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Review

Chemistry, pharmacology and medicinal properties of *Heracleum persicum* Desf. Ex Fischer: A review

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***Heracleum persicum* is known as Persian Hogweed. *H. persicum* extracts and essential oil are important areas in drug development with numerous pharmacological activities in the Middle East especially in Iran. For a long time *H. persicum* has been used in traditional medicines for the relief of flatulence, stomachs as well as flavoring, as a digestive and an antiseptic. *H. persicum* has recently been shown to have antioxidant, anticonvulsant, analgesic, anti-inflammatory and immunomodulatory activities. Pimpinellin, isopimpinellin, bergapten, isobergapten and sphondin are furanocoumarins which are reported from roots of this plant. Hexyl butyrate, octyl acetate and hexyl-2-methylbutanoate were identified as the major constituents for *H. persicum* essential oil. Due to the easy collection of the plant and being widespread and also remarkable biological activities, this plant has become both food and medicine in Iran. This review presents comprehensive analyzed information on the botanical, chemical and pharmacological aspects of *H. persicum*.**

Key words: *Heracleum persicum*, Apiaceae, antioxidant, anticonvulsant, anti-inflammatory.

INTRODUCTION

Heracleum persicum commonly known as Persian Hogweed is a flowering plant and native to Iran. It belongs to Apiaceae family in the order of Apiales that contains about 300 genera and more than 3000 species. *Heracleum* species probably originates from the Middle East, somewhere south of Caucasian, but has spread as an ornamental plant up to Northern Europe. *Heracleum* genus has 10 species in Iran (Mandenova, 1986). *H. persicum* has been known as “Golpar” in Iran and distributed in Alborz regiaon, the northern parts of Iran at an altitude ranging from 2000 to 3000 m high (Amin, 1991). *H. persicum* is a perennial herb that grows about 150 to 200 cm high (Figure 1) with many-stemmed, bristly haired, up to 50 mm thick and hollow stems that are red-brown from base. They grow in the moist and nutritious areas surrounding the spot where it is cultivated. The leaves are alternate, stalked and base pod-like. Blades are longer than wide, lower side densely haired, glabrous on top and pinnate. Leaflets (5-7) are big, shortly and broadly lobed, with blunt-toothed margins (Figure 2). The flowers are corolla regular or actinomorphic (outer florets slightly mirror-symmetrical and bigger), white and 15 to 30 mm wide. They have 5 petals, 5 stamens and are deeply notched. Sepals are stunted. The subtending bract of primary umbels fall off early but the 10 to 18 bracts of secondary umbels do not fall off (Figure 3). Fruits are broadly obovate, 7 to 8 mm long and 2-parted with slightly ridged schizocarp. Oil ducts are slightly club-shaped (Figure 4) (Zargari, 1981). The fruits contain substances which stunt the growth of other plants and can even kill the plants growing close to it. Good indicators for recognizing the species are the color of the stem’s base and the hairiness of the leaves, but the best is probably the shape of the leaflets’ lobes.

The fruits are widely used as spices, preparation of pickles and in folk medicine as carminative. The young stems are also used in the preparation of pickles (Mojab et al., 2002). For a long time, *H. persicum* has been used as a folklore medicine for treatment of various conditions such as flatulence, stomachs, and infections. It is used as flavoring agent, spices digestive, antiseptic, anti-helminthes,

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Figure 1. *H. persicum* (Persian Hogweed or Golpar).

Figure 2. *H. persicum* leaves.

diuretic and appetizer and pain killer (Hemati et al., 2010; Hajhasjemi et al., 2009). *H. persicum* fruits are rich in furanocoumarins which cause a severe, slowly healing eczema in combination with sunlight. These substances

Figure 3. *H. persicum* flowers.

Figure 4. *H. persicum* fruits.

also are effective dermal photosensitizing agents and are widely used in the treatment of leukoderma and in suntan oils and lotions (Aynehchi et al., 1978).

A number of chemical constituents, such as alkaloids, volatile substances, terpenoids, triterpenes and furanocoumarins have been isolated from different parts of the plant (Hemati et al., 2010). From current pharmaceutical studies, additional pharmaceutical applications of *H. persicum* have revealed antioxidant, anti-inflammatory, analgesic, anticonvulsant, antibacterial, antifungal and immunomodulatory effects among others (Souri et al., 2004; Sayyah et al., 2005; Hajhashemi et al., 2009; Sharififar et al., 2009).

