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Biological Activities of *Salvadora persica L.* (Meswak)

Hilal Ahmad* and Rajagopal K

Department of Biotechnology, Vels University, Pallavarm, Chennai, India

Abstract

Salvadora persica L., commonly known as the Meswak tree, occurs in shrub savannah. From northwestern India to Africa, the plant has been valued for its important biological and chemical perspectives and its use in as oral hygiene has been documented in ethno botanical reports. The present review gives a comprehensive summary of the chemical constituents and biological effects (antibacterial and antifungal) of this species. A comprehensive account of the chemical constituents with their biological activity is also included. The extracts prepared with and compounds isolated from this species have been found to possess a broad spectrum of biological and pharmacological effects, such as antidepressant effects, wound-healing, antiviral and antimicrobial activity. Moreover, the extracts and preparations from the plant, which are hopefully safe as is evident from its ethonobotanical studies, exhibited various additional biological effects like anti-gingival irritation, hypoglycemia, antioxidant, antifever, anti-ulcerogenic, anti-caries and antiplatelet-agression effect. The antibacterial activity of crude extracts can be related to the use of the herb as an oral hygiene in ancient times. The available literature indicates that it has a higher antibacterial activity against oral bacteria, and aqueous extracts were shown to possess more pronounced activity than alcoholic extracts (methanolic/ethanolic). Based on the chemical and pharmacological characteristics of *S. persica*, we concluded that this species has beneficial therapeutic properties, and has the potential for use as an effective adaptogenic herbal remedy.

Keywords: Meswak tree; Biological activity; Antimicrobial; Oral bacteria; Aqueous extracts; Remedy

Introduction

Plants are natural source of antibacterial agents. Plant-derived medicines have been a part of our traditional health care system, and the antimicrobial properties of plant derived compounds are well documented. Herbal medicines are more effective and less harmful, as they have negligible side effects. They exhibit low mammalian toxicity and can be handled easily [1].

Salvadora persica L. of the family *Salvadoraceae* is an evergreen shrub, 4-6 m tall with a short trunk, white bark and smooth green leaves. In Ayurvedic system of medicines, *Salvadora persica* L. is reported to have potent activity for dental complaints. It is also called as Meswak tree, for the roots and twinges of this tree have been used for teeth cleaning since ancient times. It is one of the most commonly used medicinal plants for oral hygiene among global Muslim community [2]. The history and the use of Meswak as an oral tool, as well as the biological effects of *S. persica* extracts are reviewed [3]. Moreover, the tree has been used by many Islamic communities as toothbrushes, and has been scientifically proven to be very useful in the prevention of tooth decay, even when used without any other tooth-cleaning methods. A variety of chemical components have been identified in *S. persica* extracts. Some of these biologically active chemical constituents as sodium chloride, potassium chloride, salvadourea, alkaloids, and oleic and linoleic acids have been suggested to contribute to the cleansing efficacy of Meswak by leaching out in saliva, and for their antifungal properties [4-6]. Moreover, the roots of *S. persica* were found to contain salvadourea, a urea derivative [7]. So, in this article different biological activities, including antibacterial, anti fungal and anti viral properties, and other biological uses of *Salvadora persica L.* extract or it's Meswak (chewing sticks), has been encompassed up to the present studies conducted.

Derivation of the botanical name and classification of *Salvadora persica* L.

The term *Salvadora*, in 1749, was put forward in honour of an apothecary of Barcelona, Juan Salvadory Bosca (1598-1681), by Dr Laurent Garcin, botanist, traveller and plant collector. While as *persica* term indicates Persia. And the standard author abbreviation L. is used to indicate Carl Linnaeus (1707–1778), a Swedish botanist, physician and zoologist, the father of modern taxonomy.

Class	*Magnoliopsida*
Subclass	*Dilleniidae*
Order	*Capparales*
Family	*Salvadoraceae*
Genus	*Salvadora*

Plant description

Much branched shrubs or small trees to 6 m high, unarmed. Branches long, often pendulous or semiscandent, glabrous or pubescent. Leaves subsucculent; blades coriaceous, landeolate to elliptic, occasionally orbicular, 1-3-10 cm long, 1-2-3 cm wide, rounded to acute at apex, cuneate to subcordate at base. Flowers small, greenish-white in lateral and terminal panicles up to 10 cm long. Petals (1)-3 mm long. Drupes red or dark red purple when ripe.

