A Review on Phytochemistry and Pharmacology of *Otostegia persica* (Burm.f.) Boiss.

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Abstract

Iran has a great wealth of various naturally occurring medicinal plants which have great potential pharmacological activities. *Otostegia persica* (Burm.f.) Boiss. is one of these plants which is a perennial shrub found in South and Southeast of Iran. The aerial parts of *O. persica* have been used in Iranian traditional medicine to treat various types of diseases (e.g., inflammatoryand pain-mediated diseases, malaria and diabetes). Research carried out using different in vivo and in vitro assays of biological evaluation support most of these claims. The active pharmacological components of *O. persica* most studied are flavonoids and terpenoids. This paper presents the traditional uses, botany, phytochemistry, and pharmacology of this medicinal plant. This is the first article reported in this review form about *O. persica* which might be helpful for scientists and researchers to find out new in modern health concept.

Keywords: ***Otostegia persica*, Lamiaceae, Pharmacology, Phytochemistry**

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Introduction

In view of the impact of medicinal plants on human fitness, there has been an upsurge in interest for phytochemical and phytopharmacology investigations to discover novel pharmacologically active drugs and fine chemical substances from plants. Exploration of the chemical compounds of the plants and pharmacological screening may provide us the basis for developing the leads for development of novel agents [1]. Additionally, medicinal plants have provided us some of the very important lifesaving drugs used in the armamentarium of modern medicine. It is estimated that close to 25% of the active compounds in currently prescribed synthetic drugs were first identified in natural sources especially in plant [2]. However among the estimated 250,000-400,000 plant species, only 6% have been studied for biological activity and about 15% have been investigated phytochemically. This shows a need for planned activity guided phytopharmacological evaluation of herbal drugs [3].

Commonly known to the Persians as Golder, *Otostegia persica* (Burm.f.) Boiss. [Syn: *Ballotapersica* (Burm.f.) Benth], is a flowering plant which belongs to Lamiaceae family in the order of Lamiales that contains about 180 genera and over 3500 species [4]. The genus *Otostegia* comprises of about 20 species which are generally shrubs and subshrubs glabrous or pubescent with simple hair and having two distinct areas of concentration, one in the regions of Asia particularly areas of Iran, Pakistan, Afghanistan and the other in the mountains of East Africa [5]. *O. persica* is the only species of this genus that is endemic to Iran, Pakistan and Afghanistan [6]. *O. persica* grows in south parts of Iran in Fars province between Shiraz and Jahrum, also in south east regions mainly in Sistaan and Baluchestan [7] and has been locally known as “Gol-e-kharu” in Iran [8].

O. persica is a shrub with 1-2 m high. Stems are covered with a dense glandular, short indumentums. Leaves are suborbicular-obovate, cuneate and 12 × 12 mm, with a prominent indumentums of glandular hairs and numerous sessile oil globules, crenate to dentate with 0.5-1 mm spines. Petiole up to 10 mm. Spines up to 20 mm present in axils of lower and upper leaves. Verticillasters include few-flowered and remote. Bracts are spiny, 10 mm long, horizontally spreading. Calyx densely pilose, clearly 10-nerved or ribbed; tube 8 mm long; limb spreading 10mm in diameter, straw-colored, membranous, irregularly lobed and toothed. Corolla is whitish, 20 mm long; tube length of calyx tube; upper lip 10 mm falcate, densely villous. Stamens included or exerted. Nutlets are obovoid, 2-5 mm, rounded at apex with oil globules often only one maturing [7].

The aerial parts of *O. persica*, in particular, have been used traditionally as herbal medicine in Iranian, Asian and Arabic folklores as a remedy for various ailments since ancient times [8, 9, 10].

A number of chemical constituents such as volatile substances, terpenoids and flavonoids have been isolated from the plant [4].

From current pharmaceutical studies, additional pharmaceutical applications of

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O. persica have revealed antibacterial, antioxidant, antiplasmodial, antidiabetic, antiglycation and cytotoxic effects among others [4, 8, 9, 10, 11].

Since no review on chemistry, pharmacology and clinical properties of *O. persica* have not been reported, we prompted to provide the currently available information on traditional and local knowledge, ethno biological and ethno medicinal issues, identification of pharmacologically important molecules and pharmacological studies on this useful plant. The present review is to introduce *O. persica* as a medicinal plant by highlighting its traditional applications as well as the recent findings for pharmacological and clinical applications. The data presented in this paper were collected using all scientific data come from encyclopedia, articles, books, journals and websites such as Pubmed, Scopus and Google Scholar from 2003 to 2011.