Since review and systemic analysis of chemistry, pharmacology and clinical properties of *H. persicum* 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.

This aim of this present review is to introduce *H. persicum* as a potent medicinal plant by highlighting its traditional applications as well as the recent findings for novel pharmacological and clinical applications.

Chemical composition

The commonly known phytochemical compounds from *H. persicum* are volatile substances, terpenoids, triterpenes, furanocoumarins, flavonoids and alkaloids (Hemati et al., 2010). Hexyl butyrate (56.5%), octyl acetate (16.5%), hexyl-2-methylbutanoate (5.2%) and hexyl isobutyrate (3.4%) were identified as the major constituents of the *H. persicum* fruit essential oil. The oil contained about 95% of aliphatic esters, 4% of aliphatic alcohols and 1% of monoterpenes 37 esters and 17 monoterpenes (Hemati et al., 2010). *H. persicum* leaves contain 0.13% of an essential oil that contains trans anethole (82.8%) as the major component and also include β-pinene, ρ-cymene, terpinolene, α-caryophylene, α-bergamotene, α-farnesene, zingiberene, spathulenol, cis-anethole, stragole, 2,5-dimethyl styrene and β-springene (Mojab et al., 2002).

The main components of stem oil before flowering were (e) -anethole (47.0%), terpinolene (20.0%), [gamma]-teipinene (11.6%) and limonene (11.5%), while stem oil at the full flowering stage contained (e) -anethole (60.2%), terpinolene (11.3%) and [gamma]-terpinene (7.1%). The main constituents of the unripe and ripe seed oil of *H. persicum* were hexyl butyrate (22.5 and 35.5%), octyl acetate (19 and 27%) and hexyl isobutyrate (9.1 and 3.2%), respectively (Sefidkon et al., 2004).

Although (e) -anethole was main component of all oils obtained from the leaves, flowers (Sefidkon et al., 2002), and stems of *H. persicum*, it was only found in seed oil as a trace component. In other words, there was a sharp difference between the chemical compositions of the seed oil with the oils of other parts of this plant (Sefidkon et al., 2004).

Pimpinellin, isopimpinellin, bergapten, isobergapten and sphondin are furanocoumarins, which are reported from roots of *H. persicum* (Aynehchi et al., 1978) (Figure 5). Such furanocoumarins are also in the leaves and seeds of this plant (Merijanian et al., 1980). Quercetin, a flavonoid aglycone, has been isolated from the ether extract of *H. persicum* fruits.

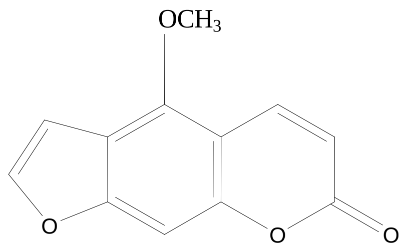
The amount of total phenolic compounds of methanol extract of *H. persicum* was determined as 59.6 µg per mg of crude extract, which is relatively high (Coruh et al., 2007).

Potential of *H. persicum* in phytotherapies

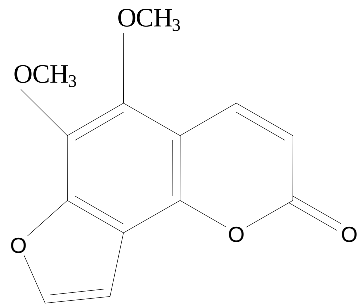
H. persicum is used in traditional Iranian medicine to treat various diseases such as flatulence, stomachs, and infections. It is used as flavoring agent, spices digestive, antiseptic, anti-helminthes, diuretic and appetizer and pain killer (Hemati et al., 2010; Hajhasjemi et al., 2009). Although the antioxidant, anti-inflammatory, analgesic effects of *H. persicum* fruits and roots extracts have been well documented, so far the therapeutic potential has not been exploited by the Western countries (Souri et al., 2004; Sayyah et al., 2005; Hajhashemi et al., 2009; Sharififar et al., 2009). In recent years, accumulating evidence indicated that not only is *H. persicum* important in treating inflammation and pain, but that it also contains anticonvulsant, antibacterial, antifungal, immuno-modulatory and cytotoxic effects (Souri et al., 2004; Sayyah et al., 2005; Hajhashemi et al., 2009; Sharififar et al., 2009; Moshafi et al., 2009).

