TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 5, Issue 3, Summer 2020

Review

Bunium persicum: A Review of Ethnopharmacology, Phytochemistry, and Biological Activities

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Received: 21 Jul 2020 **Accepted:** 29 Jul 2020

Abstract

Bunium persicum (Boiss) B. Fedtsh (Apiaceae, Persian name: Zireh Kermani) has been used to treat various diseases in traditional and folkloric medicine including gastrointestinal, respiratory, nasopharyngeal, cardiac, ocular, neurological, rheumatological and urinary tract diseases. Its essential oil contains different monoterpenes, sesquiterpenes and phenyl propenes. Other chemical constituents identified in *B. persicum* are phenolic compounds, fatty acids, carboxylic acids, and carbohydrates. Wide range of biological and pharmacological activities including antioxidant, analgesic, anti-inflammatory, acetylcholinesterase inhibitory, anticonvulsant, HMG-CoA reductase inhibitory, anti-pancreatic lipase, anticancer, antidiabetic, antihistamine, antidiarrheal, antispasmodic, antihematoxic, antityrosinase and antimicrobial activities have been reported from this plant in modern medicine. This article summarizes comprehensive information attributing traditional uses, phytochemistry, and pharmacological activities of Zireh Kermani.

Keywords: *Bunium persicum; Carum persicum;* Zireh Kermani; Traditional medicine; Pharmacology; Phytochemistry

Citation: Majidi Z, Bina F, Kahkeshani N, Rahimi R. ***Bunium persicum***: **A Review of Ethnopharmacology, Phytochemistry, and Biological Activities.** Trad Integr Med 2020; 5(3): 150-176.

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Introduction

Bunium persicum (Boiss) B. Fedtsh (syn. *Carum persicum* Boiss) from Apiaceae family is native of Iran, Afghanistan, Pakistan and some Central Asian countries, which is locally known as Zireh Kermani in Iran, as Zeera in central Asian countries (Uzbekistan, Tajikistan, Kyrgyzstan and Pakistan), and as Kala Zira in India [1,2].

This plant is a branched and perennial herb that grows up to 40 to 60 cm. The glandular root is irregular spherical in shape. The leaves are freely, pinnate, finely dissected and filiform. The flowers are small, white in color, with readily symmetrical small sepals, petals and stamens, and are present in compact umbels. The bracts are linear, sometimes divided, and with asymmetrical rays. The fruits are darkish-brown. The fruits of *B. persicum* are sometimes confused with the fruits of *Carum carvi*, another plant from Apiaceae family. The fruits of Zireh Kermani, though, are hotter to the taste, darker in color, and longer in shape [2].

This plant is widely used as a spice and also used for various medicinal purposes in traditional and folkloric medicine of different countries [3,4]. Various compounds have been identified in Zireh Kermani. In addition, different pharmacological activities have been reported from this plant. The present review summarizes comprehensive information concerning traditional uses, phytochemistry, and pharmacological activities of Zireh Kermani.

Methodology

Databases including PubMed, Google Scholar, Scopus and Web of Science were searched for studies focusing on ethnomedicinal use, natural compounds and pharmacological activities of Zireh Kermani. Data were collected from 1980 to 2018 (up to December). The search terms were ‘‘Zireh Kermani’’ or ‘‘Kala zira’’ or ‘‘Zeera’’ or ‘‘*Bunium persicum*’’.

Ethnopharmacology

Bunium persicum had been used traditionally in Asian countries for various medicinal purposes including gastrointestinal (diarrhea, flatulence), respiratory tract (asthma, orthopnea,

Table 1: Ethnomedicinal uses of *Bunium persicum*

Region	Plant part(s) used	Ethnomedicinal uses	References
Iran	Aerial parts Fruits	Aerial parts: diuretic, digestive disorders, asthma, anticonvulsant, antihelmintic, antiflatulent, analgesic Fruits: stomach, liver and kidney tonic, appetizer, carminative, digestive disorders, antidiarrheal, diuretics, control colic pain and dysmenorrhea, urinary tract disorders, emmenagogue, anticonvulsant, antihelmintic, antiflatulent, analgesic, curing geophagy, hiccup, asphyxia, asthma, dyspnea, spleen edema, nasal bleeding, eye diseases, toothache	[4] [4,41,50,51]

India	Leaves	Leaves: curing abdominal pain	[5]
	Fruits	Fruits: stimulant, carminative, antidiarrheal, dyspepsia, stomachache, fever, cold, headache, flatulence, hemorrhoids, obstinate hiccup, tuberculosis, foul breath, joint pain, lumbago and weak memory, remedy for abdominal and colic pain	[5,53-57]
	Flower heads	Flower heads: carminative	[53]
Pakistan	Fruits	Fruits: carminative, stimulant, antidiarrheal, stomachache, lactagogue, antiseptic, vermifuge, curing indigestion, gastrointestinal disturbances and abdominal pain, heart problems, asthma, sterility, flatulence, cold and used as spice	[6,58-61]
Uzbekistan	Fruits	Stomach diseases and used as spice	[62]

dyspnea), and urinary tract disorders [4,5]. It is also considered as a potent analgesic and antiseptic agent in traditional medicine [5,6]. Table 1 shows the detailed ethnomedicinal uses of *B. persicum* in different countries.

Phytochemistry

Table 2 shows the structure and phytochemical category of compounds isolated from different parts of *B. persicum*.

