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Review

Phytopharmacology and medicinal properties of *Salix aegyptiaca* L.

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Salix aegyptiaca* L. is known as Musk Willow. *S. aegyptiaca* extracts and essential oils are important areas in drug development with some pharmacological activities in the Middle East, especially in Iran. For a long time *S. aegyptiaca* has been used in traditional medicines for the relief of anemia and vertigo, as a cardiotonic agent, as well as a fragrance additive in the preparation of local candies. *S. aegyptiaca* has recently been shown to have antioxidant, anxiolytic activity and hypocholestrolemic effect. High amounts of phenols and flavonoids such as gallic acid, caffeic acid, myricetin, catechin, quercetin as well as salicin, are reported from the leaves of this plant. 1,4-dimethoxybenzene, phenylethyl alcohol, carvone, citronellol, methyleugenol, eugenol, *n*-tetradecane and 4-methoxyacetophenone were identified as the major constituents of the essential oil in leaves of *S. aegyptiaca*. Due to the easy collection of the plant, being widespread and also its 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 *S. aegyptiaca.

Key words: *Salix aegyptiaca*, Salicaceae, Musk Willow, essential oil.

INTRODUCTION

Salix aegyptiaca commonly known as Musk Willow is a flowering plant and generally cultivated in some provinces of Iran for hedge and ornamental purposes (Sonboli et al., 2010). It belongs to Salicaceae family in the order of Malpighiales that contains about 55 genera and more than 1000 species. The species of the genus *Salix* are deciduous trees and shrubs with simple, stipulate leaves alternately arranged on woody stems. Based on several publications (Fang-Zhen, 1987; Argus, 2007; Ohashi, 2000), about 526 distinct species are recognized for the genus worldwide. Former Soviet Union includes 120 species, the New World 103, China 275, Europe 65, Pakistan 26 and Iran 31 species and 6 hybrids (Maassoumi, 2009). *Salix* species probably originates from the Middle East, especially in Egypt and somewhere in Turkey, Iran, Iraq, Armenia, Turkmenistan and Afghanistan, but has spread as an ornamental plant up to Europe, America and Australia. *S. aegyptiaca* has been known as “Bidmeshk” in Iran and distributed in many parts of Iran especially in Urmia, North West of Iran (Rabbani et al., 2011). *S. aegyptiaca* is a deciduous shrub growing to 4 - 5 m. It is a vigorous, fast growing, bushy, deciduous small tree with purplish-red, thick branches (Figure 1). Leaves are oblong, serrated, deep green above, underside hairy, up to 15 cm long (Figure 2). The inflorescence is catkin; catkins are fragrant and grey. Individual flowers are either male or female, but only one sex is to be found on one plant, so both male and female plants must be grown if seed is required and are pollinated by bees. Male catkins are 4 cm long with yellow anthers and probably include one of the used parts of this plant (Figure 3). Female catkins are 7.5 cm long. The plant is not self-fertile (Zargari, 1988).

The male inflorescences distillate of the plant has long been used in Iranian folklore medicine as cardiotonic, treatment of anemia and vertigo, as well as a fragrance additive. The aqueous extract and essential oil of these inflorescences are also being used in confectionary, flavorful syrups and especially in the preparation of a local candy (Noghl-e Urmia) (Karimi et al., 2011). Ethnobotanically, rheumatic pains, affecting mainly the elderly, can be relieved by a decoction or infusion of *S. aegyptiaca* bark (Leporatti and Impieri, 2007). The decoction of the leaves or barks has also been used as

Figure 1. *Salix aegyptiaca* (Musk Willow).

an antihelminthic and vermifuge remedy. The effect of *Salix* leaves, along with clove bud and *Nigella,* in the treatment of common wart has been reported (Rezaei et al., 2008). In addition, *S. aegyptiaca* is used as laxative, cardioprotective, nervous, sedative, hypnotic, somnolent, aphrodisiac, orexigenic, carminative and gastro-protection. The decoction of *S. aegyptiaca* leaves in honey still is used as a nervonic functional food. This decoction plus sugar has been used among Iranian and Turkish people for maladies like depression, neuropathic pain and rheumatoid arthritis (Karimi et al., 2011).

The *Salix* family is famous due to its endogenous salicylate compounds e.g., salicylic acid and acetyl salicylic acid (ASA, Aspirin®). This class of compounds exerts anti-inflammatory effects. The anti-inflammatory and antinociceptive properties of extracts of *Salix* family may be related to its phytochemicals such as salicin, myricetin, kaempferol, quercetin, rutin and luteolin (Qin and Sun, 2005; Nahrstedt et al., 2007). These compounds have immunomodulatory and anti-inflammatory activities by inhibiting pro-inflammatory cytokine production and their receptors (Qin and Sun, 2005; Nahrstedt et al., 2007). The considerable myricetin, rutin and catechin content of musk willow extracts could potentially contribute to the anti-inflammatory functions of willow extracts (Enayat and Banerjee, 2009). According to Unani medicine, *S. aegyptiaca* has warm humor nature and ethnic herbalists prescribed it for cholelithiasis, cholecystitis, arthritis and rheumatism. The essential oil of *S. aegyptiaca* is febrifuge and is dubbed among Iranian people for its calming effect on heart and possibly its antihypertensive effect (Karimi et al., 2011).

