PHARMACOLOGICAL, THERAPEUTIC AND PHYTOCHEMICAL ATTRIBUTES OF “SALVADORA PERSICA” PLANTS

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ABSTRACT

Toothbrushes and dentifrices are widely used in the modern era for cleaning teeth. For centuries, twigs from medicinal plants were used as natural toothbrushes. Arabs, Greeks and Romans used twigs and chewing sticks as oral hygiene aids since 3500 BC [1]. The twigs of plants were considered teeth cleaners in the age of Babylonians, some 7,000 years ago [1,2]. Ancient Egyptians, Israelites, Romans [3] and Arabian ancestors utilized these twigs to make their teeth white and shiny. More than 180 plant species have been used as teeth cleaning and chewing twigs in different parts of the world. The most popular and most extensively used of these have been Miswak twigs from the Salvadora persica tree [4]. Miswak contains many phytochemical constituents, making it a good oral hygiene aid.

Dental caries and periodontal diseases are caused by bacterial plaque. Dental plaque removal is very effective in treating gingivitis [5]. Mechanical and chemical methods are available for the maintenance of dental plaque removal and oral health. The use of Miswak for oral hygiene serves a dual function, i.e., mechanical plaque control by friction between plant fibers and tooth surfaces and chemical plaque control due to its phytochemical composition [2]. The Miswak chewing stick removes plaque from interproximal sites as well as more accessible sites. [6] As subgingival microbiota is similar irrespective to gender and ethnicity, [7] the benefits of Miswak provide a means of progressive dental hygiene.

In 1986 and 2000, the World Health Organization (WHO) endorsed the use of Miswak twigs in an international consensus statement on oral hygiene for regions where its use is customary, and concluded that further research was required to document its effects [8-12]. Several pursuant studies suggest it contains a number of medically beneficial properties, including being antiseptic, astringent, abrasive, detergent, enzyme inhibiting and fluoridative [2,13-16].

Fresh samples of different parts of the S. persica tree were collected in replicate from different geographical locations, viz., Yemen, Sudan, Egypt, Algeria, Saudi Arabia, Syria, India and Pakistan, and were chemically analyzed. Phytochemical data found approximate qualitative agreement with other investigators while quantitative results varied slightly from location to location and season to season. Samples from Yemen, Sudan and Egypt showed slightly higher yields on average compared to yields in the samples from other countries.

S. persica is a large, well-branched, evergreen shrub or a tree resembling Salvadora oleoides found in the Middle East, Africa and the arid regions of India and Pakistan. S. persica has multiple reports of potential medicinal characteristics. S. persica is identified to have antiurolithiatic [17], antiplaque, analgesic, anticonvulsant, antibacterial, antymycotic, cytotoxic, antifertility, deobstruent, carminative, diuretic,
astringent, hypolipidemic, antiulcerative, antibilious and antirheumatic characteristics. This research will identify for the first time the pesticidal characteristics of *S. persica*. In addition, various phytochemical, therapeutic and pharmacological attributes, along with quantification of the chemical constituents containing periodontal health benefits from different parts of *Salvadora persica* tree are discussed in this paper.

**Keywords:** Antibacterial, hypolipidemic, Miswak, Salvadoras persica

1. **INTRODUCTION**

*Salvadora persica* Linn., commonly known as Arak [18], *Galena asiatica*, Siwak or Meswak or Miswak, Peelu, Pilu, *Salvadora indica*, or toothbrush tree or mustard tree, is a species of *Salvadora* [19,20]. It is widely distributed in the Middle East, Africa and the arid regions of Indo-Pak sub-continent and often on saline soils too. The use of *Miswak* predates the inception of Islam, which was adhered to by the ancient Arabs to get their teeth white and shiny [2,21]. Elvin Lewis has mentioned that *Miswak* root and bark have been traditionally used over 1000 years as a chewing-stick or natural toothbrush to strengthen the gums [22]. The end of a pencil-sized stick is shaped into a brush through biting or chewing on one end, which serves to separate its fibers frayed into a brush and release the healing herbal powers of the twig.

The beneficial effects of *Miswak* with respect to oral hygiene and dental health are partially due to its mechanical action and partly owing to its pharmacological action. Some investigators have identified various chemical constituents in different parts of *Miswak* tree, which are responsible for its pharmacological activities, e.g., Farooqui, *et al.* isolated benzyl isothiocyanate from the root of *S. persica* and claimed to have found saponins along with tannins, silica, a small amount of resin, trimethylamine and a fairly large amount alkaloidal constituents [23]. Ray, *et al.* isolated δ-sitosterol [Fig. 6], m-anisic acid, and salvadoure (1,3-Bis-(3-methoxy-benzyl)-urea) [24]. Lewis and Elvin-Lewis reported high minerals content of 27.06% in the root [25].

1.1 **Botanical & Ecological Descriptions**

1.1.1 **Taxonomy**

**Kingdom:** Plantae  
**Division:** Magnoliophyta  
**Class:** Magnoliopsida  
**Authority:** L.  
**Order:** Brassicales  
**Family:** Salvadoraceae  
**Genus:** Salvadoras  
**Species:** Salvadoras persica persica oleoides  
**Unranked:** Angiosperms; Eudicots; Rosids  
**Synonym(s):** Salvadoras cyclophylla Chiov., Salvadoras indica Wight, Salvadoras wightiana Planch [26].

1.1.2 **Common Names:** Aarak, Arak, Arrak, Arraka, el Rak, Kabats, Shaow, Shau, Aiwak, Siwak, Sewak, Swak (Arabic); Darakhte Miswak (Persian); Mustard tree, Salt bush, Toothbrush tree (English); Arbre a cure-dents, Arbre a frotte-dents (French); Regree mosterdboom (Afrikaans); Msuake, Msuaki, Musuake (Swahili); Ade, Adhe (Somali); Mejaka (Ethopian), Mswaki (Tanzanian), Aday, Yeharer-mefaqya (Amharic); Adai, Hadai (Tigrigna); Kayu Sugi (Malay); Misvak (Turkish); שלｖודﺮﻩ ﻲ ﻦése (Hebrew); Koyoji (Japanese), Khakhin Kickni (Marathi); Pelu, Peelu, Pilu, Peelo, Miswak, Meswak, (Urdu); Jhak, Harjal, Datun (Hindi); Kharijal (Gurjati); Jal (Bengali); Kalawa, Karkol, Perungoli, Ughaiputtai, Vivay; (Tamil); Ghunia (Telgu); Goni-Mara (Kanada); Kotungo (Oriya) [27,28].

Its generic name was given by a famous botanist, Dr. Laurent Garcin, in 1749 in the honor of Juan Salvadory Bosca (1598-1681), an apothecary of Barcelona. The true specimen of this species came from
Persia (Iran), as its specific name ‘persica’ indicates and the abbreviation L. is used to indicate Carl Linnaeus (1707-1778), a Swedish botanist, physician and zoologist, the father of modern taxonomy. The Botanic Gardens Conservation International has counted totally eight S. persica plants in conservation [29].

1.1.3 Vegetal Characteristics

S. persica is Phanerophyte, upright evergreen shrub or a small tree, reaching normally to a maximum height of about 3 m. The main trunk, which is seldom > 1 foot in diameter, is erect or trailing with profusely branched, wide crown of crooked, straggling and drooping branches [Fig. 2] and has soft whitish yellow wood. The young branches are green and the bark is soft, scabrous and cracked, whitish with pendulous extremities. But, the bark of old stems is rugose, drooping, glabrous, terete, finely striate, shining and almost white [Fig. 1].