Essential oil

The average range yield of essential oil of the dried fruits of the different population of *B. persicum* was 1.92-9.1% v/w. The most prominent compounds in *B. persicum* essential oil are hydrocarbon monoterpenes, oxygenated monoterpenes, sesquiterpenes and phenyl propenes. γ-terpinene (0.8-46.1%), cuminaldehyde (5.96-40.66%), α-terpinene-7-al (0.4-37.2%), caryophyllene (0.08-27.81%), γ-terpinene-7-al (8.3-26.91%), ρ-cymene (2.8-19.15%), limonene (0.5-15.7%), β-pinene (0.2-15.62%), cuminyl acetate (0.09-14.57%), α-terpinene (0.1-11.3%), camphor (1.75-10.43%), terpinolene (0.05-8.27%), cumin alcohol (0.21-7.4%), and 2-carene-10-al (2.69-6.92%) are major components of essential oil [7-25]. The variation in chemical composition of essential oil of *B. persicum* depends on several factors such as climatic, seasonal, and geographic conditions [11,26,27]. Figure 1 shows the structures of some main active compounds in essential oil of *B. persicum.*

Carbohydrates

Various groups of carbohydrates such as mono- and oligosaccharides, water-soluble polysaccharides, pectin substances, and hemicellulose have been detected in ethanolic extract of *B. persicum.* The mono- and oligosaccharides group contained glucose, fructose, mannitol, sucrose, and raffinose [28].

Fatty acids

Fatty acids including linoleic acid, octadeca

noic acid, palmitic acid, petroselinic acid and 8, 11, 14-eicosatrienoic acid were detected in *B. persicum* fruits [15,22,28].

Phenolic compounds

Different phenolic compounds including phenolic acids (caffeic acid, ρ-coumaric acid) and flavonoids (kaempferol) have been identified in methanolic extract of *B. persicum* [24].

Miscellaneous substances

Some major example of miscellaneous substances containing carboxylic acids (acetic acid, Oxalic acid), alcohols (acetylphenylcarbinol, 4-(2-butyl) phenol), ester (iso octyl phthalate) and miscellaneous silicates (silicic acid) have been found in essential oil of *B. persicum* [11,13,15,22].

Table 2: Phytochemical constituents of *Bunium persicum*

Compound	Chemical category	Part/extract	References
α-Bergamotene	Monoterpene hydrocarbon	Fruit/essential oil	[22]
trans-α-Bergamotene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
Camphene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
δ-2-Carene	Monoterpene hydrocarbon	Fruit/essential oil	[19]
δ-3-Carene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
α-Curcumene	Monoterpene hydrocarbon	Fruit/essential oil	[22]
ρ-Cymene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
σ-Cymene	Monoterpene hydrocarbon	Fruit/essential oil	[24]
Limonene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
ρ-Menth-3,8-diene	Monoterpene hydrocarbon	Fruit/essential oil	[14]
1,3,8-ρ-Menthatriene	Monoterpene hydrocarbon	Fruit/essential oil	[15]

Myrcene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
Myrcene-β	Monoterpene hydrocarbon	Fruit/essential oil	[18]
allo-Ocimene	Monoterpene hydrocarbon	Fruit/essential oil	[12]
(E)-β-Ocimene	Monoterpene hydrocarbon	Fruit/essential oil	[12]
(Z)-β-Ocimene	Monoterpene hydrocarbon	Fruit/essential oil	[18]
α-Pinene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
β-Pinene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
Sabinene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
iso Sylvestrene	Monoterpene hydrocarbon	Fruit/essential oil	[19]
α-Terpinene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
β-Terpinene	Monoterpene hydrocarbon	Fruit/essential oil	[7]
γ-Terpinene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
Terpinolene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
α-Terpinolene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
α-Thujene	Monoterpene hydrocarbon	Fruit/essential oil	[10]
2-Thujene	Monoterpene hydrocarbon	Fruit/essential oil	[16]

Borneol	Monoterpene alcohol	Fruit/essential oil	[16]
trans-3-Caren-2-ol	Monoterpene alcohol	Fruit/essential oil	[15]
trans-iso Carveol	Monoterpene alcohol	Fruit/essential oil	[18]
Carvacrol	Monoterpene alcohol	Fruit/essential oil	[16]
Citronellol	Monoterpene alcohol	Fruit/essential oil	[7]
Cumin alcohol	Monoterpene alcohol	Fruit/essential oil	[9]
meta-Cuminol	Monoterpene alcohol	Fruit/essential oil	[19]
ρ-Cymene-7-ol	Monoterpene alcohol	Fruit/essential oil	[18]
ρ-Cymene-8-ol	Monoterpene alcohol	Fruit/essential oil	[10]
iso Geraniol	Monoterpene alcohol	Fruit/essential oil	[15]
Limonene-1,2-diol	Monoterpene alcohol	Fruit/essential oil	[22]
Limonene-6-ol, pivalate	Monoterpene alcohol	Fruit/essential oil	[11]
Linalool	Monoterpene alcohol	Fruit/essential oil	[23]
ρ-Menth-2-en-7-ol	Monoterpene alcohol	Fruit/essential oil	[19]
ρ-Mentha-1,4-dien-7-ol	Monoterpene alcohol	Fruit/essential oil	[21]
cis-ρ-Menth-2,8-dien-ol	Monoterpene alcohol	Fruit/essential oil	[11]

trans-ρ-Menth-2-en-7-ol	Monoterpene alcohol	Fruit/essential oil	[19]
trans-o-Menth-2-en-7-ol	Monoterpene alcohol	Fruit/essential oil	[8]
Perillyl alcohol	Monoterpene alcohol	Fruit/essential oil	[7]
Sabinol	Monoterpene alcohol	Fruit/essential oil	[21]
cis-Sabinene hydrate	Monoterpene alcohol	Fruit/essential oil	[10]
trans-Sabinene hydrate	Monoterpene alcohol	Fruit/essential oil	[10]
Terpinen-4-ol	Monoterpene alcohol	Fruit/essential oil	[10]
α-Terpineol	Monoterpene alcohol	Fruit/essential oil	[10]
Thymol	Monoterpene alcohol	Fruit/essential oil	[19]
2-Carene-10-al	Monoterpene aldehyde	Fruit/essential oil	[16]
Citral	Monoterpene aldehyde	Fruit/essential oil	[7]
Cuminaldehyde	Monoterpene aldehyde	Fruit/essential oil	[10]
ρ-Menth-1-en-7-al	Monoterpene aldehyde	Fruit/essential oil	[10]
ρ-Menth-3-en-7-al	Monoterpene aldehyde	Fruit/essential oil	[1]
Perill aldehyde	Monoterpene aldehyde	Fruit/essential oil	[19]