S. aegyptiaca male catkins are rich in volatile components such as p-methoxybenzene, eugenol, carvone, cedrene oxide, and geraniol (Salehi-Surmaghi, 2009). A number of chemical constituents such as flavonoids and volatile substances have been isolated from different parts of the plant (Karimi et al., 2011; Enayat and Banerjee, 2009). From current pharmaceutical studies, additional pharmaceutical applications of *S. aegyptiaca* have revealed antioxidant, antiinflammatory, analgesic, anxiolytic and antihyperchlosterolemic

Figure 2. *Salix aegyptiaca* leaf.

effects among others (Sonboli et al., 2010; Rabbani et al., 2011; Karimi et al., 2011; Karawya et al., 2010).

Since the review and systemic analysis of chemistry, pharmacology and clinical properties of *S. aegyptiaca* 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 aim of the present article is to introduce *S. aegyptiaca* as a 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 *S. aegyptiaca* are volatile substances, flavonoids and phenolics (Sonboli et al., 2010). p-Methoxybenzene (60%), eugenol (21%), decanol (4%), cedrene oxide (2.5%) and ocimene (2.3%) were identified as the major constituents of *S. aegyptiaca* male catkins essential oil collected from Urmia, North West of Iran, while carvone (16%), cedrene oxide (16%), geraniol (10%), carvacrol (9%), citronellol (4%) and p-methoxybenzene (2.3%) were characterized as the major ones of the essential oil of *S. aegyptiaca* male catkins collected from Shiraz, South of Iran (Salehi-Surmaghi, 2009).

The essential oil of *S. aegyptiaca* leaves contains 1,4-dimethoxybenzene (61.5%) as the main component accompany with methyleugenol (21%), phenylethyl alcohol (10.9%), citronellol (8%), carvone (6%), eugenol (6%) and 4´-methoxyacetophenone (3%) (Karimi et al., 2011). 1,4-Dimethoxybenzene also known as “hydro-quinone dimethyl ether” is the para form of dimethoxybenzene, a volatile aromatic ether with a sweet floral odor. It occurs naturally in *Salix* species (Dötterl et al., 2005). The presence of high amounts of phenolics including gallic acid, caffeic acid, vanillin, p-coumaric acid, myricetin, catechin, epigallocatechin gallate and flavonoids such as rutin, quercetin and salicin are indicated in the leaves of S. aegyptiaca (Enayat and Banerjee, 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 Sarvari, 2009). As a result, the search for other alternatives seems necessary and beneficial. Many cells and mediators are involved in proceeding inflammation. For example, macrophages are representative

Figure 3. *Salix aegyptiaca* male catkins.

inflammatory cells involved in acute or chronic inflamematory 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 *Salix* family is famous due to its endogenous salicylate compounds e.g., salicylic acid and acetyl salicylic acid (ASA, Aspirin®) (Karimi et al., 2011). This class of compounds exert anti-inflammatory effects throughout the inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) leading to the inhibition of prostaglandin synthesis (Yu et al., 2002; Mahdi et al., 2006). The anti-inflammatory and antinociceptive properties of extracts of *Salix* species may be related to their phytochemicals such as salicin, myricetin, kaempferol, quercetin, rutin and luteolin (Qin and Sun, 2005; Nahrstedt et al., 2007). These compounds have anti-inflammatory activities by inhibiting pro-inflammatory cytokine production and their receptors (Qin and Sun, 2005; Nahrstedt et al., 2007). The considerable myricetin, rutin and catechin content of *S. aegyptiaca* extracts could potentially contribute to the anti-inflammatory functions of other *Salix* species extracts (Enayat and Banerjee, 2009).

Salicin, the major phenolic glycoside present in the bioactive extracts in *Salix* species is considered to be the pharmacologically active principle due to its structure similarity to aspirin. In animal models, the extracts from *S. aegyptiaca* leaves and male flowers have shown anti-inflammatory effects in carrageenan-induced paw edema and hot plate tests (Karawya et al., 2010; Rabbani et al., 2010). The aqueous extract of *S. aegyptiaca* male flowers at a dose of 0.3, 0.6 and 1.2 mg/kg showed a significant analgesic effect compared to control group treated with ASA. In addition, it is demonstrated that the analgesic effect of 0.6 mg/kg of the extract was higher than ASA 300 mg/kg (Karawya 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 and Gutteridge, 1990; 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., 1990; Wiseman et al., 1997; Hogg, 1998; Mates et al., 1999; Aruoma, 2003; Cho et al., 2006).