Anti-inflammatory and analgesic properties

Although a number of steroidal or non-steroidal anti-inflammatory drugs have been developed, researchers are changing their focus to natural products to develop new anti-inflammatory agents due to the side-effects of chemical drugs (Hyun and Kim, 2009; Shokrzadeh and Saeedi , 2009). As a result, the search for other alternatives seems necessary and beneficial. *H. persicum* fruits are an open door for new and effective compounds (Hajhashemi et al., 2009). Many cells and mediators are involved in proceeding inflammation. For example, macrophages are representative inflammatory cells involved in acute or chronic inflammatory responses by over-production of pro-inflammatory cytokines [for example, tumor necrosis factor (TNF)-a, interleukin (IL)-1b and granulocyte/ macrophage colony stimulating factor (GMCSF)] and inflammatory mediators (Rhee et al., 2009; Lundberg, 2003; Walsh, 2003). The fruits of *H. persicum* have been functionally used as a traditional crude drug as a pain killer (Hemati et al., 2010). In animal models, the essential oil and hydroalcoholic extract from *H. persicum* fruits have shown analgesic activity in acetic acid-induced writhing and formalin tests and anti-inflammatory effect in carrageenan-induced paw edema. In acetic acid-induced writhing test, both essential oil and



A



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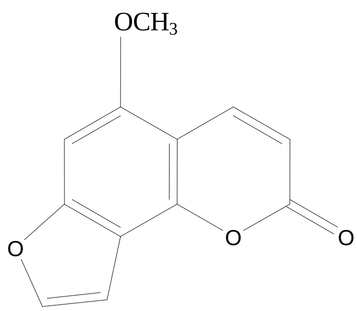

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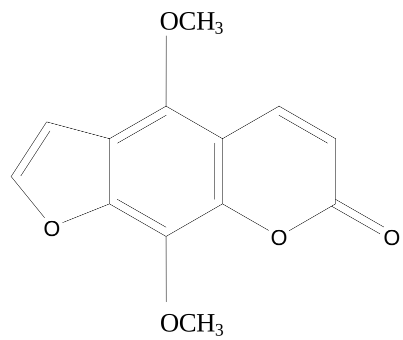

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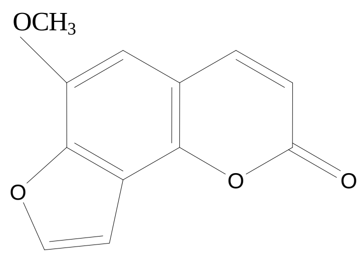

E

Figure 5. Structures of A= Bergapten; B= Pimpinellin; C= Isobergapten; D= Isopimpinellin; E= Sphondin from *H. persicum* (Aynehchi et al., 1978; Tosum et al., 2008).

hydroalcoholic extract when given orally or i.p. inhibited abdominal twitches. In this test indomethacin, a well-known nonsteroidal anti-inflammatory drug (NSAID) at a dose of 10 mg/kg produced about 80% reduction of writhes. i.p. administration of hydroalcoholic extract at a dose of 500 mg/kg significantly reduced pain response. Oral administration of essential oil at doses of 100 and 200 mg/kg produced 33 and 48% inhibition of carrageenan-induced paw edema respectively.

Hydroalcoholic extract only at a dose of 400 mg/kg could exert a significant reduction of paw swelling (Hajhashemi et al., 2009).

Based on well known involvement of free radicals in inflammatory processes (Conner and Grisham, 1996), it seems that at least a part of anti-inflammatory effects of the essential oil and hydroalcoholic extract of *H. persicum* fruits may be attributed to their antioxidant constituents especially furanocoumarins. Hydroalcoholic extract of *H. persicum* contains a furanocoumarin named Sphondin which has shown inhibitory effect on IL-1 beta-induced cyclooxygenase-2 expression (Yang et al., 2002). Since this enzyme has a key role in pain and inflammation, it may explain the observed effects of *H. persicum* fruits hydroalcoholic extract (Hemati et al., 2010).