α-Terpinene-7-al	Monoterpene aldehyde	Fruit/essential oil	[10]
γ-Terpinene-7-al	Monoterpene aldehyde	Fruit/essential oil	[10]
Caranone	Monoterpene ketone	Fruit/essential oil	[10]
Borneol acetate	monoterpene Oxygenated	Fruit/essential oil	[19]
iso Bornyl acetate	Oxygenated monoterpene	Fruit/essential oil	[17]
Camphor	Oxygenated monoterpene	Fruit/essential oil	[25]
3-Carene, 10-(acetylmeth-yl)	Oxygenated monoterpene	Fruit/essential oil	[11]
trans-Chrysanthenol	Oxygenated monoterpene	Fruit/essential oil	[17]
Citronellol acetate	Oxygenated monoterpene	Fruit/essential oil	[22]
Cuminyl acetate	Oxygenated monoterpene	Fruit/essential oil	[16]
1,8-Cineole	Oxygenated monoterpene	Fruit/essential oil	[10]
trans-Decalone	Oxygenated monoterpene	Fruit/essential oil	[13]
Geranyl acetate	Oxygenated monoterpene	Fruit/essential oil	[23]
Limonene epoxide	Oxygenated monoterpene	Fruit/essential oil	[22]
ρ-Menth-8-en-3-1, trans	Oxygenated monoterpene	Fruit/essential oil	[22]

E-Myroxide	Oxygenated monoterpene	Fruit/essential oil	[17]
iso Geraniol	Monoterpene alcohol	Fruit/essential oil	[15]
Limonene-1,2-diol	Monoterpene alcohol	Fruit/essential oil	[22]
Limonene-6-ol, pivalate	Monoterpene alcohol	Fruit/essential oil	[11]
Linalool	Monoterpene alcohol	Fruit/essential oil	[23]
ρ-Menth-2-en-7-ol	Monoterpene alcohol	Fruit/essential oil	[19]
ρ-Mentha-1,4-dien-7-ol	Monoterpene alcohol	Fruit/essential oil	[21]
cis-ρ-Menth-2,8-dien-ol	Monoterpene alcohol	Fruit/essential oil	[11]
trans-ρ-Menth-2-en-7-ol	Monoterpene alcohol	Fruit/essential oil	[19]
trans-o-Menth-2-en-7-ol	Monoterpene alcohol	Fruit/essential oil	[8]
Perillyl alcohol	Monoterpene alcohol	Fruit/essential oil	[7]
Sabinol	Monoterpene alcohol	Fruit/essential oil	[21]
cis-Sabinene hydrate	Monoterpene alcohol	Fruit/essential oil	[10]
Perillyl alcohol	Monoterpene alcohol	Fruit/essential oil	[7]
Sabinol	Monoterpene alcohol	Fruit/essential oil	[21]

cis-Sabinene hydrate	Monoterpene alcohol	Fruit/essential oil	[10]
trans-Sabinene hydrate	Monoterpene alcohol	Fruit/essential oil	[10]
Terpinen-4-ol	Monoterpene alcohol	Fruit/essential oil	[10]
α-Terpineol	Monoterpene alcohol	Fruit/essential oil	[10]
Thymol	Monoterpene alcohol	Fruit/essential oil	[19]
2-Carene-10-al	Monoterpene aldehyde	Fruit/essential oil	[16]
Citral	Monoterpene aldehyde	Fruit/essential oil	[7]
Cuminaldehyde	Monoterpene aldehyde	Fruit/essential oil	[10]
ρ-Menth-1-en-7-al	Monoterpene aldehyde	Fruit/essential oil	[10]
ρ-Menth-3-en-7-al	Monoterpene aldehyde	Fruit/essential oil	[1]
Perill aldehyde	Monoterpene aldehyde	Fruit/essential oil	[19]
α-Terpinene-7-al	Monoterpene aldehyde	Fruit/essential oil	[10]
γ-Terpinene-7-al	Monoterpene aldehyde	Fruit/essential oil	[10]
Caranone	Monoterpene ketone	Fruit/essential oil	[10]
Borneol acetate	monoterpene Oxygenated	Fruit/essential oil	[19]

iso Bornyl acetate	Oxygenated monoterpene	Fruit/essential oil	[17]
Camphor	Oxygenated monoterpene	Fruit/essential oil	[25]
3-Carene, 10-(acetylmeth-yl)	Oxygenated monoterpene	Fruit/essential oil	[11]
trans-Chrysanthenol	Oxygenated monoterpene	Fruit/essential oil	[17]
Citronellol acetate	Oxygenated monoterpene	Fruit/essential oil	[22]
Cuminyl acetate	Oxygenated monoterpene	Fruit/essential oil	[16]
1,8-Cineole	Oxygenated monoterpene	Fruit/essential oil	[10]
trans-Decalone	Oxygenated monoterpene	Fruit/essential oil	[13]
Geranyl acetate	Oxygenated monoterpene	Fruit/essential oil	[23]
Limonene epoxide	Oxygenated monoterpene	Fruit/essential oil	[22]
ρ-Menth-8-en-3-1, trans	Oxygenated monoterpene	Fruit/essential oil	[22]
E-Myroxide	Oxygenated monoterpene	Fruit/essential oil	[17]
Myrtenyl acetate	Oxygenated monoterpene	Fruit/essential oil	[17]
iso Pulegolacetate	Oxygenated monoterpene	Fruit/essential oil	[25]
Pinocarvyl acetate	Oxygenated monoterpene	Fruit/essential oil	[23]

