.4%) samples heated for 10 minutes showed the best activity [53]. It was determined that the essential oil obtained from fresh *P. crispum* by hydrodistillation inhibited α-amylase enzyme (1.35±0.05 mM acarbose equivalent/g EO) but did not inhibit α-glucosidase [55].

Albino mice with streptozotocin-induced gestational diabetes were administered aqueous extract of *P. crispum* (1 ml/150 g/bw) from the 7th to the 19th day of the experiment. Developmental changes such as thin skin, thin muscles, absence of eyelids, and kyphosis occurred in the fetuses of diabetic mice. More normal morphological development was observed in the group given parsley. It has been determined that parsley reduces the harms of hyperglycemia [61].

Analgesic Activity

The aqueous extract of *P. crispum* was evaluated for analgesic activity at doses of 2, 5, and 10 g/kg using hot plate and acetic acid-based writhing methods. The extract also showed significant ($p<0.01$) analgesic activity in both methods, and additionally enhanced morphine and aspirin-induced analgesia [62]. The analgesic activity of the hydroethanolic extract and polyphenolic fraction prepared from the aerial parts of *P. sativum* was investigated by abdominal writhing and formalin tests in rats. The acetic acid method was used in the abdominal writhing test and hydro-ethanolic extract (1000 mg/kg, 38.96%) and polyphenols (200 mg/kg, 29.23%) showed a significant decrease. In the formalin

test, in the first stage, 1000 mg/kg decreased the response time by 33.32% and 500 mg/kg decreased the response time by 25.86%. In the second stage, hydroethanolic (500 mg/kg, 28.55%; 1000 mg/kg, 37.35%) and polyphenol extracts, and polyphenols (200 mg/kg, 30%) revealed a significant decrease in response time. Tramadol used as a standard, was found to be more effective [36].

Activity on the Gastrointestinal System

In a study evaluating the activity of parsley on gastric damage caused by oxidative stress, aqueous extract of parsley (28 g/kg) was given to rats with gastric damage and it was examined microscopically and biochemically after 7 days. Histopathologically significant difference was observed in rats with gastric stress given parsley ($p<0.05$), standard diet ($p<0.05$), and lansoprazole ($p<0.05$). It was determined that MDA levels decreased in the groups given extract and lansoprazole. Parsley was found to increase the average glutathione (GSH) level, catalase (CAT), and superoxide dismutase (SOD) activities [63].

The effect of carbinol extract of *P. crispum* seeds (500 μg/ml) on iron absorption was examined *in vitro*. The extract enabled 8.24% of the iron applied to Caco-2 cells to be absorbed by the cells and showed lower permeability (2.01×10^{7} cm/s). It was concluded that parsley is a good source of chlorophyll and iron and increases the absorption of iron from human intestinal cells [64].

Antiplatelet Activity

The antiplatelet activity of the aqueous extract from the aerial parts (major component is apiin) of its flat leaf was investigated by *in vivo* and *ex vivo* experiments. It was found that the extract, when administered intravenously (25 mg/kg body weight-bw) and orally (125 mg/kg bw) five minutes before thrombosis induction, inhibited venous thrombosis formation by 98.2% and 76.2%, respectively. 15 or 25 mg/kg extract was found to increase carotid artery occlusion time by 37.0±6.44 minutes (150%) and more than 60 minutes (240%), respectively, when administered orally 60 minutes before induction of thrombosis. Parsley has been reported to be a potential drug candidate for the treatment of thromboembolic disease [23].

Antiurolithiatic Activity

The antiurolithiatic effect of ethanol extract was investigated *in vivo* by administering (500 mg/kg) to the rats. Subsequently, the kidneys of the rats were removed and evaluated histopathologically. Calcium oxalate crystals were found to be significantly ($p<0.001$) low in both histological sections and urine samples after treatment with parsley. It was concluded that parsley acts by decreasing urinary calcium and protein excretion, as well as increasing urinary pH and diuresis [65].