The leaves are light to dark green, sharp-tipped, somewhat fleshy, glaucous, 3.8-6.3×2-3.2 cm in size, oblong-elliptic lanceolate or ovate, less commonly rounded, obtuse and often mucronate at the apex, which is broadly tapering to rounded, and sometimes with wart-like glandular dense dots. The base is broadly tapering and usually acute. The main nerves are in 5-6 pairs. The petioles are 1.3-2.2 cm long and glabrous. The leaves grow in opposite pairs [Fig. 4]. The tree sheds the leaves from late December to January. The leaves break with a fine crisp crackle when stepped over.

The flowers are pedicellate, greenish-white or greenish-yellow, very small, slender-branched with 5-12.5 cm long axillary and terminal panicles, numerous in the upper axils, 1.5-3 mm long pedicels with bracts underneath, ovate and very caducous. The calyx is 1.25 mm long, glabrous, cleft halfway down with rounded lobes. The corolla is very thin, 3 mm long, deeply cleft, persistent, with 2.5 mm long lobes, oblong, obtuse and much reflexed. The stamens are shorter than corolla, but exerted owing to reflexed corolla lobes. The drupe is 3 mm in diameter, globose or round and smooth, which becomes red when ripe [Fig. 4]. The flowering period is usually from January to April.

The fruit is small, pea-sized, spherical berry, fleshy, single seeded, 5-10 mm in diameter and pink to scarlet in color when mature [Fig. 3]. And the seeds are (1-4 mm) sub-globose, smooth, semi-transparent when mature and turn from white to pink or purple-red. The root bark is light brown (sand like color) and the inner surface has even lighter brown shade.
1.2 Distribution

1.2.1 Geographic Distribution

It is widely distributed in the Middle East and most of the African countries [30], like Algeria, Angola, Cameroon, Chad, Egypt, Eritrea, Ethiopia, Kenya, Libyan Arab Jamahiriya, Malawi, Mali, Mauritania, Mozambique, Niger, Nigeria, Republic of Sudan, Zambia, Zimbabwe, Senegal, Tanzania, Uganda, Somalia, South Africa, Kingdom of Saudi Arabia, The Hashemite Kingdom of Jordan, Syrian Arab Republic, Sultanate of Oman, Republic of Yemen, Islamic Republic of Iran, Israel, Republic of India, Islamic Republic of Pakistan and Sri Lanka [5,26,31,32].

1.2.2 Natural Habitat

S. persica is widespread, notably in thorn shrubs, desert floodplains, river and stream bank vegetation and grassy savannahs. It prefers areas where groundwater is readily available, e.g., by riverbanks, perimeters of waterholes, seasonally wet sites and along the drainage lines in the arid zones. It is also found in valleys dunes and termite mounds. S. persica is a thermophilous plant; hence able to tolerate a very dry environment with mean annual rainfall of less than 200 mm. It is highly salt tolerant and hence can also grow on coasts and inland saline soils [26]. In Pakistan, these sturdy trees are more closely associated with the graveyards.

1.2.3 Biophysical Limits

Altitude: 0-1800 m; Rainfall: 300-1000 mm; Soil / Weather Type: S. persica prefers clays, but also found on loam, black soils and sand. It is adapted to alkaline or very saline soils, usually clay-rich, and soils without salt. Apart from salt tolerance, it is drought resistant and well-adapted to arid conditions.

1.3 Botanical Management

1.3.1 Propagation & Seedling Management

S. persica readily germinates from seeds, which exhibit no dormancy but the fruit pulp contains germination inhibitors, which should be removed before sowing. The soaked and de-pulped seed usually germinates in 24-72 hours at 30-35°C, but under saline conditions the absorption of water depends upon the osmotic pressure of the medium and the cell sap. The seeds are raised in the nursery for up to 3 years prior to transplanting in the field [26].

1.3.2 Tree Management

S. persica is generally a slow-growing tree and grown in plantations or hedges. For high seed settings and seed oil content, harvesting is recommended 3 months after seed setting. It may be due to the
utilization of food reserve in the cotyledons for the development of fruit pulp. Coppicing is beneficial for the tree’s usage as fuel. The branches are repeatedly pruned to produce short stems that are harvested for tooth-sticks [26].

1.3.3 Germplasm Management
The seeds of *S. persica* can be traditionally dried slowly under ambient conditions at 15-20% relative humidity (eRH) and stored with low moisture content. If the seeds are not properly dried and stored under optimal conditions, its storage life and viability is reduced. There are about 3400 seeds/kg [26]. Other useful literature referring to botanical, ecological and functional uses of *S. persica* are [33-51].

1.3.4 *S. persica* Twig Preservation
Some companies, such as Al-Khair, Al-Falah, Al-Areeesh International, Sewak-us-Sunnah, Siwak As-Safa, Sewak Al-Khaleej, Sewak Al-Badr, Sewak Al-Harmain, Sewak Al-Muslim, Gowo Miswak Sticks, Miswak Club Stick, Baton De Miswak, Al-Jannatal Firdous Miswak, etc., have taken initiatives to process and preserve *S. persica* tooth-sticks in vacuum-packed sachets for increasing the twig’s shelf life to a period of over six months without adding any preservative or formaline- soaking and use it for commercial purpose.

1.4 Traditional Uses of Various Parts of *S persica* Tree
Multiple functional uses of *S. persica* tree have been extensively reviewed in the literature [52-54]. Some traditional uses of different parts or products of the tree are as follows:

1.4.1 Food: Its fruit has a sweet, agreeable, aromatic, slightly pungent and peppery taste and can be eaten raw, cooked or dried and stored [Fig. 5]. When ripe, the fruit (with or without seeds) contains about 1.7-1.86% sugars. In some parts, fermented drink is reported to be made out of its fruits. The fresh leaves of *S. persica* are slightly bitter and aromatic with a mustard-like taste and cooked to be used as sauce and eaten with couscous or as green vegetable in the eastern tropical part of Africa. The tender shoots and leaves are eaten as salad too. Its seeds and seed oil are edible and edible salts are obtained from its ashes.

1.4.2 Fodder: The leaves and young shoots are browsed by all livestock but the cattle are usually not reared in the driest part of the *S. persica* distribution range. Hence, the leaves and young shoots are used as the fodder for the camels, sheep and goats. Due to high water content, between 15-36%, its leaves make a good forage. The high salt content in the leaves is believed to affect the taste of milk increase the lactation in cows.

1.4.3 Apiculture: *S. persica* is also reported as a good source of nectar.

1.4.4 Fuel: Sometimes the wood is used for firewood and charcoal but not used to cook the meat as it leaves a foul taste.

1.4.5 Timber: The wood being soft, white, easy to work, and above all safer to termite attack, is used for coffins and clubs.

1.4.6 Gum or Resin: The resin that drips from the tree is used in the production of varnishes.
1.4.7 Lipids: The seeds of *S. persica* have bitter taste and contain about 30-40% of a greenish-yellow non-edible oil that has > 50% of *lauric*, *myristic* and *palmitic* acids. The unrefined oil has unpleasant odor with high melting point but the low percentage of C₈ and C₁₀ fatty acids in its oil is the most important aspect and of course of great economic significance. This oil is an alternative source of oil for soap and detergent industries.