cis-epoxy-Ocimene	Oxygenated monoterpene	Fruit/essential oil	[20]
Aromadendrene	Sesquiterpene hydrocarbon	Fruit/essential oil	[11]
Bourbonene	Sesquiterpene hydrocarbon	Fruit/essential oil	[10]
cis-α-Bisabolene	Sesquiterpene hydrocarbon	Fruit/essential oil	[10]
α-Bisabolene	Sesquiterpene hydrocarbon	Fruit/essential oil	[10]
β-Bisabolene	Sesquiterpene hydrocarbon	Fruit/essential oil	[11]
Caryophyllene	Sesquiterpene hydrocarbon	Fruit/essential oil	[23]
β-Caryophyllene	Sesquiterpene hydrocarbon	Fruit/essential oil	[10]
trans-Caryophyllene	Sesquiterpene hydrocarbon	Fruit/essential oil	[16]
9-epi-β-Caryophyllene	Sesquiterpene hydrocarbon	Fruit/essential oil	[19]
γ-Cadinene	Sesquiterpene hydrocarbon	Fruit/essential oil	[7]
α-Cedrene	Sesquiterpene hydrocarbon	Fruit/essential oil	[11]
ar-Curcumene	Sesquiterpene hydrocarbon	Fruit/essential oil	[10]
Copaene	Sesquiterpene hydrocarbon	Fruit/essential oil	[22]
β-Elemene	Sesquiterpene hydrocarbon	Fruit/essential oil	[10]

γ-Elemene	Sesquiterpene hydrocarbon	Fruit/essential oil	[23]
Elixene	Sesquiterpene hydrocarbon	Fruit/essential oil	[11]
E-β-Farnesene	Sesquiterpene hydrocarbon	Fruit/essential oil	[10]
E,E-α-Farnesene	Sesquiterpene hydrocarbon	Fruit/essential oil	[10]
(Z)-β-Farnesene	Sesquiterpene hydrocarbon	Fruit/essential oil	[11]
β-cis-Farnesene	Sesquiterpene hydrocarbon	Fruit/essential oil	[22]
β-Germacrene	Sesquiterpene hydrocarbon	Fruit/essential oil	[41]
Germacrene D	Sesquiterpene hydrocarbon	Fruit/essential oil	[10]
α-Humulene	Sesquiterpene hydrocarbon	Fruit/essential oil	[10]
γ-Muurolene	Sesquiterpene hydrocarbon	Fruit/essential oil	[10]
β-Sesquiphellandrene	Sesquiterpene hydrocarbon	Fruit/essential oil	[10]
α-Selinene	Sesquiterpene hydrocarbon	Fruit/essential oil	[23]
β-Selinene	Sesquiterpene hydrocarbon	Fruit/essential oil	[41]
α-Zingiberene	Sesquiterpene hydrocarbon	Fruit/essential oil	[10]
Cedr-8-en-13-ol	Sesquiterpene alcohol	Fruit/essential oil	[11]

Cedrol	Sesquiterpene alcohol	Fruit/essential oil	[22]
epi Globulol	Sesquiterpene alcohol	Fruit/essential oil	[11]
ent-Spathulenol	Sesquiterpene alcohol	Fruit/essential oil	[11]
Spathulenol	Sesquiterpene alcohol	Fruit/essential oil	[23]
β-Sinensal	Sesquiterpene aldehyde	Fruit/essential oil	[41]
Caryophyllene oxide	Oxygenated sesquiterpene	Fruit/essential oil	[10]
diepi-α-Cedrene epoxide	Oxygenated sesquiterpene	Fruit/essential oil	[11]
Nerolidol acetate	Oxygenated sesquiterpene	Fruit/essential oil	[11]
Anethole	Phenyl propene	Fruit/essential oil	[25]
Apiol	Phenyl propene	Fruit/essential oil	[22]
Caffeic acid	Phenyl propene	Fruit/methanol extract	[24]
ρ-Coumaric acid	Phenyl propene	Fruit/methanol extract	[24]
Croweacin	Phenyl propene	Fruit/essential oil	[23]
Dillapiole	Phenyl propene	Fruit/essential oil	[41]
Elemicin	Phenyl propene	Fruit/essential oil	[16]

Myristicin	Phenyl propene	Fruit/essential oil	[12]
Kaempferol	Flavonoid	Fruit/methanol extract	[24]
8,11,14-Eicosatrienoic acid	Fatty acid	Fruit/essential oil	[15]
Linoleic acid	Fatty acid	Fruit/essential oil	[22]
Octadecanoic acid	Fatty acid	Fruit/essential oil	[22]
Palmitic acid	Fatty acid	Fruit/essential oil	[15]
Petroselinic acid	Fatty acid	Fruit/essential oil	[28]
3-Cyclohex-1-enyl-1-methylprop-2-ynyl ester	Ester	Fruit/essential oil	[15]
iso Octyl phthalate	Ester	Fruit/essential oil	[11]
Cyclohexanone	Hydrocarbon	Fruit/essential oil	[20]
Acetylphenylcarbinol	Alcohol	Fruit/essential oil	[13]
9-t-Butyltricyclo [2.2.1.1(2,5)]decane-9,10-diol	Alcohol	Fruit/essential oil	[11]
α-Methyle-benzene methanol (1-Phenylethanol)	Alcohol	Fruit/essential oil	[41]
2-Methylenecholestan-3-ol	Alcohol	Fruit/essential oil	[11]
4-(2-Butyl)phenol	Alcohol	Fruit/essential oil	[22]