Biologically active compounds of *S. persica*

The aqueous extracts of *S. persica* contains important phytoconstituents such as vitamin C, salvadorine, salvadourea, alkaloids, trimethylamine, cyanogenic glycosides, tannins, saponins and salts mostly as chlorides [8-11]. Emira Noumi et al. [12] were succeeded to evaluate the chemical composition of *S. persica.* As given in Table 1, they identified fifteen compounds using GC and GS-MS techniques. According to their study, the essential oil obtained from

***Corresponding author:** Hilal Ahmad, Department of Biotechnology, Vels University, Pallavarm, Chennai, India, E-mail: hhiillaallbiotech@gmail.com

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the stems of *S. persica* was rich in benzyl isothiocyanate (52.5%), benzyl nitrile (38.3%), carvacrol (3.3%), benzaldehyde (2.5%), aniline (0.7%) and naphthalene (0.6%). A list of different compounds extracted from the crude extracts of *S. persica* is mentioned in Table 1.

Moreover, Alali and Al-Lafi [8] reported that the GC-MS analysis of the volatile oil extracted from *S. persica* L. leaves from Jordan reveal seven major components (Benzyl nitrile 53.96%; Isotymol 15.39%; thymol 11.37%; eugenol 10.49%; β-caryophyllene 4.72%; eucalyptol 79% and isoterpinolene<0.5%). In their study, Alali et al. [13] identified chemical composition of the essential oil of the stem of *S. persica* L. using gas chromatography-mass spectrometry (GCMS). The oil they obtained by hydrodistillation (yield: 0.6% w/w) was determined as a mixture of monoterpenes hydrocarbons (11%), oxygenated monoterpenes (54%), and sesquiterpene hydrocarbons (21%). Sixteen components were identified, and the major components identified were 1,8-cineole (46%), α-caryophyllene (13.4%), β-pinene (6.3%) and 9-epi-(E)-caryophyllene (6.3%) [13]. Ashraf Taha Khalil in 2006 [14] isolated four Benzylamide compounds, which were identified as butanediamide, N1, N4-bis(phenylmethyl)-2(S)-hydroxy-butanediamine (1), *N*-benzyl-benzamide (2), *N*-benzyl-2-phenylacetamide (3), and benzyl urea (4). They found that Compound 1 was inactive against all tested organisms, while compound 2 was only moderately active against *Escherichia coli* at a concentration of 87 pg/mL. However Compound 2, together with other constituents of *S. persica* stems such as lignans and flavonoids, with reported antimicrobial activity [15], were deemed accountable for the oral hygienic effects caused by the stems. Three lignin glycosides were isolated from the stems of this species [16], whereas an indole alkaloid was reported in the leaves [17]. The flavonoids rutin and quercetin were detected in the stems [18]. Salvadourea, $(m\text{-}MeOC_6H_4CH_2NH)_{2CO}$, has been reported in the roots [19]. Benzylisothiocyanate was also isolated from the roots, and is claimed to be responsible for antiviral activity against HSV-1 [20], moreover, recently it was that it induces G2/M phase arrest and apoptosis in human melanoma A375.S2 cells through reactive oxygen species (ROS), and both mitochondria-dependent and death receptor-mediated multiple signaling pathways [21].

Compounds	%	KI
Benzaldehyde	2.5	963
Sabiene	0.1	972
1, 8-cineole	0.3	1032
Linalool	0.1	1098
Myrcenol	0.1	1114
Benzyl isocyanate	0.3	1123
Benzyl nitrile	38.3	1162
Benzyl ester	0.1	1172
Naphtalene	0.6	1189
Methyl chavicol	0.3	1201
Analine	0.7	1247
Trans-anethol	0.2	1287
Carvacrol	3.3	1305
Benzyl isothiocyanate	52.5	1394
Diphenyl ether	0.2	1411

Table 1: List of identified components (99.5%) from extract of *S. persica* with %age, in the order of their elution on polar column (HP-20M). MS: mass spectroscopy, KI: Kovats index- EmiraNoumi et al. [12].

Biological activity of different components of *S. persica*

The chemical constituents of *S. persica* such as flavonoids, salvadorine, cyanogenic glycosides, lignans, saponins, alkaloids, tannins, linoleic acid, steraric acid, salvadourea, vitamin C, silica and different salts are also known to possess significant antimicrobial activity [16,22,23] (Table 2).

Anti-microbial activity of *Salvadora persica* L.

With the agreement of earlier investigations, it is confirmed that *S. persica* exhibited significant antimicrobial activity against both aerobic as well as anaerobic bacteria collected from teeth with inflamed gums and necrotic pulps [24,25]. It has also been found that *S. persica* posses anti-plasmodia activity, and is used as part of remedies to treat malaria [26]. Recently found that Meswak extract from Hoggar displayed a strong antimicrobial effect, both *in vitro* and *in vivo,* which more significantly inhibited the growth of Gram negative bacteria from the dental plaque than Gram positive ones [27].