Antioxidant activity

An antioxidant is defined as ‘any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate’ (Rhee et al., 2009; Halliwell et al., 1995; Wiseman et al., 1997; Mates et al., 1999). Antioxidants are of interest to biologists and clinicians because they help to protect the human body against damages induced by reactive free radicals generated in atherosclerosis, ischemic heart disease, cancer, Alzheimer's disease, Parkinson's disease and even in aging process (Aruoma, 2003; Hemati et al., 2010). There are many evidences that natural products and their derivatives have efficient anti-oxidative characteristics, consequently linked to anti-cancer, hypolipidemic, anti aging and anti-inflammatory activities (Rhee et al., 2009; Halliwell et al., 1995; Wiseman et al., 1997; Hogg, 1998; Mates et al., 1999; Aruoma, 2003; Cho et al., 2006).

Anti-oxidative capacities of *H. persicum* were evaluated by determining its effect on DPPH radical scavenging, and lipid peroxidation inhibition (Mozaffarian, 1996; Zargari, 1988; Coruh et al., 2007).

In DPPH radical-scavenging activity assay, the IC50 value was 0.438 mg/ml which was much weaker than that of quercetin (IC50 value = 0.006 mg/ml) as standard. Furthermore, lipid peroxidation inhibition effect of *H. persicum* extract was 0.503 mg/ml, which was comparable with its DPPH scavenging activity as expected (Coruh et al., 2005).

Some furanocoumarins isolated from *H. persicum* have shown antioxidant activity such as Sphondin which inhibits IL-1 beta-induced cyclooxygenase-2 expression (Yang et al., 2002).

The effect of *H. persicum* extract on glutathione-S-transferase (GST) activity was investigated along with its antioxidant capacities, since the GST enzymes account for the defense against oxidative stress, and they detoxify endogenous harmful compounds such as the breakdown products of lipid peroxidation or DNA hydroperoxides (Hayes and Pulford, 1995; Nordberg and Arner, 2001).

Another reason, to attract the interest on GST activity is the ability of resistant tumor cells to promote GST catalyzed GSH conjugation of the pharmacologically active compounds such as antitumor drugs (Guadiano et al., 2000; Zanden et al., 2004). Therefore, elevated GST activity is regarded as an indicator for the resistance to chemotherapy. In this respect, inhibitory effects of antioxidant agents on GST activity are continuously investigated by researchers (Gyamfi et al., 2004).

H. persicum extracts have shown considerable inhibition on cytosolic GST activity with a value of 130.28 lg/ml. These results are in good correlation with the total phenolics content of the extract because researches have suggested that high GST inhibitory activity of plant extracts could be attributed to the high polyphenolic content, as indicated in the literature for the GST inhibitory effects of naturally occurring plant polyphenols (Coruh et al., 2005).

Anticonvulsant activity

The fruits acetone extract of *H. persicum* possesses a dose-dependent anticonvulsant activity in both *maximal electroshock (*MES) and Pentylenetetrazole (PTZ) seizure models (Syyah et al., 2005).

The ED50 value of 265.8 mg/kg against MES induced seizures, and 205.9 mg/kg against PTZ- induced clonic seizures have been obtained for the extract.

These values indicate that the extract is more effective against clonic seizures induced by PTZ than tonic seizures induced by MES (Syyah et al., 2005). The MES test is considered to be a predictor of likely therapeutic efficacy against generalized tonic–clonic seizures. By contrast, the PTZ test represents a valid model for human generalized myoclonic and also absence seizures (Loscher and Schmidt, 1988). Therefore, it seems that the extract could be effective in these two types of human seizures.

The fruits acetone extract contains alkaloids, terpenoids, triterpenes and steroids, while flavonoids were absent (Syyah et al., 2005). As triterpenes, some alkaloids and monoterpens are reported to possess anticonvulsant activity in some experimental seizure models like PTZ, MES and electrical kindling (Kasture et al., 2002; Ameri et al., 1997; Librowski et al., 2000; Brum et al., 2001), it seems that the anti-seizure profile of *H. persicum* may be related in part to terpenoids, triterpenes and alkaloids present in the fruits.