3-Methyl benzaldehyde	Aldehyde	Fruit/essential oil	[19]
Acetic acid	Carboxylic acid	Fruit/essential oil	[15]
Oxalic acid	Carboxylic acid	Fruit/essential oil	[15]
Cyclopentanone	Ketone	Fruit/essential oil	[13]
Silicic acid	Miscellaneous silicates	Fruit/essential oil	[13]
Pectin	Polysaccharide	Fruit/ethanol extract Root, steam/raw material	[28,63]
Hemicelluloses	Polysaccharide	Root, steam/raw material	[63]
Water-soluble-polysaccha-ride	Polysaccharide	Fruit/ethanol extract Root, steam/raw material	[28,63]
Arabinose	Monosaccharide	Fruit/ethanol extract Root, steam/raw material	[28,63]
Fructose	Monosaccharide	Fruit/ethanol extract	[28]
Galactose	Monosaccharide	Fruit/ethanol extract Root, steam/raw material	[28,63]
Glucose	Monosaccharide	Fruit/ethanol extract	[28]
Mannitol	Monosaccharide	Fruit/ethanol extract	[28]
Mannose	Monosaccharide	Fruit/ethanol extract Root, steam/raw material	[63]
Raffinose	Monosaccharide	Fruit/ethanol extract	[28]

Rhamnose	Monosaccharide	Fruit/ethanol extract Root, steam/raw material	[28,63]
Sucrose	Monosaccharide	Fruit/ethanol extract	[28]
Xylose	Monosaccharide	Fruit/ethanol extract Root, steam/raw material	[28, 63]

Biological and Pharmacological Activities

Table 3 lists the pharmacological activities of *B. persicum*.

In vitro Studies

Antioxidant Activity

Evaluation of antioxidant activity of *B. persicum* methanolic extract demonstrated the half maximal inhibitory concentration (IC50) of about 45.7 µg/ml [24]. Another report found that the methanolic extract from the fruits expressed significant antioxidant activity varied from 9.2 to 14.4 mg Trolox equivalents. Antioxidant activity of fruits was attributed to total flavonoids and total phenolics [10]. In regard to the essential oil of fruits, the IC50 was about 23.4 µg/ml, lower than the standard BHT (IC50 = 20.3µg/ml) [24]. The same observation demonstrated that the essential oil of fruits has an antioxidant activity (IC50 = 1.52 mg/ml) lower than TBHQ (IC50 = 0.002 mg/ml) and α-tocopherol (IC50 = 0.006mg/l) [29]. Furthermore, its essential oil showed remarkable radical scavenging (IC50 = 4.47 mg/mL) [18]. The oil showed significant anti-lipid peroxidation (IC50 (β-carotene bleaching) = 0.22 mg/mL) activities [18]. Another study has been reported that different extracts and essential oil obtained from the fruits of *B. persicum,* showed antioxidant effects in the β-carotene and ammonium thiocyanate test, with the most pronounced activity of the essential oil (26.2 mm, 93.5% inhibition) and methanolic extract (18.7 mm, 88.0% inhibition), which was comparable to the standard BHT (30.4 mm, 99.0% inhibition). Presence of γ- terpinene and phenolic compounds in essential oil and methanolic extract seems to be responsible for their antioxidant activity respectively [24]. Essential oil of fruits demonstrated antioxidant activities (IC50 = 7.5 mg/ml, 0.716 ppm) in ABTS°+ free radical decolourization assay and hydrogen peroxide scavenging activity test, even though lower than TBHQ (IC50 = 130.9 mg/ml, 0.04ppm). The antioxidant activity has been attributed to phenolic compounds [29]. Additionally, the methanolic extracts of the fruits displayed a moderate antioxidant activity. Antioxidant activity varied from 6.1 to 10.9 mg/g in the Fe-reduction test. In the correlation analysis total flavonoids and total phenolics were well correlated with Fe-reduction ($r = 0.96$ and $r = 0.68$, $p = 0.029$, $p < 0.001$). In general, the essential oil of fruits indicat-