Ethnomedicinal/Traditional Uses

The flowers of *O. persica* are widely used as an additive to yoghurt, buttermilk and meat [12]. The aerial parts of this plant have also been used in Iranian traditional medicines as analgesic in toothache and arthritis [12]. *O. persica* is traditionally used to alleviate opium withdrawal syndrome In Iran, Sistan-Baluchestan province [13]. There is also a traditional usage in some regions of Iran, especially in Sistan-Baluchestan and Kerman where there is a strong belief in the anti-diabetic effects of *O. persica* [11]. For a long time, the decoction of the aerial parts of the plant has been used as antispasmodic, antihistaminic, antimalaria and anti-arthritis [8].

Phytochemical Contents

Of all parts of the plant, the flowering aerial parts have been the subject of extensive chemical investigations because of its high medicinal values. Various reports have been published regarding the phytochemical content of the aerial parts. Attempts to isolate and identify bioactive compounds from the plant had started since 2003 with the identification of maureen and quercetin as the main flavonoids of this plant [14]. This was followed by Ayatollahiet al. [8] in identifying a flavonoid derivative (3´, 7-dihydroxy-4´,6,8-trimethoxy-flavone) and Ayatollahiet al. [4] in reporting the presence of ceryl alcohol, hentriacontane, caffeic acid, ρ-hydroxybenzoic acid, β-sitosterol, β-sitosterol acetate, β-amyrin, campesterol and stigmasterol.

Dillapiole (43.1%), trans-verbenol (9.6%) and hexadecanoic acid (5.7%) were identified as the major constituents of *O. persica* aerial parts essential oil [15] while the main compounds of the essential oil of the flowers were α-pinene (17.2%), 1-octen, 3-ol (13.4%) and cubenol (7.3%). Diisooctyl phthalate (45%) and hexadecanoic acid (11.1%) were the major constituents of the essential oil of the fruits [9].

Ayatollahiet al. [16] have isolated four diterpenoids belonging to the clerodane and tetracyclic type diterpenes from the flowering aerial parts of this plant.

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Pharmacological Properties

Various studies have revealed the different pharmacological potentials of *O. persica* in a range of in vitro and in vivo test models. The aerial parts of the plant, in particular, has been demonstrated to possess antibacterial, antifungal, antioxidant, antiglycation, antihyperglycemic, anti-Alzheimer and antiplasmodial activities at different doses/concentrations. These have been described in greater detail in the following subsections.

Antibacterial Activity

Hexan, chloroform and methanol extracts of *O. persica* have been found to possess good antibacterial activity against gram positive bacterial strains including *Listeria monocytogens, Enterococcus fecalis, Staphylococcus aureus*, and *Staphylococcus epidermidis* with MIC values from 0.62 to 20 mg/ml. The MBC values were identical, two, four or eight times higher than MIC values for the corresponding MIC for extracts. The gram negative strains; *Escherichia coli, Pseudomonas aeruginosa, Salmonella spp., Klebsiella spp*. and *Proteusspp*. were not inhibited by *O. persica* different extracts [17].

Antimalaria Activity

O. persica is usually employed as an antipyretic traditional remedy in malarious south and southeastern areas of Iran. It has been shown that 450 mg/kg concentration of *O. persica*ethanolic extract significantly decreased *Plasmodium berghei* parasitaemia in the infected mice [10].

Combination therapy in malaria is considerably recommended both in drug-sensitive and drug-resistant infections [18]. Indeed, although combination therapy could not interrupt establishment of drug resistance in malaria parasites, could considerably delay extension of the phenomenon. It is shown that *O. persica* potentiated the effectiveness of chloroquine against chloroquinesensitive strain of *P. berghei* but not on chloroquine-resistant *P. berghei*. Combination between chloroquine (CQ) and *O. persica* (Op) demonstrated marked potentiating effects on chloroquine-sensitive strain in ratios of 70% CQ + 30% Op, 50% CQ + 50% Op, 30% CQ + 70% Op. Additive effects were seen in combination between chloroquine and *O. persica* against chloroquine-resistant strain in 90% CQ + 10% Op, 70% CQ + 30% Op, 50% CQ + 50% Op and 30% CQ + 70% Op ratios, but an antagonism was detected in ratio of 10% CQ + 90% Op. The results showed that average survival time of the five mice infected with chloroquine-sensitive parasites after treating with combined doses of 70% CQ + 30% Op, 50% CQ + 50% Op and 30% CQ + 70% Op ratios with 20.4, 21.2 and 21 days respectively was longer than those treated mice infected with chloroquine-resistant strain. Potentiating the effect of chloroquine by *O. persica* in combination form against chloroquine-sensitive *P. berghei* implies that the drugs may share the similar mechanisms of action on the parasites [19].