The effect of the hydroalcoholic extract prepared from aerial parts of *P. crispum* on calcium oxalate urolithiasis was investigated *in vitro*. It has been shown to cause a decrease in the size of calcium oxalate crystals with a significant decrease in the mean diagonal (4.41 μm, $p<0.01$). It was found to significantly inhibit ($p<0.05$) calcium oxalate aggregation after 60 minutes compared to the negative control at 10 mg/ml. It has been reported that its effect may be due to polyphenols such as flavonoids. In addition, it was found that it did not show significant activity in acetylcholine (Ach)-induced contraction (*ex vivo*) in the rat ileum [66].

Antihyperuricemic Activity

The hypouricemic effect of *P. crispum* was investigated on mice at the biochemical, molecular, and cellular levels. 7 g/kg of parsley leaf aqueous extract was administered orally to hyperuricemic and control mice for 10 days, either separately or in combination. It was found that the giving parsley remarkably decreased serum blood urea nitrogen and uric acid levels, increased CAT levels, decreased MDA, GSH, glutathione peroxidase (GPx), tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-10 in hyperuricemic mice. The mRNA expression of urate transporters and uric acid excretion genes in kidney tissues were evaluated by quantitative reverse transcription polymerase chain reaction (qRT-PCR) and it was determined that regulate urate excretion associated genes (URAT1, GLUT-9, OAT-1 and OAT-3). It was found that the alterations in transforming growth factor beta 1 (TGF-β1) immunoreactivity were effectively normalized by the administration of the extract [67].

The antihyperuricemic effect of parsley was investigated *in vivo*. The leaves of *P. crispum* (3.5, 7, and 10.5 g/kg/day) were administered to oxonate-induced hyperuricemic rats for 7 days. As a result, it was determined that the serum uric acid level decreased the most when 7 g/kg/day parsley was given. It was determined that liver lesion scores decreased with all three doses, and kidney lesions decreased with a dose of 7 g/kg/day. It has been reported that parsley reduces serum uric acid levels and has the potential to improve kidney and liver damage caused by hyperuricemia [68].

Anticancer Activity

The ethanol extract (PSE) and the seed oil (PSO) of *P. crispum* were investigated by MTT assay, neutral red uptake and microscopic examination in MCF-7 cells by exposing the cells to 10 to 1000 µg/ml PSE and PSO for 24 hours. Cell viability was found by the MTT assay. PSE was found to be 81%, 57%, 33%, 8% and 5% at 50, 100, 250, 500, and 1000 µg/ml concentrations, respectively, while 90%, 78%, 62%, and 8% for PSO at 100, 250, 500, and 1000 µg/ml concentrations. PSE doses of 50 µg/ml and above and PSO concentrations of 100 µg/ml and above were determined to be cytotoxic in MCF-7 cells. It was found that 250, 500 and 1000 µg/ml doses changed the cellular morphology of MCF-7 cells in a associated with concentration, and PSE was more effective than PSO [69].

The activity of the root extract on MCF-7 and MCF-12A cell lines with lactate dehydrogenase (LDH) cytotoxicity analysis, DNA synthesis with bromodeoxyuridine (BrdU) proliferation analysis, and metabolic activity with MTT cell viability assay in the dose range of 0.01-100 µg/ml, were evaluated. In LDH analysis, no significant cytotoxicity was observed in either cell line, but a better result was obtained at 500 µg/ml dose. BrdU showed notable DNA synthesis inhibition of up to 80% at 10, 50, 100 and 500 µg/ml in the proliferation assay. According to MTT analysis, 63% and 75% inhibition of metabolic activity in MCF-7 and MCF-12A were reported at only 500 µg/ml. It has been noted that parsley shows antiproliferative activity in both cell lines [70].

The anticancer effect of aqueous and methanol extracts of the aerial parts of *P. crispum* against human glioblastoma cells U87MG was evaluated. The adhesion test was performed on various protein matrices of the extracts at doses of 10, 20, 50, and 100 µg/ml. It was found that the methanol extract specifically inhibited the adhesion of human glioblastoma cells U87MG to fibrinogen, fibronectin, and non-specific substrate Poly-L-Lysine (PLL), and the IC_{50} value was 19.4±0.15 and 23.86±0.92 and 20.25±0.59 mg/ml, respectively. When the activity of the samples on tumor cell proliferation was examined, it was found that only methanol extract could entirely reduce cell proliferation at a concentration of 1 mg/ml after four days of incubation [71].