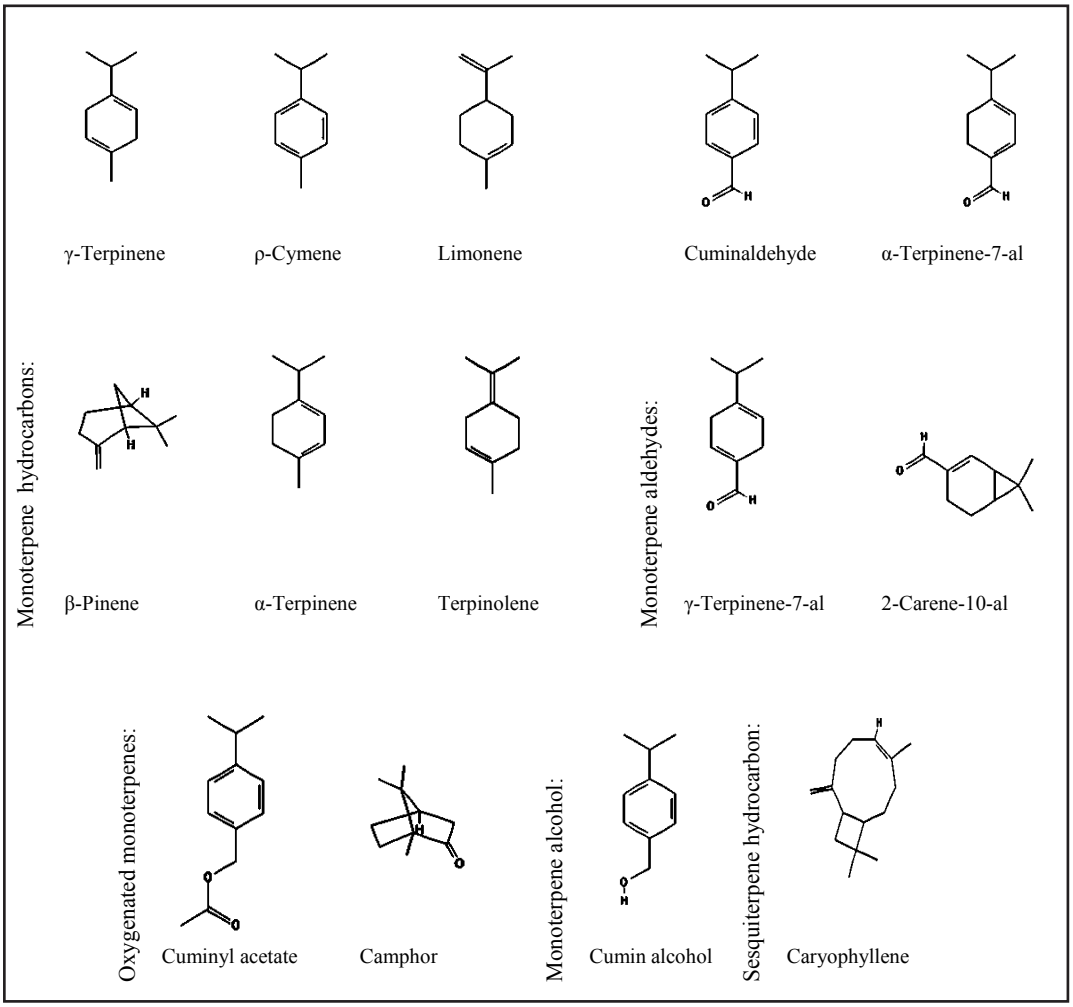

Figure 1. The structure of some main active compounds in essential oil of *B. persicum*

ed higher activity than solvent extracts from the fruits [24]. Altogether, *B. persicum* fruits appear to display low to moderate antioxidant potential [30].

Antidiabetic Activity

Aqueous and hydro-alcoholic extracts from *B. persicum* fruits in low concentrations (0.05, 0.1mg/ml) were able to significantly increase insulin secretion from the isolated Langerhans of the mice. This effect was similar to the effect of glyburide 1 μM on the secretion of insulin in glucose 2.8 mM medium as well as glyburide 10 μM in glucose16.7 mM medium. Another study indicated that the methanolic, ethyl acetate and n-hexane extracts from *B. persicum* fruits showed significant inhibitory effect on α-amylase activity (range of 40–72.3% of inhibition at 250 μg/mL) [31].

Antispasmodic Activity

The effect of 0.1 to 1000 μg/ml essential oil of *B. persicum* on ruminal and abomasal smooth muscle of twenty-four healthy sheep and ileum preparations of six rats has been evaluated in vitro. Results revealed that the essential

oil profoundly alters gastrointestinal smooth muscle contraction in a dose-dependent and tissue-specific manner. This effect may be due to spasmogenic and spasmolytic components such as pinene, cuminaldehyde, thymol, camphor, and γ-terpinene [15].

Antityrosinase Activity

IC50 rate of hydro-alcoholic and methanol extracts of *B. persicum* was determined by dopachrome method with L-DOPA assay. IC50 value of hydro-alcoholic and methanolic extracts of *B. persicum* was found 0.38 and 1.14 mg/mL respectively. This result may be attributed to some components of *B. persicum* essential oil like cuminaldehyde, kaempferol, caffeic acid and ρ-coumaric acid [32,33]. They could bind to free enzyme and enzyme-substrate complex and reduced the affinity of substrate for the mushroom tyrosinase [33].

Antimicrobial Activity

In vitro antibacterial investigation of the essential oil of *B. persicum* showed high sensitivity of gram-positive bacteria such as *Listeria monocytogenes* [34]. Staphylococcus aureus and Bacillus cereus and relative sensitivity of gram-negative bacteria including Escherichia coli and *Salmonella typhimurium*. Monoterpenes such as cuminaldehyde are principal components of *B. persicum* essential oil that have been claimed to be responsible for antimicrobial activity [11,35]. Moreover, *B. persicum* extracts showed significant inhibitory activity against various pathogenic bacteria including *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Helicobacter pylori* and also against pathogenic fungus, Candida albicans [36,37]. Amber et al., assessed antibacterial activity of *B. persicum* at concentration of 50 mg/ml against *Staphylococcus aureus, Escherichia coli* and *Klebsiella pneumoniae* by agar well diffusion method. They showed that among alkaloids, Flavonoids, and Saponins of plant, alkaloids produced significantly high inhibition zones against bacteria. The minimum inhibitory concentration and minimum bactericidal concentration of phytochemicals and crude methanolic extracts against tested bacterial strains ranged between 12.5–50 mg/ml and 25–50 mg/ml, respectively [38].

Larvicidal Activity

Larvicidal activity of essential oil, extracts and fractions of *B. persicum* fruits against malaria vector *Anopheles stephensi* was assessed by Vatandoost et al., essential oil, total extract, petroleum ether fraction and methanol fraction of *B. persicum* showed remarkable potency against *An. stephensi* larvae [39].

scolicidal effect

Mahmoudvand et al., assessed scolicidal effect of *B. persicum*, for this purpose, protoscoleces were aseptically aspirated from sheep livers having hydatid cysts. Various concentrations of the essential oil (3.125-50 mcL/mL) were used for 5-30 min. The viability of protoscoleces was confirmed using the eosin exclusion test (0.1% eosin staining). The *B. persicum* essential oil at the concentrations of 25 and 50 mcL/mL after 5 min of exposure killed 100% protoscoleces. The mean mortality rate of protoscoleces af-

ter 10 min of exposure to the concentration of 12.5 mcL/mL was 100% [40].