Antioxidant Properties

Antioxidants are of interest to biologists and clinicians because they help to protect the human body against damages induced by

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reactive free radicals generated in atherosclerosis, ischemic heart disease, cancer, Alzheimer's disease, Parkinson's disease and even in aging process [20, 21]. There are many evidences that natural products and their derivatives have efficient anti-oxidative characteristics, consequently linked to anti-cancer, anti-aging and anti-inflammatory activities [20, 22, 23, 24].

Anti-oxidative capacities of *O. persica* were evaluated by using test systems namely DPPH free-radical scavenging, beta-carotene bleaching and lipid peroxidation [9, 14].

In DPPH radical-scavenging activity assay, the IC_{50} value of the flower oil was 19.88 µg/ml which was almost similar to BHA and ascorbic acid (15.2 and 17.4) respectively. IC_{50} value was determined equal as 29.2 µg/ml for fruits essential oil [9]. In the ammonium thiocyanate system, the inhibition rate of oxidative of linoleic acid was estimated 93.5 for the flowers oil while it was estimated 63.0 for the fruits oil. The higher activity of the flowers oil may be attributed to its high content of monoterpenes, especially oxygenated ones [9].

In an interesting study in Iran, antioxidant activity of hexane, chloroform and methanolic extracts of *O. persica* were evaluated according to the beta-carotene bleaching method [25, 26]. The methanolic extract of *O. persica* exhibited orange band while the other fractions had no color bands. Two flavonoids, maureen and quercetin established to be responsible for antioxidant activity of methanolic fraction of *O. persica* [14].

Antidiabetic Effects

Recently, the consumption of natural anti-diabetes agents that occur in some higher plants and in different parts of them, have risen up regarding the side effects of synthetic ones. Anti-diabetic properties of *O. persica* have been confirmed in several invitro and invivo studies [8, 11, 27]. Anti-diabetic activity of the alcoholic extract of *O. persica* was investigated on streptozotocin diabetic rats. Animals received a daily oral dose of *O. persica* extract at 200, 350, and 500 mg/kg, respectively, for 3 weeks. The extract produced a dose-dependent decrease in the blood glucose level especially in the group which received 500 mg/kg. These results indicate that *O. persica* has a strong anti-diabetic action and can decrease blood glucose levels [11].

Treatment of diabetic rats with *O. persica* extract (100, 200 and 300 mg/kg) for 6 and 14 days and at 300 mg/kg for 3 days also significantly decreased glucose serum levels. The extract at different doses for 3, 6 and 14 days significantly decreased cholesterol and triglycerides serum levels. Extract was more effective than glibenclamide in reducing glucose and triglycerides serum levels in diabetes [27].

Agents with antioxidative or metal-chelating property may retard the process of AGEs (Advanced Glycation End products) formation by preventing further oxidation of Amadori product and metal-catalyzed glucose oxidation [28]. It was observed that 3´,7-dihydroxy-4´,6,8-trimethoxy-flavone (Figure

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1), a flavonoid isolated from the aerial parts of *O. persica* could 65% inhibit the glycation process at 3 mM concentration while the standard inhibitor, Rutin showed 83% inhibition [8].