1.4.8 Medicine: The roots and small branches of about 3-5 mm diameter of *S. persica* have been used as toothbrushes for oral hygiene for over thousands of years [3]. The chewing-stick from *S. persica* is an ancient traditional way to clean the teeth. The best Siwak is that taken from the subterranean roots of *S. persica*. It has a pleasant fragrance but pleasantly bitter taste. *S. persica* twig is still a popular chewing-stick throughout Arabian Peninsula and the wider part of Muslim world [55] including India, Pakistan and African countries for its virtues quoted and extolled from the Prophet Muhammad (m.p.b.u.h.) [56]. Apart from strengthening the gums, it prevents tooth decay, eliminates toothaches and halts further decay that had already set in. It creates a fragrance in the mouth, eliminates bad odor, improves the sense of taste and causes the teeth to glow and shine [21].

Akhtar, *et al.*, have reported that other parts of the *S. persica* tree also have therapeutic values as corrective, deobstruent, liver tonic, diuretic, analgesic, anthelmintic, astringent, lithontriptic, carminative, aphrodisiac, and stomachic [21]. Al-Lafi, Homer and Almas, *et al.*, have demonstrated in vitro that the aqueous extracts of *S. persica* have growth inhibitory effects on several oral microorganisms [57-59]. Its natural antiseptics have a bactericidal action, killing harmful microorganisms in the mouth, the *tannic acid* it contains has astringent qualities, which protect the gums from disease, and its aromatic oils increase salivation. Because of its built-in antiseptics, the *S. persica* needs no cleaning.

Several biologically active chemical constituents identified in its bark and wood have been suggested to prevent dental *caries* [60] and the *antimicrobial* agents suppress the bacterial growth and formation of plaque. Apart from cleaning teeth, the tooth-stick made of its root relieves from toothache and gum diseases. Decoctions of *S. persica* leaves are used as a mouthwash and ground leaves for tooth and gum problems. The leaves are also used in traditional medicine for cough, asthma, scurvy, rheumatism, piles, de-obstruent, astringent to the bowels, tonic to the liver, diuretic, analgesic, anthelmintic, useful in *sputum* and other nasal problems, scabies, leukoderma, lessening inflammation and strengthening of teeth. Its pungent leaves are considered as antidote to all sorts of poisons in Punjab, a northern state in India, and an external application in the treatment of rheumatism in Mumbai and Kokan belt on the southern west coast of India. The flowers are used as a stimulant and are mildly purgative.

The fruits of *S. persica* possess *deobstruent*, *carminative*, *diuretic*, *lithontriptic* and *stomachic* properties and used in biliousness and rheumatism. The stem bark is used as an ascariduge and a remedy in gastric troubles. Herbal Practitioners (both Greek and *Ayurvedic*) have used the decoction of its root to treat gonorrhea, spleen sufferings, general stomachache, body pain, back pains, vesical catarrh and some chest diseases. Its roots are prepared as a salve and rubbed on the face for headaches. The paste of the root is also applied as a poultice or substitute to mustard plaster to heal boils and the latex from scratched bark is used for treating sores. The root bark is used as a vesicant and employed as an ingredient of snuff. A decoction of the bark is used as a tonic in amenorrhea, a stimulant in low fevers and an *emmenagogue*. The seeds of *S. persica* are used as purgative, diuretic and tonic and its oil is externally applied in case of rheumatism [61,62]. In Pakistani province of Sindh, it is believed that its fruit has curative effect on snakebites.
1.4.9 **Shade & Shelter:** *S. persica* is planted as shelterbelts and windbreaks to protect habitation of farms, gardens and orchards.

1.4.10 **Reclamation & Anti-desertification:** *S. persica* is planted for reclaiming sand dunes and saline soils. Dr. Rami Mohammed Diabi, an internist at the University of Kentucky Albert B. Chandler Hospital, Lexington, Kentucky, USA, reported that *S. persica* is contributing to fight against desertification, fixing the soil and affecting the environment and global climate [63,64].

1.4.11 **Some Other Uses:** Crusted leaves of *S. persica* with the leaves of *Pergularia tomentosa* were used earlier to remove the hair from tanned hides. Its roots contain a *urea* derivative, called **salvadourea**.

2. **PHYTOCHEMICAL COMPOSITION & THEIR USEFUL IMPACTS**

Different parts of the *S. persica* plant have shown various chemical components when analyzed by different methods [25,65-68]. The chemical and phytochemical analysis of *S. persica* root bark showed containing large amount of chlorine, carbohydrates and/or a *tri-methylamine*, an *alkaloid*, which may effectively be *salvadorine*, and a resin [69]. Further investigations revealed it to contain chloride, sulfur, terpenes, vitamin C, glycosides, large amounts of fluoride and silica, small amounts of tannins, saponins, flavonoids and sterols [32,69,70]. El-Mostehy, *et al.*, also reported finding *Tri-methylamine*, an *alkaloid*, chlorides, high amounts of fluoride, Silica (*SiO₂*), Sulfur, vitamin C, and small amounts of tannins, saponins, flavonoids and sterols [71]. Manu Arora, *et al.*, isolated the flavonoids and flavonoids glycosides from *S. persica* [72].

Dr. William Carl, a Senior Cancer Dental Surgeon at Roswell Park Cancer Institute and Clinical Associate Professor of Fixed Prosthodontics at the UB School of Dental Medicine, reported that *S. persica* sticks not only serve as natural toothbrushes when used correctly, but contain oral health promoters, such as chlorides, fluoride, silica, vitamin C and flavonoids [16]. Some investigators listed the presence of *sinigrin*, *salicylic acid*, *calcium oxide* and *sodium bicarbonate* in the *S. persica* extracts. Attar also indicated that *S. persica* plant fibers contain *sodium bicarbonate* [73]. Akhtar and Ajmal found resin and large amounts of salts containing chloride [70] and Chawla reported that *S. persica* contain a reasonable amount of fluoride [74].

When the extract of *S. persica* stem was subjected to more advance phytochemical investigations, it yielded octacosanol, 1-triacanotanol, β-sitosterol, and β-sitosterol-3-O-β-D-glucopyranoside [75]. During initial screening, Thin Layer Chromatography (TLC) revealed that the stem extract is a mixture of two compounds, which were later separated by Column Chromatography. One of the compound in this mixture in white needle shape was characterized having a melting point (m.p.) of 136-7°C, *m/z* = 414 (mass) and molecular formula C_{29}H_{50}O (C = 83.75%, H = 12.25%). It gave positive Salkowski, Liebermann, Burchard reaction, Noller reaction, Brieskron, Tschagajew and yellow color with *tetracentratmethane* [76-78]. In Infrared (IR) spectrum, the peaks at \( V_{\text{max}}^{\text{KBr}} \) 3500, 1450, 1470, and 1145 cm\(^{-1}\) identified this compound to be β-sitosterol. The other white crystalline compound was found having a m.p. of 265-68°C, molecular formula C_{35}H_{60}O_{6} (C = 72.9%, H = 14%) and *m/z* [α]_{D}^{29} -36.2 gave positive result for *saponin* and on hydrolysis yielded β-sitosterol and glucose, identified as β-sitosterol-3-O-β-D-glucopyranoside. The essential oil contained α- and β-thujones, *camphor*, *cinoloe*, β-cyrene, limonene, β-myrence, borneol, *linalool* and bornyl acetate, whereas the nonvolatile fraction contained *humulene*, *caryophyllene*, β-santatol and *farnesol* [79]. Farooqui and Srivastava reported that the chemical analysis of *S. persica* demonstrated the presence β-sitosterol, *m-anisic acid*, chlorides, *salvadourea*, *gypsum*, organic compounds (such as, *pyrrolidine*, *pyrrole*, and *piperidine derivatives*),


glycosides (such as, salvadoside and salvadoraside) and flavonoids, including kaempferol, quercetin, rutin and quercetin glucoside [23].