In vivo Studies

Analgesic Activity

Analgesic activity of essential oil of *B. persicum* fruits has been evaluated by using an acetic acid-induced writhing test. According to the results, the essential oil of *B. persicum* (0.001, 0.01, 0.05, 0.1, 0.5, and 1%) elicited antinociceptive effects dose-dependently. In addition, the analgesic activity of *B. persicum* was significantly attenuated by pre-treatment with cimetidine, naloxone and chlorpheniramine. These results have suggested that *B. persicum* induced analgesia is mediated via opioidergic and histamine H1 and H2 receptors [41]. In a similar study, hydro-alcoholic extract (400 and 800 mg/kg, i.p.) and essential oil (100 - 400 µl/kg, p.o.) of fruits significantly reduced acetic acid-induced pain in writhing test. They also significantly reduced the pain response of both early and late phases in the formalin test [4]. Flavonoids, polyphenolic components and terpenoid compounds such as ρ-cymene, γ-terpinene and terpenoid oxide are responsible for this activity [4,41].

Anti-inflammatory Activity

The anti-inflammatory activity of *B. persicum* fruits was evaluated by the carrageenan-induced paw edema and croton oil-induced ear edema tests in rats. The results indicated that hydro-alcoholic extract (200-800 mg/kg, i.p) and essential oil (100-400 µl/kg, i.p) displayed considerable anti-inflammatory response. Flavonoids and polyphenolic compounds in essential oil and hydro-alcoholic extract inhibited histamine release from mast cells, and led to anti-inflammatory effects [4].

Anticonvulsant Activity

The methanolic extract and essential oil of *B. persicum* were tested for anti-convulsant effect. The essential oil and methanolic extract prolonged the onset of clonic and tonic seizures in Pentylenetetrazole (PTZ) test. The essential oil at dose of 1 mL/kg and higher doses inhibited the tonic seizures in both tests. The methanolic extract prevented PTZ-convulsions at dose of 3 g/kg and was ineffective against maximal electroshock (MES) induced convulsion. This activity might be due to its monoterpene content [42].

Antihyperlipidemic Activity

A study on forty male hypercholesterolemic mice demonstrated that administration of 6-week endurance training accompanied by *B. persicum* extract significantly increased cardiorespiratory capacity and HDL level. Moreover, total cholesterol, LDL and TG concentrations were significantly reduced, but body weight changes were not significant between different groups [43].

Antihistamine Activity

For antihistamine activity estimation of aqueous and macerated extracts and essential oil, 20 nM chlorpheniramine, and saline were evaluated by performing the cumulative log concentration-response curves of histamine

induced contraction of isolated guinea pig Tracheal chains. It has shown improvement in maximum response and EC50 (effective concentration of histamine causing 50% of maximum response). The results indicated that *B. persicum* showed competitive antagonistic effect on histamine H_1 receptors, inhibitory effect on muscarinic receptors, and stimulated the β-adrenergic receptors [44].

Antidiarrheal Activity

The antidiarrheal activity of *B. persicum* essential oil (20-80 mg/kg) on upper gastrointestinal transit and on castor oil-induced diarrhea was investigated in rats. As a result, the essential oil from *B. persicum* (20 and 80 mg/kg) fruits reduced diarrheal parameters dose-dependently and significantly protected rats against castor oil-induced diarrhea. The maximal effect of the essential oil was similar to loperamide [45].

Antiulcerogenic Activity

Treatment of ethanol and indomethacin induced ulcer with *B. percicum* essential oil at the doses of 40 and 80mg/kg/bw in wistar rats significantly prevented gastric ulcers. This activity can be related to terpenoids and flavonoids [46].

Antihematoxic Activity

This activity was estimated by measuring reactive oxygen species (ROS) level and hematological parameters in blast cells from the tibia and femur in rats. The methanolic extract of *B. persicum* showed significant decrease in ROS level (300 mg/kg/d ethyl acetate fraction in 0.5 mL Tween) and blast cells count (300 mg/kg/d butanol and ethyl acetate fractions in 0.5 mL Tween) [47].

Antimicrobial Activity

The study of *B. persicum* on *Listeria monocytogenes* in a fish model system for 12 days at 4C° exhibited strong inhibitory activity against *L. monocytogenes* [20].

Anticandidiasis

A randomized, triple blind clinical trial study was carried out on 90 non-pregnant women infected with *Candida vulvovaginitis*, who received the capsule made from *B. persicum* fruits for 7 days. The obtained results showed that all signs and symptoms of vaginal candidiasis reduced significantly 4 days after beginning of treatment and 7 days after completion of treatment. The reduction in soreness and vulva irritation was more significant than the other symptoms. These effects were attributed to cuminaldehyde [48].

Gastrointestinal protection

A randomized, double blind, crossover clinical trial study was carried out on 93 patients with breast cancer and refractory chemotherapy induced nausea and vomiting, who received outpatient high emetogenic chemotherapy, the patients received Persumac (semi-ground of *B. persicum* fruits mixed with *Rhus Coriaria*) for 7 days. They showed that Persumac had significant effect in decrease of frequency and severity of nausea and vomiting [49].