Antifungal properties

The extract of *S. persica* show positive results against oral fungal infections. In this regard, a number of tests have been conducted. Using disc diffusion and microdilution assays, Noumi et al. [3] conducted a

Components	Biological activity
Silica	As an abrasive material to remove stains giving the teeth whiteness [57].
Tannins (tannic acid)	Reduces the clinically detectable gingivitis [58] and reducing plaque and gingivitis [59].
Resins	Forms a layer over the enamel and thus protects against caries.
*Alkaloids (*Salvadorine*)*	Bacteriocidal effect and stimulatory action on the gingival [60].
Essential (volatile) oils	Exert carminative, antiseptic action [57].Their mild bitter taste stimulates the flow of saliva, which is antiseptic 61].
sulfur	Their pungent taste and smell have a bactericidal effect [62].
Vitamin C	Helps in the healing and repair of tissues.
Sodium bicarbonate (baking soda) $NaHCO_3$	Having a mild germicidal action [63].
chloride	Its high concentration inhibits calculus formation and help in removing stains from the teeth [60].
Calcium	With saliva saliva it inhibits deminer-alizalion and promotes remineralization of tooth enamel [59].
Benzyl nitrate and Benzylisothiocyanate (BIT)	Act as chemo-preventive agents [64], virucidal, antibacterial and anti-fungal agents [65,66].
Butanediamide, ~ N4-bis(phenylmethyl)-2(S)-hydroxy-butanediamide	Antimicrobial agent against Gram positive and Gram negative bacteria [14].
N-benzyl-2-phenylacetamide	Inhibitory effect on human collagen-induced platelet aggregation, and a moderate antibacterial activity against *Escherichia coli* [14].
Trimethylamine	Decreasing plaque accumulation, Antibacterial and antiphlogistic [67].
Fluoride	Anti-decay effects [58].

Table 2: Biological activity of different components of *S. persica*

study for the first time, in order to investigate the anticandidal activities of fresh and dry *S. persica*. Their results showed that diluted acetone extract of dry *S. persica* has some antifungal activity against some oral *C. albicans, C. glabrata and C. parapsilosis* strains (zone of inhibition range: 10.33-15 mm), using the extract concentration of 300 mg/ml. However, previously the work of Al Bagieh and Almas [28] showed that aqueous extracts of miswak could reduce the growth of *C. albicans* for up to 36 h, and at a concentration of 15%.

Antibacterial activities

S. persica exhibited significant antimicrobial activity against both aerobic as well as anaerobic bacteria collected from teeth by different researchers in the various parts of world. Previous studies have reported that *S. persica* extracts were effective against *Streptococcus mutans* [29] and *Streptococcus faecalis*, even using low extract concentrations. In 2000, Almas and Stakiw [30] reported that the aqueous extract (50% v/v) of the chewing sticks *S. persica* inhibit the growth of *Streptococcus faecalis,* with 2 mm as a diameter of inhibition zone. In 2004, Alali and Al-Lafi [8] reported that the volatile oil of Jordanian *S. persica* stems exhibits potent antibacterial activity against both Gram-positive and Gram-negative bacteria. Recently, Al-Bayati and Sulaiman [31] tested the activity of aqueous and methanol extracts of Iraquian *S. persica* against seven isolated oral pathogens. The strongest antibacterial activity was observed using the aqueous extract against *S. faecalis* (Zone of inhibition: 22.3 mm; MIC: 0.781 mg/ml). As reported by Sher et al. [24] and supported by others, the extract of *S. persica* is found to be effective against *S. pyrogenis*, *S. faecalis*, *P. aeruginosa* and *Lactobacillus acidophilus* [25,31,32].