Khalil, has also isolated Benzylationamide. The compounds isolated were identified as butanediadime, N1, N4-bis(phenylmethyl)-2(S)-hydroxy-butadime, N-benzyl-2-phenylacetamide, N-benzyl-benzamide, and benzyl urea. The compound N-benzyl-2-phenylacetamide has a significant inhibitory effect on human collagen-induced platelet aggregation and a moderate antibacterial characteristics against Escherichia coli [80]. Ezmirly, et al., have isolated glutotropaeolin from S. persica [81]. Mohammed A., et al., have found the root of S. persica containing a steam-distillable oil composed of 90% benzyl isothiocyante and 10% benzyl nitrate [82]. Feras Alali, et al., when subjected the volatile oil extracted from S. persica L. leaves to GC-MS analysis, could identify benzyl nitrile, eugenol, thymol, isothymol, eucalyptol, isoterpinolene, and g-caryophyllene [83].

However, the leaf galls contain heavy metals, which possess some growth promoting principles. Table 1 represents the metal contents in the Control and the Gall samples of S. persica plants from different countries of origin. The data obtained indicates generally higher contents of Iron (Fe), Copper (Cu), Zinc (Zn), Sulfur (S), Manganese (Mn), Cobalt (Co), Nickel (Ni), Cadmium (Cd), Molybdenum (Mo), Lead (Pb), Vanadium (V), Cerium (Ce), Titanium (Ti) and Mercury (Hg) in the galls when compared to their respective contents in the control. These metals are known to interact with biological systems and plant diseases, which result from the excess or the lack of the element(s) [84].

<table>
<thead>
<tr>
<th>Sample Source / Metals</th>
<th>India/Pakistan</th>
<th>Egypt/Sudan</th>
<th>Algeria</th>
<th>Saudi Arabia/Syria</th>
<th>Yemen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron (Fe)</td>
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<td>51.5</td>
<td>5.40</td>
<td>48.20</td>
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<tr>
<td>Copper (Cu)</td>
<td>5.7</td>
<td>7.3</td>
<td>7.5</td>
<td>8.7</td>
<td>5.9</td>
</tr>
<tr>
<td>Zinc (Zn)</td>
<td>4.6</td>
<td>4.8</td>
<td>4.7</td>
<td>4.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Sulfur (S)</td>
<td>6.2</td>
<td>8.3</td>
<td>7.4</td>
<td>8.8</td>
<td>7.6</td>
</tr>
<tr>
<td>Manganese (Mn)</td>
<td>17.3</td>
<td>21.9</td>
<td>18.0</td>
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<td>19.5</td>
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<tr>
<td>Cobalt (Co)</td>
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<td>14.6</td>
<td>12.2</td>
<td>10.81</td>
<td>10.64</td>
</tr>
<tr>
<td>Nickel (Ni)</td>
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<td>10.3</td>
<td>8.4</td>
</tr>
<tr>
<td>Cadmium (Cd)</td>
<td>0.18</td>
<td>0.20</td>
<td>0.18</td>
<td>0.19</td>
<td>0.20</td>
</tr>
<tr>
<td>Molybdenum (Mo)</td>
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<td>0.50</td>
<td>0.26</td>
<td>0.35</td>
<td>0.18</td>
</tr>
<tr>
<td>Lead (Pb)</td>
<td>0.16</td>
<td>0.18</td>
<td>0.21</td>
<td>0.24</td>
<td>0.16</td>
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<tr>
<td>Vanadium (V)</td>
<td>0.005</td>
<td>0.14</td>
<td>0.003</td>
<td>0.006</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 1: Average Concentration of Metals in Control & Galls of S. persica Plant (ppm)
2.1 Seasonal Changes in the Proteins and Amino Acid Contents

Notable changes in protein contents and amino acid concentrations in all samples of *S. persica* were observed during summer, winter and monsoon seasons. Earlier Maggio, *et al.*, had also reported such changes after analyzing 12 samples from soil (0-15) and plant materials every month from three saline habitats of *S. persica* near Bhavnagar, India. The results obtained in the samples of *S. persica* plant for Asparagine, Aspartic, Alanine, Arginine, Glycine, Glutalic Acid, Glutamina, Isoleucine, Leucin, Prolin and Valin are presented in Tables 2; whereas, Table 3 represents the seasonal variation of the mineral contents (Meq g⁻¹ d.wt.) in *S. persica* leaf and stem. Minerals determined were Sodium (Na⁺), Potassium (K⁺), Calcium (Ca²⁺), Magnesium (Mg²⁺), Chloride(Cl⁻) and Ash [85-87]. The range of variations in average concentrations found in the samples from different countries of origin, viz., Yemen, Sudan, Egypt, Algeria, Saudi Arabia, Syria, India and Pakistan, are indicated by ± values.

<table>
<thead>
<tr>
<th>Proteins / Amino Acids</th>
<th>Stems</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Leaves</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Summer</td>
<td>Monsoon</td>
<td>Winter</td>
<td>Summer</td>
<td>Monsoon</td>
<td>Winter</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Asparagine</td>
<td>370±105</td>
<td>336±81</td>
<td>268±94</td>
<td>279±92</td>
<td>184±46</td>
<td>165±35</td>
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<tr>
<td>Aspartic</td>
<td>445±72</td>
<td>619±88</td>
<td>356±76</td>
<td>432±76</td>
<td>310±48</td>
<td>504±172</td>
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<tr>
<td>Alanine</td>
<td>160±21</td>
<td>122±23</td>
<td>98±10</td>
<td>226±25</td>
<td>232±34</td>
<td>180±26</td>
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<tr>
<td>Arginine</td>
<td>95±34</td>
<td>59±26</td>
<td>133±44</td>
<td>136±62</td>
<td>76±33</td>
<td>129±44</td>
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<tr>
<td>Glycine</td>
<td>33±10</td>
<td>35±5</td>
<td>27±7</td>
<td>56±17</td>
<td>56±17</td>
<td>83±26</td>
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<tr>
<td>Glutalic Acid</td>
<td>68±12</td>
<td>56±14</td>
<td>61±15</td>
<td>94±24</td>
<td>93±11</td>
<td>111±28</td>
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<tr>
<td>Glutamina</td>
<td>67±13</td>
<td>55±18</td>
<td>65±12</td>
<td>98±23</td>
<td>90±12</td>
<td>110±27</td>
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<tr>
<td>Isoleucine</td>
<td>59±23</td>
<td>54±13</td>
<td>21±6</td>
<td>89±34</td>
<td>66±16</td>
<td>62±17</td>
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<tr>
<td>Leucin</td>
<td>78±24</td>
<td>63±11</td>
<td>23±8</td>
<td>110±46</td>
<td>79±15</td>
<td>76±26</td>
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<tr>
<td>Prolin</td>
<td>26±9</td>
<td>29±4</td>
<td>22±5</td>
<td>40±6</td>
<td>35±10</td>
<td>24±9</td>
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<tr>
<td>Valin</td>
<td>44±12</td>
<td>190±25</td>
<td>41±11</td>
<td>47±19</td>
<td>77±14</td>
<td>65±25</td>
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Table 2: Seasonal Variations in Average Proteins & Amino Acid Contents in *S. persica* Plant