The hydroalcoholic extract of the seeds of parsley was evaluated against A375 human melanoma cells and dendritic cells. It was reported that parsley extract showed significant apoptotic potential. It was determined that parsley extract had a cell growth inhibition of 24.9-2.9% ($p<0.0001$) after 60 µg/ml and 72 hours of incubation. It was observed that the amount of caspase 3 protein increased significantly ($p<0.001$) with 30 µg/ml parsley extract and decreased at 60 µg/ml [72].

The different concentrations (3.25-200 mg/ml) of silver nanoparticles prepared from methanol extract of *P. crispum* seeds (AgNPs@PCS) were examined by MTT assay against MCF-7 cell line. The IC_{50} value was found to be 200 mg/ml after 24 hours of exposure [73].

Antihepatotoxic Activity

Oils [*α*-pinene (26.6%) and myristicin (20.3%)] obtained from *P. crispum* leaves by hydrodistillation were administered to rats with carbon tetrachloride (CCl_4)-induced hepatotoxicity. It was found that increased serum aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and gamma glutamyl transpeptidase levels decreased ($p<0.05$) and increased SOD and GSH activity. It has been observed that 0.5 ml of peppermint oil is effective in reducing MDA. In rats with CCl_4-induced hepatotoxicity, urea level was seen to be remarkably reduced by parsley oil administration [41].

The effect of the aqueous extract prepared from the leaves of *P. crispum* against oxidative liver damage caused by bile obstruction was evaluated *in vivo*. The extract was administered orally at a dose of 2 g/kg to rats with ligated bile ducts for 28 days. AST, ALT, bilirubin levels in serum, as well as SOD, GSH, MDA, Na^+/K^+-ATPase and 8-hydroxyguanosine for evaluation of oxidative stress,

myeloperoxidase for inflammation, caspase-3 for apoptosis, TGF-β and hydroxyproline for fibrosis were investigated. It has been determined that the extract reduces increased ALT, AST and bilirubin levels and improves oxidative damage parameters. It has been shown that *P. crispum* extract is protective against bile obstruction-induced hepatic damage and fibrosis in rats owing to its antioxidant and anti-inflammatory effects [74].

The effect of the hydroalcoholic extract prepared from *P. crispum* leaves against lead (Pb)-induced liver damage was examined *in vivo*. The extract was administered to rats together with Pb at doses of 100 or 200 mg/kg via oral gavage for 21 days. It was determined that Pb-increased liver enzymes, MDA, TAC, CAT, and SOD activities decreased, Bax and TNF-α gene expressions related to apoptosis increased and B-cell lymphoma gene-2 (Bcl-2) gene expression decreased. It was determined that oxidative and apoptosis changes were significantly improved by administration of parsley extract. It was concluded that parsley has a direct protective effect on the damaged liver by regulating the expression of genes related to antioxidant activity and apoptosis [75].

The protective effect of the hydroethanolic extract of the aerial parts of *P. crispum* on paracetamol-induced hepatotoxicity was examined *in vivo*. Rats were given extract (200 mg/kg) and paracetamol (200 mg/kg) for 15 days. It has been observed that the extract significantly reduces ALT, AST, ALP, and LDH levels in the liver, which are increased by paracetamol. In addition, histopathological examinations revealed less congestion and mononuclear cell infiltration in the liver tissue [76].

Antinephrotoxic Activity

The *in vitro* antinephrotoxic potential of the seeds of *P. crispum* against CCl_4-induced oxidative damage in mammalian kidney (Vero) cells was investigated. Antiradical experiments of the tested extracts showed that the DPPH radical scavenging effect of *P. crispum* extract had equal potential as BHT. Treatment with the extract greatly reduced the number of CCl_4-induced necrotic cell populations, with higher ($p<0.05$) potency than ketosteril (25.56%). Treatment with extract suppressed CCl_4-induced toxicity by inhibiting major necrotic mediators [77].