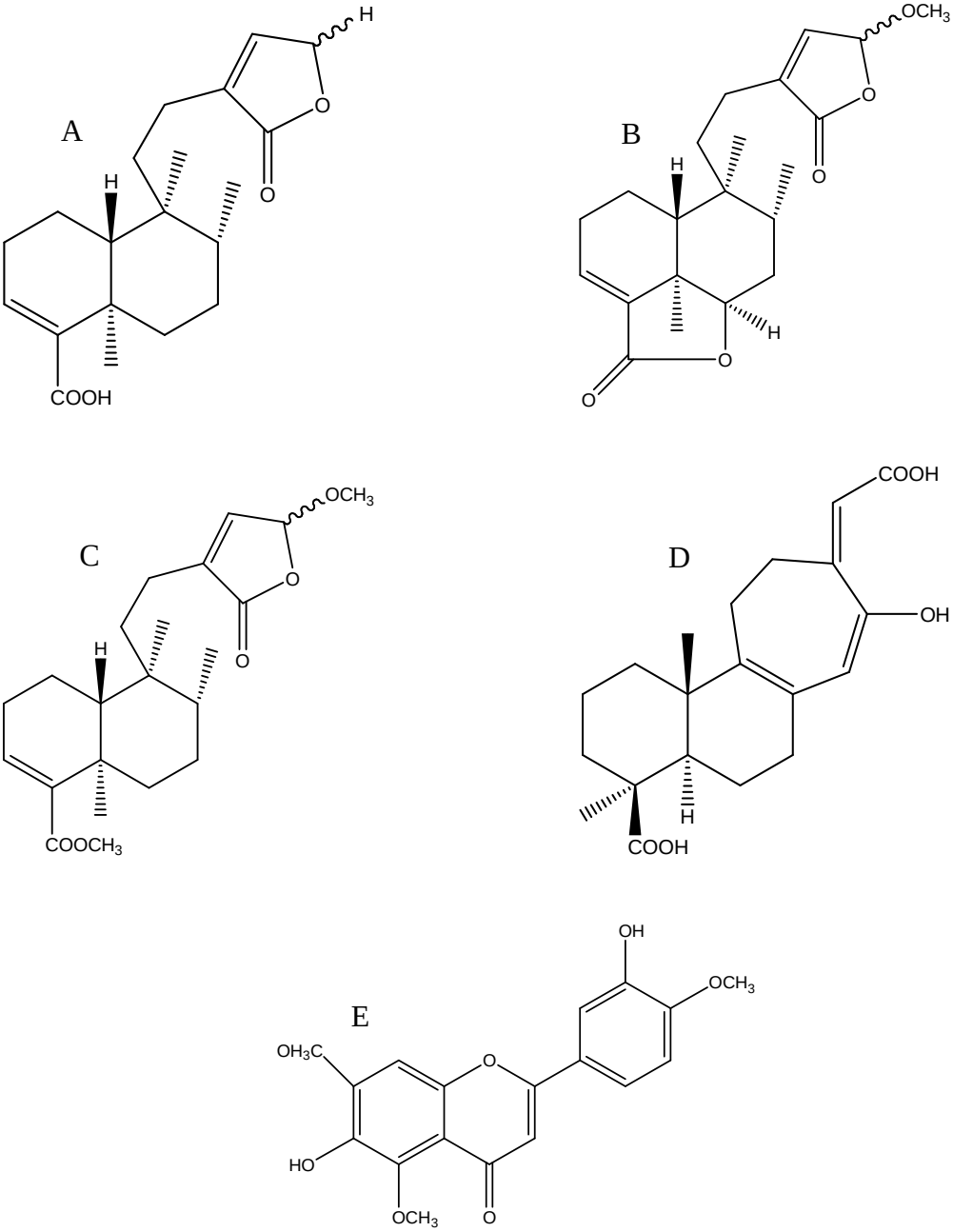

Figure 1- Structures of diterpenoids belonging to the clerodane and tetracyclic diterpene types (A, B, C and D) and a flavonoid (E) from *O. persica.* A (Limbatenolide A), B (Limbatenolide B), C (Limbatenolide B methyl ester), D (Limbatenolide C) and E (Eupatorin) [8, 16].

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Newly, anti-diabetic effects of aqueous extract of *O. persica* (400 mg/kg) on the blood glucose, insulin and histopathology of pancreas of streptozotocin (STZ) induced diabetic rats were evaluated [29]. It was found that this extract has preventive effect on loss of the β- cells and regulates the serum lipids and sugars in diabetic animals by reducing insulin resistance, serum glucose concentration and improving insulin functions [29].

Maureen, quercetin, camphorol, and isovitexin, the flavonoids present in *O. persica*, have strong antioxidant activity which is related to increasing of insulin absorption, glucose uptake andglycation inhibition [28, 30]. These compounds especially quercetine are capable of normalizing glucose levels in alloxan diabetic rats and increasing the liver glycogen levels. Also, studies have shown that quercetin can reduce hepatic output through its effects on the hepatic gluconeogenesis and glycogen breakdown [31].