<table>
<thead>
<tr>
<th>Plant Parts / Seasons / Ions</th>
<th>Stems</th>
<th></th>
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<th></th>
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<th>Leaves</th>
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<tbody>
<tr>
<td></td>
<td>Summer</td>
<td>Monsoon</td>
<td>Winter</td>
<td>Summer</td>
<td>Monsoon</td>
<td>Winter</td>
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<tr>
<td>Na⁺</td>
<td>1.16±0.16</td>
<td>0.71±0.35</td>
<td>0.72±0.03</td>
<td>2.66±0.70</td>
<td>1.50±0.35</td>
<td>1.87±0.19</td>
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<tr>
<td>K⁺</td>
<td>0.49±0.06</td>
<td>0.39±0.07</td>
<td>0.39±0.04</td>
<td>0.23±0.06</td>
<td>0.31±0.05</td>
<td>0.20±0.02</td>
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<tr>
<td>Na/K</td>
<td>0.05</td>
<td>0.04</td>
<td>0.03</td>
<td>0.26±0.04</td>
<td>0.07±0.03</td>
<td>0.14±0.03</td>
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<tr>
<td>Ca²⁺</td>
<td>1.58±0.13</td>
<td>0.16±0.14</td>
<td>0.45±0.16</td>
<td>2.64±0.11</td>
<td>2.31±0.04</td>
<td>2.38±0.05</td>
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<tr>
<td>Mg²⁺</td>
<td>0.66±0.08</td>
<td>0.53±1.05</td>
<td>0.64±0.09</td>
<td>1.51±0.26</td>
<td>0.94±0.06</td>
<td>1.14±0.15</td>
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<tr>
<td>Cl⁻</td>
<td>2.10±0.22</td>
<td>1.62±0.15</td>
<td>1.72±0.15</td>
<td>3.52±0.05</td>
<td>2.17±0.15</td>
<td>2.91±0.16</td>
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</tbody>
</table>

Table 3: Seasonal Variations of Average Mineral Ions in *S. persica* Leaf & Stem (Meq g⁻¹ d.wt.)
2.2 Analytical Techniques Applied

For the elemental analyses, Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) and Atomic Absorption Spectroscopy (AAS) techniques were used. For the characterization of organic composition, various techniques were applied, viz., Liquid Chromatography Organic Carbon Detection (LC–OCD), Pyro/Gas Chromatograph Mass Spectrometer (GC–MS), Specific UV Absorbance (SUVA), Fourier Transform Infrared (FT–IR) Spectroscopy and Solid State $^{13}$C-Nuclear Magnetic Resonance (NMR) Spectroscopy.

2.3 Useful Impacts of Different Phytochemical Constituents

2.3.1 Fibers: Various explanations for the cleansing efficacy of the *S. persica* have been offered, e.g., the mechanical effects of its fibers, the release of beneficial chemicals or a combination of both [88].

2.3.2 Silica: Silica found in *S. persica* acts as a mild abrasive material to remove stains and deposits from the tooth surface giving the teeth whiteness [1].

2.3.3 Tannins: *Tannin* or *tannic acid* is a mixture of *gallic acid* esters and *glucose* with varying composition depending to the source. *Tannic acid* is an *astringent* that precipitates *albumin*. Its topical use is limited to the treatment of sores, minor ulcerations, etc. [89]. *Tannic acid* shows anti-tumor characteristics on animals [90]. Treating denture bases with *tannic acid* reduced *Candida* <3/Mv?/75 attachments to the surfaces [91]. *Tannins* also inhibit the action of *glucosyl transferase* thus reducing plaque and gingivitis [92]. It exerts an astringent effect on the mucous membrane, thus reducing the clinicially detectable gingivitis [89].

2.3.4 Resins: The resins are amorphous end-products of metabolism which are physically usually hard, transparent or translucent and soften or melt when heated. Chemically, resins are complex mixtures of resin acids (*resinolic* acids), resin alcohols (*resinols*), resin *phenols* (*resinotannols*), esters, and chemically inert compounds [89,93]. Resin usually forms a coating over the tooth enamel, which protects against microbial actions/caries.

2.3.5 Alkaloids: The *alkaloids* are usually the derivatives of Nitrogen-ring compounds found in plants having strong physiological or toxic effects on animal body. These are colorless crystals, bitter in taste, soluble in alcohol and partially soluble in water. The *alkaloid* found in *S. persica* is *salvadorine*, which yields *trimethylamine* on hydrolytical cleavage [94] that exerts a *bacteriocidal* and stimulatory effects on the gingiva [28].

2.3.6 Sulfur: The sulfur compounds found in *S. persica* have a *bactericidal* activity [95].

2.3.7 Essential (Volatile) Oils: The essential *volatile oils* found in *S. persica* possess characteristic aroma, exert *carminative* and *antiseptic* actions [71] and its mild bitter taste stimulates and increases salivation, which is antiseptic [96].

2.3.8 Vitamin C: The vitamin C in *S. persica* helps in promoting healthy gingivae by healing and repairing tissues.

2.3.9 Sodium bicarbonate: The Sodium bicarbonate or baking soda (NaHCO$_3$) is an alakinizing agent, which subsequently buffers acid. It has mild abrasive properties that is used as a dentifrice [97] in addition to its mild germicidal action [98].
2.3.10 Chlorides: High concentrations of chloride found in S. persica inhibit calculus formation and help in removing stains from the teeth [23,28,99,100].

2.3.11 Calcium: The calcium saturation of saliva inhibits demineralization of tooth enamel and promotes remineralization [92,99,100].

2.3.12 Fluoride: The effectiveness of a topical fluoride released in fresh S. persica saps depends on its ability to wet the tooth enamel and adequately reach caries susceptible sites such as pits, fissures and interproximal areas.

2.3.13 Organic Compounds: Benzyl isothiocyanate is reported to have a broad-spectrum bactericidal activity [12,101]. Al-Bagieh, et al., reported that benzyl isothiocyanate inhibits the growth and acid production of streptococcus mutans [12,57].

3. PHARMACOLOGICAL PRACTICES

Various practices of S. persica are cited in Greek and Ayurvedic systems but many of them are also substantiated by modern pharmacology, as reported by Hoor, et al., that S. persica is a unique plant with anti-inflammatory, analgesic, antibacterial, antifungal, anti-ulcer, anti-seizure, antioxidant, anti-platelet, diuretic and lipid-lowering characteristics hidden within a single plant [102].

3.1 Healing of Full-Thickness Wound Characteristics

Wound is a breach formed in the normal continuum of the cellular and molecular structure of the body, thereby creating a disruption in the cellular, anatomic and as well as in their functional continuity. Wound healing or wound repair is an intricate process in which the skin or organ or tissue repairs itself after injury [103]. Mahran, et al., studied the effect of phonopheresis and topical S. persica on wound healing in rats. 5% gel of S. persica aqueous extract was prepared in Carbopol 934P and applied. Results from repeated measures ANOVA test revealed a significant sequential reduction in Wound Surface Area throughout the treatment phases. Both the transdermal drug delivery, known as or phonopheresis, and the topical applications of S. persica extract gel exhibited positive effects in accelerating wound healing process in rats [104]. The phonopheresis method, which is introducing the gel using ultrasonic therapy, provide better results than the topical method. The acceleration of wound-healing process may be attributed to the phytochemical constituents present in S. persica, either any individual property or the combined effect.