In a study on the effects of 5% aqueous extract of *P. crispum* (administered *ad libitum*), on diuretic activities, electrolyte composition, antioxidant capacities, and their effects on the kidney by histopathological consultation of the kidney tissue after their application were evaluated. It was determined that lipid peroxidation decreased, GSH levels increased, and the activities of antioxidant enzymes (GPx, SOD, and CAT) in kidney tissue were recovered with oral parsley administration. It has been shown that the best diuretic effect, electrolyte excretion, DPPH radical scavenging effect is provided by parsley extract. Parsley has been suggested for the avoidance of kidney diseases [78].

The ameliorating effect of ethanol extract (500 mg/kg bw) of *P. crispum* leaves and stems on the toxicity of orellanin in rat kidney was examined. It was observed that there was a decrease in body weight, relative kidney weight, and an increase in creatinine, uric acid, and urea levels in the group given orellanin. Additionally, it was determined that cystatin C levels increased while GPx activity decreased. In histopathological examination, it was determined that the toxicity caused by orellanin, especially in the kidney cortex, nephron, and proximal tubules, was improved by parsley [79].

The protective effect of the hydroethanolic extract of the aerial parts of *P. crispum* on paracetamol-induced nephrotoxicity and proteinuria was examined *in vivo*. The extract (200 mg/kg) was administered to rats receiving paracetamol by oral gavage for 15 days. It was determined that the increase in blood urea, creatinine, and triglyceride levels was inhibited by the extract. It was observed that the extract reduced urinary protein excretion compared to control groups and increased urinary creatinine and urea excretion compared to paracetamol control groups [76].

The protective effects of ethanol extract of *P. crispum* seeds (5 mg/kg) on the kidneys of pregnant rats aborted using prostaglandin were examined. The extract was applied for 18 days and MDA, total antioxidant status, creatinine, and urea levels were monitored, and histopathological examination was performed. As a result, it was reported that parsley reduced the dysfunction caused by prostaglandin-induced abortion in rat kidneys and was useful in reducing the progression of prostaglandin-induced edema [80].

Neuroprotective Activity

Mice poisoned with cadmium (Cd) were administered parsley juice at two doses (5 g/kg/day and 10 g/kg/day) via gastric intubation. Cd has been shown to cause behavioral abnormalities, histopathological and biochemical disorders in mice. It was determined that especially low dose (5 g/kg/day) fruit juice significantly improved Cd-related behavioral changes. It was found to reduce the increase of lipid peroxidation and normalize the Cd effect on reduced peroxidase and GSH activities in the brain of treated mice, reducing neuronal aberrations in the brain [81].

The activity of *P. crispum* extract against morphine-induced damage in the prefrontal cortex of rat brain was evaluated. The extract was giving rats intraperitoneally (*i.p.*) at doses of 50, 100, and 150 mg/kg alone or in combination with morphine. In the group given morphine, the density of neurons and neuronal dendritic spines, total antioxidant capacity significantly decreased, and nitric oxide (NO) levels have been increased ($p<0.05$). It was observed that these effects have been reversed ($p<0.05$) at all doses in the groups given the extract alone or in combination with morphine. It has been determined that *P. crispum* provides protection against morphine induced oxidative stress via its antioxidant effect [82].

The neuroprotective effect of the aqueous extract of *P. crispum* leaves on oxidative damage that may occur in the brain of rats with bile duct ligation induced biliary cirrhosis was examined. The extract (2 g/kg) was administered orally for 28 days. It was determined that lipid peroxidation, sialic acid, and NO levels decreased and GSH levels and CAT activities increased significantly in the extract-administered group. It was determined that there was no significant change in total protein, GST, SOD, and boron levels. It was observed that histological findings also supported the results of biochemical analysis. It has been found that parsley is effective in regressing the oxidant damage caused by cirrhosis in brain tissues [83].