One of the anti-diabetics effects of herbal plants is increasing the size and number of pancreatic β- cells and restoration of these cells [32]. Quercetin protects pancreatic tissue from abnormal compression of Langerhans islets, degeneration, degranulation and necrotic changes caused by STZ injuries [33]. After 30 days of *O. persica* treatment, pancreases were returned to the normal state [29].

Effects on Morphine Withdrawal Syndrome

O. persica is traditionally used to alleviate opium withdrawal syndrome In Iran, Sistan-Baluchestan province. This activity has been confirmed by Hajhashemi et al [13]. It was indicated that both oral and i.p. administration of the hydroalcoholic extract of *O. persica* reduced the number of jumping episodes in a dose dependent manner. Oral doses of 500, 1000 and 1500mg/kg of hydroalcoholic extract produced 18, 45 and 89% reduction of jumps, respectively. i.p. injection of the same doses decreased the number of jumps by 58, 82 and 91% respectively. Oral and i.p. administration of hydroalcoholic extract also significantly reduced the number of rearing. The effects of the high dose of hydroalcoholic extract on these signs were comparable to those of the standard drug, clonidine. Diarrhea, piloerection, ptosis and tremor were also suppressed by clonidine and the hydroalcoholic extract. Flavonoids found in the plant may have some role in observed pharmacological effects [13].

Anti-Alzheimer Activity

The diterpenoids belonging to the clerodane and tetracyclic diterpene types isolated from *O. persica* (Figure 1), have been previously reported from *O. limbata* and all of them have shown inhibitory activity against butyrylcholinesterase [34]. It has been found that butyrylcholinesterase inhibition may be an effective approach for the treatment of Alzheimer-disease and related dementias. These compounds have also displayed inhibitory activity against acetylcholinesterase [34]. Acetylcholinesterase is known to be a key component of cholinergic brain synapses and neuromuscular junctions as it reduces memory deficiency in patients suffering from Alzheimer -

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disease by potentiating and affecting the cholinergic transmission process [35].

Conclusion

In the present paper, we have reviewed the relevant literature to congregate the botanical, ethnobotanical, phytochemical, and pharmacological information on *O. persica*. This plant is believed to be is the only species of the genus *Otostegia* that is endemic to Iran, Pakistan and Afghanistan. The flowering aerial parts of the plant have been famously used as medicinal herbs in the Asian, Iranian and Arabic traditional medicines since ancient times. The claimed medicinal uses of this plant throughout the countries such as Iran, Pakistan and Afghanistan include for the treatment of inflammatory, pain-associated ailments (i.e., toothache, rheumatism), metabolic system-related ailments (i.e., diabetes), relief of malaria, fever, allergy and alleviate opium withdrawal syndrome. Most of these claims have been confirmed via in vitro and in vivo techniques of biological evaluation.

Based on the literature survey, *O. persica* demonstrated various pharmacological activities. However, detail and careful analysis of the reported data leads us to conclude that the plant only possessed promising antinociceptive, antimalaria, antibacterial, anti-Alzheimer, antioxidant and antidiabetic activities. Despite the large number of diseases for which the plant finds use as a medicine, our critical analysis of the literature revealed that its therapeutic efficacy has been assessed only in a few studies. In view of the wide range of medicinal uses of *O. persica* in Asian, Iranian and Arabic folklores as described in ethnobotanical surveys, it is necessary to conduct more clinical and pharmacological studies at molecular level to investigate untapped potential of this plant. For these reasons, extensive pharmacological and chemical experiments, together with human metabolism, will be a focus for future studies. Recent increase in interest on herbal medicines accompanied by increased laboratory investigation into the pharmacological properties of the bioactive ingredients and their ability to treat various diseases has contributed to numerous drugs/herbal extracts entering the international market. As the recent information shows, it is also possible that 3´, 7-dihydroxy-4´,6,8-trimethoxy-flavone might be useful in the development of new drugs to treat hyperglycemia and diabetes. However, clinicians should remain alert until more definitive studies demonstrate the safety, efficacy and quality of the compound. Last but not the least, this paper emphasizes the potential of *O. persica* to be employed in the development of new therapeutic drugs and provide the basis for future research on the application of transitional medicinal plants.

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