Getie, et al., explained the healing mechanism as follows: The flavonoids are known to reduce lipid peroxidation, not only by preventing or slowing the onset of cell necrosis, but also by improving vascularity. Any drug that inhibits lipid peroxidation is believed to increase the strength of collagen fibers or the viability of collagen fibril, increase the circulation, prevent the cell damage and by promote the DNA synthesis [105]. Tsuchiya, et al., mentioned that flavonoids promote the wound-healing process mainly due to their astringent and antimicrobial property, which seems to be responsible for wound contraction and increased rate of epithelialization [106]. It is also explained that the results achieved may be due to the presence of benzyl isothiocyanate component in the extract of S. persica in addition to the flavonoids.

3.2 Anti-hypolipidemic Characteristics

The stem decoction of S. persica shows distinctive hypcholesterolemic properties. Galati, et al., studied the hypolipidemic characteristics of the extract of S. persica in rats [107]. The effect of prolonged
administration of a lyophilized stem decoction of S. persica was evaluated in diet-induced hypercholesterolemic rodents. The preparation was administered for 15 and 30 days and the Cholesterol, High Density Lipids (HDL), Low Density Lipids (LDL) and Triglycerides (TG) levels were assayed. The S. persica decoction significantly lowered the Cholesterol and LDL plasma levels in rodents, and was found more active at 30 days of treatment. The systemic administration of Triton resulted in the rise of plasma Cholesterol and TG levels. The results thus obtained showed that S. persica decoction was inactive at 18 hours after treatment, whereas at 27 hours it was able to reduce Cholesterol and LDL plasma levels. In all these experiments, the HDL and TG levels remained unchanged [107].

3.3 Anti-diabetic Characteristics
The aqueous extract of S. persica at 500mg/kg dose level in comparison to other extracts was reported to have significant hypoglycemic and hypolipidemic effects and regenerated pancreatic beta cells in streptozocin treated diabetic rats [108].

3.4 Antiulcer Characteristics
The antiulcer activity of decoction of S. persica has been reported in rats. The Ulcer Index decreased significantly after the treatment with a lyophilized decoction of S. persica (500 mg/kg, os), once daily for 7 days, with respect to controls [109]. S. persica possesses significant protective action against ethanol and stress-induced ulcers. A study was designed to confirm the antiulcer activity of S. persica decoction using optical microscopy. The elements of gastric mucosa tended to be re-established normally when tested in treated rodents [110].

3.5 Anticonvulsant & Sedative Characteristics
The effect of S. persica was identified as an anticonvulsant using the extracts from the stem. On rodents, the stem extracts are reported to show potentiation of Sodium pentobarbital characteristics and also on generalized tonic-clonic seizure produced by pentyl entertazol (PTZ). The extracts of S. persica extended sleeping-time, decreased induction-time induced by Sodium pentobarbital and showed protection against PTZ-induced convulsion by increasing the latency period and diminishing the death rate [111].

3.6 Antifertility Characteristic
S. persica extract did not have much effect on female mouse fertility although it significantly decreased the relative weights of ovary and increased the weights of uterine. Exposure of male mice to S. persica extracts resulted in the reduction of pregnancies by 72% in untreated females impregnated by test males. The relative weights of testes and preputial glands were found significantly increased whereas the seminal vesicles significantly decreased in the test males. These results indicate that S. persica has adverse effects on male and female reproduction systems and fertility [112].

3.7 Antiplaque Characteristics
S. persica inhibits the formation of dental plaque chemically and the value of Miswak is due primarily to its mechanical cleaning action [113]. Lower plaque scores were reported following the proper use of Miswak as an oral hygiene aid comparing to those using conventional toothbrushes [114]. In a study, which compared the efficacy of Miswak with the use of toothbrush, revealed that the use of Miswak was associated with a significant reduction of dental plaque and gingivitis along with comparable or superior oral hygiene effect [115]. It was also reported that the habitual Miswak users had lower gingival bleeding [116,117].
3.8 Antibacterial Characteristics

Al-Bayati, et al., reported that extracts of *S. persica* possesses several biological characteristics, including antibacterial [57,118]. Several in vitro studies have indicated that *S. persica* contains substances that possess dental plaque-inhibiting and antimicrobial properties against oral microbes [57,59,77,98,119-122]. Studies have indicated that *S. persica* contains substances that possess plaque inhibiting and antibacterial properties against several types of cariogenic (conducive to caries) bacteria and periodonto pathogens, which are frequently found in the oral cavity [78]. The growth of these bacteria and acid produced by them is inhibited by its acid inhibition properties [25,57,98,119]. Al-Lafi, et al., reported that the use of *S. persica* inhibits the formation of dental plaque chemically and exert antimicrobial effect against many oral bacteria [57]. They tested its antibacterial characteristics against some oral aerobic and anaerobic bacteria and reported that the extract of these sticks had a drastic effect on the growth of *Staphylococcus aureus*, and a variable effect on other bacterial species [57]. Farooqui and Srivastava reported that the Salvadorine, an alkaloid present in *S. persica* may exert a bactericidal effect and stimulate the gingival [23].

In a clinical study, after professional instruction of the proper use of Miswak and toothbrush, Miswak was found to be more effective than use of tooth brush for reducing plaque and gingivitis in a sample of male Saudi Arabians [123,124]. Gazi, et al., also reported that plaque and gingivitis were significantly reduced when Miswak was used 5 times a day compared with conventional toothbrush [117]. Almas showed that *S. persica* extracts had antimicrobial effects on *Streptococcus mutans* and *E. faecalis* [77]. In another study, pieces with identical size and weight of *S. persica* were tested against *Streptococcus mutans*, Lactobacillus acidophilus, Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis and Haemophilus influenzae. The results showed strong antibacterial effects against all bacteria tested due to the presence of a volatile active antibacterial compounds. Al-Otaibi M., et al., also observed that the use of Miswak significantly reduced the amount of *A. actinomycetemcomitans* in the subgingival plaque indicating that the *S. persica* extracts might interfere with the growth and leukotoxicity of *A. actinomycetemcomitans* [125]. In another in vitro study, the derivatives of *S. persica* also demonstrated strong antimicrobial effects on the growth of *Streptococcus sp.* and *Staphylococcus aureus* gram stain [57]. Similarly, the benzyl isothiocyanate is considered the main antibacterial component in *S. persica* root that has strong bactericidal characteristic against oral pathogens involved in periodontal disease, such as the Gram-negative periodontal pathogens *A. actinomycetemcomitans* and *P. gingivalis* [126]. Elvin-Lewis, et al., and Almas suggested that this effect may be due to the interaction with bacteria, which prevents their attachment on the tooth surface [77,127]. Ezmirly, et al., reported that the extracts of *S. persica* root yielded 8-sitosterol together with elemental Sulfur (S₈, a monoclinic form) as a constituent that has shown antibacterial characteristics. They found Sulfur-containing oil in the ash of the roots as high as 4.73% [60].