Şener et al. [84] investigated the protective effect of the aqueous extract of *P. crispum* leaves (2 g/kg, oral, 14 days) on the brains of rats with scopolamine-induced Alzheimer's disease using the novel object recognition test and Morris water maze test methods. It was observed that the M1 receptor expression in the hippocampus and frontal cortex, Bcl-2/Bcl-2 associated x protein (Bax) ratio, and GSH levels decreased with scopolamine, and the increased MDA levels, caspase-3/9 expressions, and acetylcholinesterase (AChE) activity were reversed by the extract. It has been determined that parsley has a healing effect on spatial and recognition memory, M1 receptor expression, apoptosis, oxidative stress, and increased AChE activity. In another study, the protective effects of the aqueous extract of *P. crispum* leaves (2 g/kg) against damage to the lens tissues of the scopolamine-induced experimental Alzheimer's model were investigated. Reduced GSH, SOD, CAT, GPx), glutathione reductase, glutathione-S-transferase parameters, which were found to decrease with scopolamine, were shown to increase significantly again with the extract. It was determined that lipid peroxidation, NO, and advanced oxidation protein products, which increased with scopolamine, decreased with the extract. As a result, it was concluded that it can reduce oxidative damage and protect lens tissue against oxidative damage due to Alzheimer's disease, owing to its rich content of phenolics and flavonoids [85].

Activity on Some Hormones and Reproductive Functions

The effect of parsley leaf essential oil against the detrimental effects of CCl_4 on the thyroid gland and testicles of mice was investigated. Mice that received *i.p.* 3 ml/kg CCl_4 twice weekly for 4 weeks had a decrease in CAT, SOD activities ($p<0.05$), and an increase in MDA levels in testes and thyroid glands ($p<0.05$). In addition, it was determined that luteinizing hormone (LH), follicle stimulating hormone (FSH), and thyroid hormones (thyroid stimulating hormone (TSH), free triiodothyronine (fT_3), total triiodothyronine (T_3), free thyroxine (fT_4), and total thyroxine (T_4)) decreased significantly. Parsley essential oil was applied at 0.5 ml/kg/day. The essential oil has been found to reduce testicular and thyroid oxidative stress significantly. It has also been found to increase LH, FSH, fT_3, T_3, fT_4 and T_4 [86].

The *in vivo* estrogenic effect of the hydroethanolic extract and polyphenolic fraction of the aerial parts of *P. sativum* was examined. Female rats were administered 308.33 mg/kg clomiphene citrate (positive control), 500 and 1000 mg/kg *P. sativum* hydroethanolic extract, or 220 mg/kg polyphenolic fraction for 4 weeks. As a result, it was determined that there was no change in ovarian weights with the

extracts, and uterine weights increased by approximately 30%. It was determined that 1000 mg/kg hydroalcoholic extract, clomiphene citrate, and polyphenolic fraction decreased ovarian cholesterol by 56%, 50%, and 40%, respectively. It was found that 1000 mg/kg hydroethanolic extract increased uterine protein levels by 73% and polyphenolic fraction by 65%. 1000 mg/kg hydroalcoholic extract increased serum estradiol by 43%, 220 mg/kg polyphenolic fraction increased by 31%, and clomiphene citrate increased by 64%. It was concluded that parsley has an estrogenic effect owing to its components such as ferulic acid, gallic acid, and quercetin [35].

Wound Healing Activity

The burn wound healing activity of hydroethanolic extract and polyphenolic fraction prepared from the aerial parts of *P. sativum* in vaseline (10% w/w) was examined in rats. It was determined that ointments prepared from hydroethanolic extract and polyphenolic fraction produced high wound shrinkage of 97.17% and 94.98%, respectively, in 25 days. It was determined that the hydroethanolic extract provided complete wound healing on the 20th day compared to the polyphenol fraction and positive control (Madecassol®) [36].