Role of *S. persica* in dental plaque control

Dental plaque is a general term used for the diverse microbial community (predominantly bacteria) found on the tooth surface, embedded in a matrix of polymers of bacterial and salivary origin. Plaque develops naturally on teeth, and forms part of the defense systems of the host by helping to prevent colonization of enamel by exogenous (and often pathogenic) microorganisms (colonization resistance) [33]. Plaque is found preferentially at protected and stagnant surfaces, and these are at the greatest risk of disease [34]. Moreover, the attachment, growth, removal and reattachment of bacteria to the tooth surface are a continuous and dynamic process. Dental plaque, biofilms of microorganisms on tooth surface, plays an important role in the development of caries and periodontal disease. Plaque is found preferentially at protected and stagnant surfaces, and these are at the greatest risk of disease [34]. It was established that mutans group of *Streptococci* are the key agents causing dental caries [35]. According to studies, mutans *Streptococci* can colonize the tooth surface and initiate plaque formation by their ability to synthesize extracellular polysaccharides from sucrose, using glucosyl transferase [36,37]. This sucrose dependent adherence and accumulation of cariogenic streptococci is critical to the development of pathogenic plaque [37]. Some types of interactions are thought to be of primary importance in the colonization of the periodontal environment [38]. The further accumulation of plaque around the gingival and subgingival region may lead to a shift in its microbial composition from *Streptococcus*-dominated to a larger number of *Actinomyces spp.,* and an increased number of capnophilic and obligatory anaerobic bacteria, such as *Porphyromonas gingivalis* [39]. Several *in vitro* studies have indicated that *Salvadora persica* contains substances that possess dental plaque inhibiting properties against oral microbes [40-43]. Almas [41] showed amazing antibacterial effects of Miswak on *Streptococcus mutant* and *fecalis,* which are the key agents of plaque formation. However, among the studies conducted at mass level, Danielsen [44] studied two groups of students in Kenya. One group used chewing sticks plus toothpaste, and the other group used only chewing sticks. There were no extra effects in removing dental plaques in the group that used tooth-paste in addition to chewing sticks. Wolinsky et al. [45] showed that *S. persica* decreases the ability of some *Streptococcus* to colonize on teeth surfaces, which in turn affects the rate of plaque formation. The studies conducted by Sofrata et al. [46] reported that the difference in plaque pH between Meswak extract and water rinse was statistically significant at 30 min ($p<0.001$). Rinsing with Meswak extract stimulated parotid gland secretion ($p<0.01$). Meswak extract raised the plaque pH, suggesting a potential role in caries prevention. Almas [9] concluded that toothbrushes and Meswak (chewing sticks) are widely used for the mechanical removal of plaque.

Other biological uses of *S. persica*

Meswak (*Salvadora persica*) is one of the most commonly used medicinal plants for oral hygiene among global Muslim community [2]. *S. persica* is found to be a multipurpose plant and possesses several agro-pharmaceutical applications. Toothbrushes prepared from the roots and small branches of *S. persica*, to be highly useful as maintainer of teeth [3,47]. Plant possess anti-microbial, anti-plaque, aphrodisiac, alexiteric, analgesic, anti-inflammatory, anti-pyretic, astringent, diuretic and bitter stomachic activities [48]. It has great medicinal use in the treatment of nose troubles, piles, scabies, leucoderma, scurvy, gonorrhea, boils and toothache, to treat hook worm, venereal diseases, for teeth cleaning, in rheumatism, cough and asthma, to lower cholesterol plasma levels, reestablishment of the components of gastric mucosa, and as a laxative [8,49]. Elvin-Lewis et al. [50] showed that the dental loss in adults is very low in the countries where Meswak is used widely. *S. persica* seed oil is useful for the treatment of some skin diseases and joint pain [51]. Mansour et al. [52] also reported that the plant extract itself has an analgesic effect against heat stimuli, but not the chemical stimuli. In Greco-Arab system of medicine, the fermented juice prepared from the fresh fruits is a strong aphrodisiac agent, and is also used as general body tonic [51,53].

Discussion

In several studies, medicinal plant extracts, plant products and isolated phytochemical constituents showed highly significant antimicrobial activity, On the other hand, the observed bacterial resistance and undesirable side effect of certain antibiotics led scientific community to find new antibacterial compounds from medicinal plants, or to prepare synthetic and semi-synthetic antibacterial drug products with low toxicity, which ultimately added more to encourage research on such potential natural drugs. *S. persica*, commonly called Meswak or Toothbrush tree, is one of the most popular medicinal plants that has proved to be effective in the prevention of tooth decay and mouth infections [29]. Recently, *S. persica* extract has been used in some toothpastes under different trade names like Ouali Meswak, Pharba, Sarakan, Backenham UK, Basaraj and Epident [54]. The traditional use of *S. persica* as antimicrobial toothbrush stick for oral hygiene, and to treat gum inflammation, is a centuries old practice, and a part of Greeko-Arab system of medicine [2,55,56]. *S. persica* is known to contain several biologically active constituents such as volatile oils, flavonoids, alkaloids, steroids, terpenoids, saponins and carbohydrates [4-6]. Roots of *S. persica* were found to contain salvadourea, a urea derivative [7]. *S. persica* and other related plants are reported to be effective against broad spectrum microbes that are imperative for the

development of dental plaque. Keeping in view the popular use of miswak in the whole Muslim world and Saudi Arabia, in particular, the present endeavour was initiated with the aim to prepare an inventory of the ethnobotanical and ethno pharmaceutical importance of *S. persica*. The present study will also add important points to the disciplines of ethno pharmacy and medicine.

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