The anti-oxidative capacities of *S. aegyptiaca* male catkins were evaluated by determining its effect on 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging (Sonboli et al., 2010). In DPPH radical-scavenging activity assay, the IC50 value was 27.7 µg/ml, which was comparable to the synthetic antioxidant butylated hydroxytoluene (BHT) (IC50 value = 26.5 µg/ml) as standard. Furthermore, antioxidant potential of *S. aegyptiaca* bark was determined by IC50 value equal to19 µg/ml (Enayat and Banerjee, 2009). The barks and male catkins have the highest antioxidant activity. The molecular mechanism of radical scavenging activity of *S. aegyptiaca* could be attributed to the presence of polyphenolic compounds. It has already been exhibited that polyphenolic compounds are responsible for radical scavenging activity, due to the ease of their hydrogen atom donation to active free radicals (Ho et al., 1994). The potent antioxidant activity of *S. aegyptiaca* supports its possible use as a natural antioxidant in food industries and other pharmaceutical preparations (Sonboli et al., 2010).

ANXIOLYTIC PROPERTIES

Anxiolytic disorders are among the most prevalent disorders that are characterized by symptoms such as overriding apprehension or mental tension. Most anxiety disorders tend to run a long course and thus require long-term treatment (Berrios, 1999). A wide range of herbal anti-anxiety medicines has been used in the past to treat different forms of anxiety disorders. Although synthetic drugs such as benzodiazepines have the advantage of rapid onset of action, they have the potential to interfere with patient's normal activity and are often difficult to stop once the therapy has started. These problems and also other side effects that exist with synthetic anxiolytic drugs have prompted people to seek natural and herbal medicines (Rabbani et al., 2011).

The extract of the flowers of *S. aegyptiaca* on elevated plus-maze (EPM) model of anxiety in mice produced anxiolytic effects and reduced locomotor activity. Oral and intraperitoneal (i.p.) administration of the extract significantly increased the percentage of time spent in the open arms of the EPM at 200 and 100 mg/kg, respectively. The flowers extract at 100 and 200 mg/kg significantly decreased the animal's locomotor activity at 10 and 15 min time intervals. These doses, however, did not affect the ketamine-induced sleeping time. The 100 mg/kg dose of the plant extract when given by i.p. route seemed to be the optimal dose in producing the anxiolytic effects (Rabbani et al., 2010).

HYPERCHOLESTEROLEMIA EFFECT

Studies in both animals and humans have demonstrated that prolonged high cholesterol concentration in the circulating blood positively correlates with developing atherosclerosis (Pratico, 2001; Kurosawa et al., 2005). These changes are associated with the phenomenon that excessive load of cholesterol to the liver, above the acceptable level of its normal physiological limit, causes the liver to be unable in metabolizing the lipids, thus resulting in high cholesterol return in the circulating blood (Kushi et al., 1996).

In Iranian ethno-medicine, *S. aegyptiaca* has been prescribed for ailments like cholecystitis and cholelithiasis due to its inhibition of bile acid synthesis or antimicrobial effects of its active components like phenylethyl alcohol. With respect to the lipid profile, the results suggested a time-dependent increase in the plasma total cholesterol (TC) level. This increase in TC in *S. aegyptiaca*-treated mice could be mainly due to the lack of protective effects of the essential oil of *S. aegyptiaca* and not due to age, since the TC was also increased as early as the first week of essential oil administration. A significant increase in plasma level of HDL was also observed. This increase in HDL can solely be responsible for the observed increase in TC since the essential oil might be affecting the HDL metabolism in the liver (Eder and Gidez, 1982). However, the results support that essential oil of *S. aegyptiaca* has no therapeutic and/or prophylactic effects against incoming dyslipidemia in rabbits. The essential oil of *S. aegyptiaca* contains several serum lipid-improving phytochemical ingredients such as eugenol and citronellol (Holmes and DiTullio, 1962; Germán et al., 1998). However, the other chemical ingredients in essential oil of *S. aegyptiaca* might participate in the phenomena that hasten atherogenesis (Karimi et al., 2011).

CONCLUSION

The objective of this article has been to show the recent advances in the exploration of *S. aegyptiaca* as phytotherapy and to illustrate its potential as a therapeutic agent. With the current information, it is evident that *S. aegyptiaca* has pharmacological functions including anti-inflammatory, analgesic and antioxidant activities, among others. As the current information shows, it is also possible that phenolic glycosides and flavonoids might be useful in the development of new drugs to treat various

diseases. However, it must be kept in mind that clinicians should remain cautious until more definitive studies demonstrate the safety, quality and efficacy of *S. aegyptiaca*. For these reasons, extensive pharmacological and chemical experiments, together with human metabolism will be a focus for future studies. Finally, this article emphasizes the potential of *S. aegyptiaca* 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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