In another study, the wound healing activity of the ointment obtained by mixing the ethyl acetate extract rich in phenolic compounds prepared from the aerial parts of *P. crispum* with vaseline was investigated *in vivo*. Ointment (13% and 22% w/w) was applied topically to wounds in mice twice a day for 10 days. It was observed that *P. crispum* ointment caused a significant reduction in wound size ($p \leq 0.001$), an increase in epithelialization and angiogenesis scores ($p \leq 0.05$) and an increase in collagen scores at 22% w/w concentration compared to vaseline. It was found to increase collagen III more ($p \leq 0.05$) compared to *β*-sitosterol. It has also been found to significantly increase epidermal endothelial growth factor. As a result, it was concluded that parsley phenolic extract was more effective than vaseline and accelerated wound healing at a level comparable to *β*-sitosterol [87]. The wound healing activity of methanol, petroleum ether, aqueous extracts (500 µg/ml) prepared from *P. crispum* leaves on A549 cells was examined *in vitro* by Scratch test. It was observed that the scratch area in the wound was covered 7.46% faster with *P. crispum* compared to the control [59].

The wound healing activity of the ointment prepared by mixing AgNPs@PCS with vaseline, prepared from the methanol extract of *P. crispum* seeds, was evaluated in rats. It has been determined that the ointment prevents inflammation in the wound area, increases the number of fibroblast cells and, as a result, accelerates wound healing. In the *in vivo* examination, it was observed that the wound closure percentage was higher on the 7th and 14th days than in the control group (vaseline) and the wound was completely closed after 21 days. It has been reported that nanoparticles have the potential to be used clinically [73].

Antiobesity Activity

The TPC and antioxidant capacity (DPPH method) of extracts of *P. crispum* var. *neopolitanum* leaves prepared by different methods such as boiling, blanching, and microwaving were compared. Boiled parsley was observed to have the highest values and was administered orally to rats fed a high-fat diet at a dose of 200 mg/kg for 8 weeks. It was found to significantly reduce body weight, adipose tissue, fasting blood glucose, triglycerides, low density lipoprotein, very low density lipoprotein, liver lipids, creatinine, and urea levels and increase high density lipoprotein, and liver GSH levels compared to the positive control. It has been determined that the antioxidant capacity of parsley increases by boiling and is effective for obesity [88].

Other Activities

Apart from the activities mentioned, there are studies in the literature on the hypolipidemic [89], antianemic [90], antiosteoporotic [91], antihypertensive [2], antidepressant, anxiolytic [92] anti-acne, anti-aging [45], antifatique [30], prebiotic effect [93], enzyme inhibitory (adenosine deaminase, neurominidase, xanthine oxidase, acetylcholinesterase, tyrosinase) [55,94] activities and nutraceutical potential [33,95-97] of parsley.

Clinical Studies

In the study conducted on 37 patients with urinary tract infections, mostly women, general urinary examination and abdominal ultrasonography were performed 14 days after the capsules containing 500 mg of leaf and stem powder were given to the patients twice a day for 10 days. It is observed that the frequency of 11/17 ($p=0.011$) and 17/20 emergencies ($p<0.0001$) improved, 100% of dysuria and suprapubic pain ($p<0.0001$) were cured, and 23/31 of the patients reported improvement in low back pain ($p<0.0001$). The total symptom score showed a significant decrease from baseline scores of 5.94±0.14 ($p=0.0313$) at the second evaluation. It was stated that no remarkable side effects were observed in the patients [98].

In a double-blind, randomized clinical trial, powdered *P. crispum* (infusion of 2.5 g in a glass of water (125 cc)) was applied topically to patients with melasma (54 patients) in a medical center in Iran. At the end of eight weeks, the severity of the disease was evaluated using the melasma area and severity index (MASI). It was determined that 4% hydroquinone ($p=0.000$) and parsley ($p=0.002$) in the control group reduced the severity of melasma and the efficacy of the two groups was similar ($p=0.858$). Moreover, the total cost in the hydroquinone group was found to be approximately 10.5 times higher than the parsley group [99].