Table 3: Pharmacological activities of Bunium persicum

Pharmacological activity	Plant part	Plant extract / Active compound	Reference
Antioxidant *-in vitro*	Fruit	Methanol extract / Flavonoids, phenolic compounds	[10]
		Essential oil, petroleum ether, chloroform, methanol and aqueous extracts / γ- Terpinene and phenolic compounds	[18,24,41]
		Ethanol extract / Flavonoids	[30]
Antidiabetic *-in vitro*	Fruit	Methanol, ethyl acetate and n-hexane extracts	[31]
		Aqueous and hydro-alcohol extracts / Flavonoids, limonene and cuminaldehyde	[64]
Antispasmodic *-in vitro*	Fruit	Essential oil / Pinene, cuminaldehyde ,thymol, camphor and γ-terpinene	[15]
Antityrosinase *-in vitro*	Fruit	Hydro-alcohol extract / Cuminaldehyde, kaempferol, caffeic acid and ρ-coumaric acid	[33]
Acetylcholinesterase inhibitory *-in vitro*	Fruit	Methanol extract	[65]
AntiHMG-CoA reductase *-in vitro*	Fruit	Methanol extract	[66]
Antipancreatic lipase *-in vitro*	Fruit	Methanol extract	[67]
Anticancer *-in vitro*	Fruit	Methanol and aqueous extracts	[68]
Antimicrobial *-in vitro*	Fruit	Essential oil / Cuminaldehyde	[11]
Analgesic *-in vivo*	Fruit	Essential oil / Terpenoid components (ρ-cymene, γ-terpinene and terpenoid oxide)	[41]
		Hydro-alcohol extract and essential oil / Flavonoids, polyphenolic compounds, ρ-cymene	[64]
Anti-inflammatory *-in vivo*	Fruit	Hydro-alcohol extract and essential oil / Flavonoids, polyphenolic compounds, γ-terpinene	[4]
Anticonvulsant *-in vivo*	Fruit	Methanol extract / Monoterpenes	[42]
Antihyperlipidemic *-in vivo*	Fruit	Aqueous extract	[43]
Antihistamine *-in vivo*	Fruit	Aqueous, macerated extracts essential oil	[44]
Antidiarrheal *-in vivo*	Fruit	Essential oil	[45]
Antiulcer genic *-in vivo*	Fruit	Essential oil / Terpeneoids, flavonoids	[46]

Anti hematoxic -in vivo		Methanol extract / Terpenoids, phenolic compounds and alkaloids	[47]
Antimicrobial -in vivo		Essential oil / γ-Terpinene and ρ-cymene	[20]
Antimicrobial -Clinical trial		Capsule / Cuminaldehyde	[48]

Toxicity

The fruits and essential oil of *B. persicum* have numerous usages in Iranian diet and no toxicity has been reported from this plant [18,40]. However, traditional medicine literatures have reported yellowish staining of skin and weight loss after sustainable consumption of fruits. Emmenagogue properties of *B. persicum* should be concerned during pregnancy [50,51]. Acute toxicity study showed that essential oil of *B. persicum* had a wide margin of safety in rat and its LD50 was 375 mg/kg/bw [46].

Discussion

The present review summarized the ethnomedical uses, phytochemical, pharmacological, and toxicological aspects of *B. persicum*. The result demonstrated the traditional and ethnomedicinal use of different parts of this plant for a wide variety of diseases including neurological illness, gastrointestinal disorders, respiratory disease, heart dysfunction, microbial problems, as well as urinary tract disease. Pharmacological studies have focused on the fruits of this plant and proved that the different extracts and the isolated compounds from *B. persicum* possess various biological activities including antioxidant, analgesic, anti-inflammatory, neuroprotective, cardioprotective, antidiabetic, antihistamine, gastroprotective, antihematoxic and antimicrobial activities. Ethnomedicinal use of *B. persicum* in gastrointestinal disorders can be related to its antioxidant, analgesic, anti-inflammatory, antidiarrheal, antispasmodic and antiulcer activities. Efficacious folkloric uses of *B. persicum* in cardiac disease may be confirmed by its antioxidant, anti-inflammatory, antihyperlipidemic and antiHMG-CoA reductase activities. Beneficial effects of *B. persicum* in respiratory disease, tuberculosis and cold can be due to its antioxidant, anti-inflammatory, antispasmodic, antihistamine and antimicrobial activities. Useful effect on neurological problems may be related to its antioxidant, analgesic, acetylcholinesterase inhibitory and anticonvulsant activities. Useful effects of *B. persicum* on diabetes can be confirmed by antioxidant, hypoglycemic, antihyperlipidemic, α-amylase inhibitory and enhancement insulin secretion activities. On the other hand, the anti-glycation potential of polyphenol-rich plant extracts has been shown previously and *B. persicum* has been demonstrated to possess a high level of polyphenols; so, *B. persicum* hydroalcoholic extract have good effect on diabetic disease [52]. Moreover, the abortive property might be due to estrogenic and uterine tonic activities.

Regarding the chemical components contribut-

ed to medicinal properties, it can be concluded that monoterpenes, sesquiterpenes and phenylpropenes contribute to the majority of pharmacological activities of *B. persicum*. Phenolic compounds such as caffeic acid and ρ-coumaric acid are responsible for anti-oxidant and antityrosinase activities; flavonoids for anti-oxidant, anti-diabetic, analgesic, anti-inflammatory and antiulcergenic activities; terpenoides such as ρ-cymene and γ-terpinene for analgesic, anti-inflammatory and anti-microbial; cuminaldehyde for anti-diabetic, antispasmodic, antityrosinase, antimicrobial; and finally alkaloids for anti-hemotoxic effect. Plenty of ethnomedicinal uses and pharmacological activities have been only confirmed by in vitro experiments which might not accurately indicate the beneficial therapeutic effects on animal models and human studies. Thus, appropriate animal models and clinical studies are needed to evaluate the efficacy of Bunium persicum and to support ethnomedicinal uses of this plant.

Toxicological studies of *B. persicum* were limited. Acute and chronic toxicological studies in animal and human models are required for recognizing eligible safety properties for all parts of this plant. However, the fruit of *B. persicum* is almost safe through oral route and no toxicity has been reported from this plant. Cautiously, the fruits should not be used by pregnant woman because of their emmenagogue properties emphasized in traditional medicine and estrogenic and uterine tonic activities confirmed by current studies. In addition, traditional medicine books mentioned, that chronic consumption of this plant causes a yellowish staining of the skin and weight loss.

Various bioactive compounds have been isolated and identified in *B. persicum*, whereas many active compounds responsible for ethnomedicinal uses or proved pharmacological activities have not been completely evaluated. Therefore, new studies are proposed to isolate and identify *B. persicum* active compounds in order to explore novel natural component for rectifying the stalemate on the way of modern medicine.

Conflict of interest

The Authors declares that they have no conflicts of interest to disclose.

Acknowledgment

None.

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