But when Abd El-Rahman, et al., subjected Actinobacillus actinomycetemcomitans (ATCC 43717), Actinomyces naeslundii (40110/87) Candida albicans (ATCC 90028), Lactobacillus acidophilus (CCUG 5917), Porphyromonas gingivalis (W50 Black), Prevotella intermedia (VPI 4197) and Streptococcus mutans (CCUG 11877) strains for antimicrobial testing of the crude extracts of *S. persica*, differed from previous findings [57,59,98,119,120] that *S. persica* extracts possess considerable antimicrobial characteristics. According to this study the *S. persica* crude extracts inhibited, reduced or enhanced the growth of the test microorganisms. Most of the extracts exerted their antimicrobial activity only at the highest concentrations used while chlorhexidine and tea-tree oil showed inhibition and growth.
reduction, respectively, at much lower concentrations. S. Mutans was the most susceptible strain to all the extracts and L. acidophilus was the most resistant. Regarding inhibition, the most potent extract was the root-ethanolic extract and the weakest one was the stem-water extract. The different reactions of each strain to the various extracts indicated that each solvent extracted different chemical components of S. persica. The strength of the antimicrobial activity may also depend on the pH of the extracts since the lowest pH was shown by the root-ethanolic extract while the stem water extract demonstrated the highest pH. It appears that S. persica has a relatively low antimicrobial activity against the selected oral pathogens when compared with 0.2% aqueous chlorhexidine [12,128]. Another comparative study of alcoholic extract of S. persica to its aqueous extract with regards to antibacterial characteristics also indicated that the alcoholic extract is more effective [120]. Almas, et al., found no difference in the antibacterial characteristics between a fresh vs. one-month old S. persica extracts [119].

In a study, published in Journal of Agriculture and Food Chemistry in 2007, it was found that mints with S. persica extracts were 20 times more effective in killing bacteria than ordinary mints [12]. It showed that in 30 min 60% of bacteria was killed by mints with S. persica extracts when compared to a meagre 3.4% by ordinary mints [129]. A study was carried out comparing Miswak, Neem, Banyan and Mango sticks, which are popular among oral hygiene aids in India, concluded that Miswak is more superior in antimicrobial activity among these chewing-sticks [130]. Strong antibacterial effect of S. persica against oral pathogens was proved when an in vitro study showed both S. persica pieces embedded in the agar plate and suspended above the agar plate at a distance of 3mm showed a zone of inhibition around the stick for Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Lactobacillus acidophilus and Haemophilus influenza. It suggested the volatile antibacterial agents present in S. persica [131].

However, Feras Alali, et al., evaluated the toxicity of aroma using brine shrimp lethality test which gave an LC 50 > 1000 ppm. Using Disc Diffusion Test, it was found that the extract of the leaves of S. persica has a considerable antibacterial effect on several different oral aerobic bacteria with comparable results to known antibiotics. The extract can be used effectively as a natural tool for teeth cleaning and as a natural analgesic for the disturbing toothache [83]. In a recent study, the strongest antibacterial characteristic of the aqueous S. persica extract was demonstrated against E. faecalis [132,133].

Further, the effects of the extracts of S. persica and derum were investigated on the proliferation of Balb/C 3T3 mouse fibroblast by measuring the mitochondrial dehydrogenase characteristics. Similarly, the effect on the viability of carcinogenic bacteria was also determined. The results indicated that S. persica and derum extracts have adverse effects on the growth of cariogenic microorganisms but derum was found more active than S. persica. The extract of S. persica showed cell proliferation by 156% and the derum extract by 255% [28].

3.9 Anti-carcinogen, Anti-genotoxic, Antineoplastic, Antifungal and Anti-herpes Characteristics

Amongst the organic compounds found in S. persica, the benzyl isothiocyanate is classified as one of the chemo-preventive agents that are thought to prevent carcinogenic and other genotoxic compounds from reaching or reacting with the target sites on the treated tissue [81,134]. Al-Dosari et al., studied the effect of benzyl isothiocyanate on the epithelial changes induced by trauma and dimethyl benzanthracin in the hamster tongue. Their results indicate that benzyl isothiocyanate retarded the development of neoplastic changes induced by trauma or trauma plus dimethyl benzanthracin [12,128,135]. A recent study showed that the ethanolic extract of S. persica has good antifungal characteristic compared to clotrimazole [136]. Al-Bagieh, et al., also noted its anti-fungal characteristic [121]. Sarvesh, et al., found that the leaves of S. persica have anti-fungal, carminative and antiseptic characteristics [137]. The benzyl
isothiocyanate isolated from *S. Persica* is also reported to have a *virucidal* characteristic against *herpes simplex virus-1* (HSV-1) replication at a concentration of 133.3 mg/ml [12,136,138,139].

**3.10 Antibiotic, Anti-inflammatory, Hypoglycemic Nontoxic & Anti-oxidant Characteristics**

The aqueous and *ethanolic* extracts of *S. persica* have been screened for broad range of pharmacological activities and the data indicates its *antibiotic, anti-inflammatory* and *hypoglycemic* characteristics. *S. persica* decoction possesses significant anti-inflammatory activity. The aqueous extract showed weak *anti-inflammatory* characteristics in a conventional *foot edema* test, whereas the *ethanolic* extract showed mild *hypoglycemic* characteristics in glucose-loaded mice at 400 mg/kg. Both extracts were found *nontoxic* at doses up to 1200 mg/kg [60]. In another study, the *ethyl acetate* extract of *S. persica* showed potent *anti-inflammatory* characteristic nearly that of *indomethacin* characteristic, which may be due to the presence of *flavonoids* in *ethyl acetate* extract [104]. *S. persica* has also revealed potent *antioxidant* capacity, which may be attributed to the *furan* derivatives and the presence of *antioxidant enzymes*, such as *peroxidase, catalase, polyphenoloxidase* [140].

**3.11 Anti-mycotic Characteristics**

Faroogi and Srivastava, and Edi, *et al.*, demonstrated the aqueous extracts of *S. persica* to have an in vitro inhibitory effect on the growth of *Candida albicans*, which may be attributed to its high sulfate contents [23]. Such inhibition lasts for up to 36 hours at concentrations of 15% and above [141]. The investigation carried out by Al-Bagieh, *et al.*, also suggest similar results [123].

**3.12 Cytotoxicity, Anti-plasmodial, Anti-HIV-1-RT & Anti-hemoflagellate Characteristics**

Mohammad, *et al.*, investigated the *cytotoxic* potential of *S. persica* on *gingival* and other *periodontal* structures using the *agar overlay* method. The results showed no *cytotoxic* effect by a freshly cut and used *S. persica*. However, the same *Siwak* used after 24 hours contained harmful components. This *cytotoxicity* became evident only after 24 hours because the *agar overlay* method depends on diffusion of medicament to the *agar*. Based on these findings, it is recommended to cut off the used portion of the *Siwak* after it was used for a day and prepare a fresh part for new use [92,98,142,143]. Ali, *et al.*, studied in vitro the *anti-plasmodial, anti-hemoflagellates, cytotoxicity* and *tyrosine kinase Inhibitory effects* of *S. persica* [144].