From the dose of 200 mg/kg and at 30 min after administration, the extract produced a reduction in time spent on rotarod. This sedation and motor impairment was dose-dependent, with TD50 value of 203.8 mg/kg. At the doses employed, the extract did not exert any other noticeable effects in the animals' behavior. PI values of 0.76 and 0.98 were obtained for the extract against seizures induced by MES and PTZ, respectively. These values suggest that the therapeutic doses of the extract are close to the sedative doses (Syyah et al., 2005). Some terpene compounds such as eugenol, cineol and linalool have anaesthetic, muscle relaxant and inhibitory effect on locomotion (Dallmeier and Carlini, 1981; Santos and Rao, 2000; Brum et al., 2001). Therefore, the terpene compounds present in the fruits may be responsible for the extract's sedative effect (Scheffer et al., 1984).

LD50 value of 1103 mg/kg was obtained for the extract and TI values were 4.15 and 5.35 against seizures induced by MES and PTZ, respectively. These values suggest acceptable therapeutic effect for the extract (Syyah et al., 2005).

Immunomodulatory activity

The immune system is involved in the etiology, as well as pathophysiologic mechanisms of many diseases. Modulation of the immune responses to alleviate various diseases has been of interest for many years (Sharififar et al., 2009). Medicinal plants are a rich source of substances which are claimed to induce paraimmunity which is the non-specific immunomodulation of essentially granulocytes, macrophages, natural killer cells and complement functions (Sharififar et al., 2009). *H. persicum* can stimulate both humoral and cellular arms of the immune system. In the haemagglutination titre (HT) test, the plant showed an increased response with all the tested doses, but this increase was only significant with dose of 100 mg/kg. This activity could be due to the presence of flavonoids or furanocoumarins which can augment the humoral response by stimulating the macrophages and beta-lymphocytes involved in antibody synthesis (Sharififar et al., 2009).

An increase in delayed type hypersensitivity (DHT) response indicates that the *H. persicum* extract can have a stimulatory effect on lymphocytes and the accessory cell types required for the expression of the reaction (Sharififar et al., 2009).

Recent reports indicate that several types of flavonoids stimulate the human peripheral blood leukocyte proliferation. They significantly increase the activity of helper T cells, cytokines, interleukin 2, gama-interferon and macrophages and are thereby useful in the treatment of several diseases caused by immune dysfunction. According to the published studies, furanocoumarins and flavonoids present in *H. persicum* extract seem to be the most likely candidates eliciting immunostimulating effects (Kawakita et al., 2005).

Pathological effects

As *H. persicum* contains photosensitizing furanocoumarins, in contact with the human skin and in combination with ultraviolet radiation, a phytotoxic reaction can occur 15 min after contact, with a sensitivity peak between 30 min and 2 h causing burnings of the skin.

After about 24 h, flushing or reddening of the skin (erythema) and excessive accumulation of fluid in the skin (edema) appear, followed by an inflammatory reaction after three days. Approximately one week later a hyper-pigmentation (usually darkening the skin) occurs which can last for months. The affected skin may remain sensitive to ultraviolet for years. In addition, several furanocoumarins have been reported to cause cancer (carcinogenic) and to cause malformation in the growing embryo (teratogenic) (Nielsen et al., 2005).

CONCLUSION

The objective of this review has been to show the recent advances in the exploration of *H. persicus* as phytotherapy and to illustrate its potential as a therapeutic agent. With the current information, it is evident that *H. persicus* has pharmacological functions including anti-inflammatory, analgesic, anti-convulsant and antibacterial, antifungal and antioxidant activities, among others. As the current information shows, it is also possible that furanocoumarins might be useful in the development of new drugs to treat various diseases. However, the present results suggest a possibility that furanocoumarins can be further developed as a potential disease-curing remedy. It must be kept in mind that clinicians should remain cautious until more definitive studies demonstrate the safety, quality and efficacy of *H. persicum*. For these reasons, extensive pharmacological and chemical experiments, together with human metabolism will be a focus for future studies. Last but not the least, this review emphasizes the potential of *H. persicum* to be employed in new therapeutic drugs and provide the basis for future research on the application of transitional medicinal plants.

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