Toxicity

Studies have mostly reported that *P. crispum* is safe in wide dose ranges and does not show toxicity. In a study, the acute toxicity of ethanol extract of leaves and stems (5, 50, 300, and 2000 mg/kg bw) was examined *in vivo*. No behavioral changes or lethal effects were observed in rats after 24 hours [79]. When the ethanol extract of its leaves was examined *in vivo* and histopathologically in rats, the hematological data were analyzed using bromocresol green and Berthelot method. It was found to have hepatotoxic and nephrotoxic effects when used continuously at doses of 1000 mg/kg or more and showed no significant toxicity when taken at lower concentrations [1]. The toxicity of the hydroethanolic extract and polyphenolic fraction of the aerial parts of *P. sativum* was investigated *in vivo*. Rats were given clomiphene citrate (positive control), 500 or 1000 mg/kg hydroethanolic extract for 4 weeks. It was determined that the extract had no toxic effects on liver and kidney tissues [35]. In the studies conducted, no oral toxicity was observed with the aqueous extract of *P. crispum* leaves on hematological, biochemical parameters, liver and kidney histology. It is suggested that the LD_{50} value in wistar rats is greater than 5000 mg/kg [100].

Median cytotoxic concentration (CC_{50}) values in extracts (hexane, chloroform, ethyl acetate, methanol, ethanol, water) of leaves and stems of *P. crispum* in healthy kidney epithelial (Vero) cells derived from the African monkey cells at a concentration of 100 µL (5-640 µg/ml) were found to be 82.7±8.1 for chloroform, 105.3±4.5 for ethyl acetate and 159.3±8.0 µg/ml for hexane. No cytotoxicity was detected in ethanol, methanol, and aqueous extract [101]. It was determined that the carbinol extract of *P. crispum* seeds at different concentrations (62.5-1000 µl) did not show toxicity in Caco-2 cells by MTT assay [64].

In an ethnobotanical study conducted in Morocco, its leaves were reported to have hypotensive effects [14]. Apiol, the main component of parsley leaf and seed oil, has been reported to be used as an abortifacient [102].

Drug Interactions

Since parsley has a diuretic effect, care should be taken to avoid excessive fluid loss, dehydration and hypotension, as the effect may be increased when used together with diuretic drugs [103]. *In silico* studies, it has been reported that rutin, kaempferol, apigenin, elemicin, myristicin, estragol, caffeic acid, 4-terpinol found in *P. crispum* have the potential to interact with antihypertensive drugs [104].

The enzyme-inducing or inhibitory activity of powdered parsley (200 mg) for simvastatin (80 mg) was evaluated at the level of the metabolic enzyme cytochrome P-450. C_{max} (mean plasma maximum concentration) and $AUC_{0-\infty}$ (area under the concentration-time curve) of simvastatin were found to increase by 2 and 2.2 fold, respectively, when given with parsley ($p<0.01$). A decrease in the clearance of simvastatin ($p<0.01$) and an increase in $t_{1/2}$ between 3.2 and 6.12 hours was observed. Since parsley

can be a potential inhibitor of the enzyme that metabolizes simvastatin, it has been reported that it should be used with caution [105].

A 19-year-old female patient was immunosuppressed by sirolimus administration after renal transplantation. At the control of the patient taking 1.5 mg of sirolimus twice daily, it was observed that the blood level of the drug was high (14.8 ng/ml). At the previous control, conditions that could increase the medicine level, which ranged from 2-4 ng/ml, were excluded. A more detailed history of the patient revealed that he had been drinking about 30 g of parsley juice for seven days to lose weight and improve her health. It was observed that the medicine level returned to the normal range (4.6 ng/ml) after one week of stopping the parsley juice [106].

RESULT AND DISCUSSION

Parsley, which originated in the Mediterranean Region and is now cultivated almost all over the world, has been used worldwide for many years. It is commonly used by adding it to the meals and salads prepared in the daily diet for a healthy life. Besides its use as a food, it is used for therapeutic purposes for various conditions such as urinary tract infections, stomach disorders, menstrual pain, and some dermatological disorders in folk medicine. Its phytochemical composition includes flavonoids, coumarins, phenolic compounds, carotenoids, carbohydrates, vitamins and minerals, essential oil, and other constituents. Studies conducted on extracts of parsley and its isolated constituents show that the plant has a wide range of pharmacological activities, owing to flavonoids and phenolic compounds, especially antioxidant effects. As a result, numerous preclinical studies have demonstrated that parsley has significant therapeutic potential. Despite this data, the number of clinical studies conducted on the species is quite limited. Its effects need to be demonstrated through clinical studies and dose-toxicity studies need to be conducted for different diseases.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

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