**3.13 Analgesic Characteristic**

Mansour, *et al.*, studied the *analgesic* effect of *S. persica* decoction when injected into mice and found that *S. persica* decoction was more effective against thermal *stimuli* than chemical *stimuli*. It also showed an *analgesic* property [119,120,145-147]. Physiologically, the response of thermal *stimuli* is via skin pain receptors, whereas chemical *stimulus* has its response via *visceral* receptors. It was found that *S. persica* responds to *peripheral* pain, not the *visceral*. Hence, it sets a relief in the oral pain if applied to the oral mucosa [148]. Experiments on mice have proved that *S. persica* has a moderate analgesic effect that is related to interaction with the peripheral opiate system [149]. It has been noted that patients using *S. persica* (*Miswak*) regularly had low incidence of toothache compared to toothbrush users [150] and Eid, *et al.*, claim that *S. persica* havings analgesic, astringent and anti-inflammatory properties, makes it an effective treatment for primary periodontal diseases [151]. Should the *analgesic* characteristic of *S. persica* be confirmed in human beings to relieve dental pains, like superficial pain due to dental hypersensitivity to thermal, tactile or to chemical stimuli, *S. persica* will be of great practical value.
3.14 Calcium & Chloride Releasing Characteristic

Gazi, et al., investigated the immediate and medium-term effects of S. persica on the composition of mixed saliva and reported that S. persica significantly increased the release of calcium by 22-folds and chloride by 6-folds while decreased phosphate and pH significantly. The saturation of saliva with calcium inhibits demineralization and promotes re-mineralization of tooth enamel and high concentration of chloride inhibits calculus formation [99,100].

3.15 Anti-addiction (Curative & Preventive) Characteristics

Dr. Rami Mohammed Diabi, an internist at the University of Kentucky Albert B. Chandler Hospital, Lexington, USA, researching the effects of S. persica on health, reported its anti-addiction effects on smokers, both curative and preventive sides, in his latest publications, “Miswak Medicine Theory”, “Sewak Puncture Medicine”, “Beyond Sewak: World of Science and Research” [64,152].

3.16 Anti-Halitosis

S. persica (Miswak) is also used to clean the tongue. It helps in fighting halitosis and effectively removes the white coat that develops on the dorsum of the tongue. It is usually done by brush end of Miswak [74].

3.17 Anti-Carious Characteristics

Several epidemiological studies revealed that S. persica had strong anti-carious effects. In a dental health survey conducted in Sudan, a lower caries prevalence was reported among Miswak users than toothbrush users [153]. In subsequent studies, similar lower caries incidences were found among schoolchildren using Miswak [154-156]. Dental loss was very low in the adults where Miswak was widely used [25].

3.18 Smear Layer Removal

Soaking the healthy and periodontally diseased root dentine in S. persica extract resulted in partial removal of smear layer, and occlusion of dentinal tubules was observed in dentine specimens brushed with S. persica solution [76].

3.19 Pesticidal Characteristic

The effect of aqueous extracts from the leaves, shoots and roots of S. persica was tested at laboratory scale to assess their pesticidal characteristics on food grains stocked for 3 months. The preliminary results obtained were very encouraging but this subject requires a thorough investigation under a well-designed research project. The experimental methodology adopted was to spray (0.1-1.0% w/w) extracts obtained from the leaves, shoots and roots of S. persica over 5 pre-weighed test samples of wheat, barley, millet, rice, corn, three type of pulses and the flours of wheat and rice each. Each set of treated food grain was separately exposed to the counted number of live insects, viz., beetles, moths and mites. Moderate humidity was maintained and temperature was controlled between 21-23 °C. The activity (mobility) of these insects were noted and the number of live pets counted every 24 hours. Most of these insects started exhibiting sluggish movement beyond 3-5 days and started dying after a duration of 7-10 days. After 15 days of exposure, not a single pest was seen alive. The dead pests were separated from food grains and flours. No powder of the grains or pulses or cereals was found in the test petry dishes containing solid food grains. Further, microscopic study revealed that the food grains were
absolutely intact with no holes or pitting or damages. The grain and flour samples were weighed again. The final weights were found exactly the same as the initial weights.

The test was repeated by administering 0.1-1.0% w/w seed oil of S. persica on 5 pre-weighed test samples of wheat, barley, millet, rice, corn, three type of pulses and the flours of wheat and rice, and exposing to the counted number of live beetles, moths and mites. The results were almost the same, except that the pests in this case showed sluggishness from the second day onwards and started dying just after fifth day of exposure. Some of these characteristics are summarized in Table-4.

4. COMMERCIALLY EXPLOITED THERAPEUTIC APPLICATIONS

Due to the amazing qualities of tooth-stick, the extract of S. persica has been transformed into effective toothpastes, toothpowders, mouthwashes and chewing gum preparations. These products are now commercially available in the market.

4.1 Toothpastes

In recent times S. persica has been successfully used in commercial toothpastes by a number of overseas manufacturers to provide their oral health benefits in the most user-friendly forms. S. persica paste or its extract is used as an effective ingredient in the toothpaste for cleaning teeth [2,12], removal of plaque, naturally disinfecting the mouth, stop bleeding and refreshing the breath. It is claimed that the plant fibers, used in toothpaste, provide mild abrasive system while in contact with moisture, swell and become soft, and consequently do not cause wear on the surface of the tooth. The resins present in the plant may place a protective coating on the tooth enamel, which helps to prevent the development of sensitive teeth and tooth decay. The extract used in the toothpaste also helps to provide antimicrobial compounds that are useful to eliminate harmful plaque bacteria. It also helps in healing and repairing tissues and promotes remineralization to build tooth enamel.

Elvin Lewis claimed to have detected limited antimicrobial spectrum in the aqueous extracts for oral organisms [157]. However, suggested the possibility that the enzymatic action of saliva on the isothiocyanates of this species could release unstable products (hydrogen peroxide - $H_2O_2$) that exert antimicrobial characteristics, which is produced only in the oral environment, and helps to prevent deposits build-up (tartar and plaque formation). Other factors in selection might be its high chloride content removing tartar and other stains from the teeth, silica acting as mild abrasive, resin forming a coat over the enamel to prevent tooth decay, and vitamin C promoting healthy gingivae [158].

Research studies conducted by a Swiss Pharmaceutical Company and later confirmed by King Saud University, Riyadh (Saudi Arabia) and Indiana University, Bloomington (USA), indicated that S. persica extract contains antibacterial substances, which destroy the harmful germs in the mouth causing gum infections and tooth decay, and thus making it a ‘total’ care ingredient in the toothpastes [60].

Farooqui, et al., have claimed that toothpaste containing extracts of the plant S. persica, preserve the gums and the teeth in perfect health and give the latter a dazzling whiteness [23,159,160]. Although Dr. J. Mittleman, D.D.S., the Former President, International Academy of Preventive Medicine, USA, has also endorsed toothpaste products of S. persica, but the users of S. persica twig don’t find the toothpaste a

<table>
<thead>
<tr>
<th>Parts of the Plant</th>
<th>Characteristics Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaves</td>
<td>Antibacterial, Antifertility, Anti-pests</td>
</tr>
<tr>
<td>Stem</td>
<td>Beta-sitosterol elucidated, Hypolipidemic, Antiulcer, Anticonvulsant, Sedative, Anti-pests</td>
</tr>
<tr>
<td>Leaves &amp; Stem</td>
<td>Hypoglycemic, Hypolipidemic, Anti-pests</td>
</tr>
</tbody>
</table>

Table 4: Different Parts of S. persica Plant & their Common Uses
true alternate practice of using it in its original form. A scientific study comparing the use of *S. persica* twig with plastic toothbrushes concluded that the results were in clearly favor of the users of natural *S. persica* twig [123]. Darout, *et al.*, conducted a study among 213 males, aged 20-65 years, to evaluate the periodontal status of *S. persica* (*Miswak*) and toothbrush users and reported that the periodontal status of *S. persica* users in a Sudanese population was better than that of toothbrush users, suggesting that the efficiency of *S. persica* use for oral hygiene is comparable or slightly better than toothbrush [100]. Batwa, *et al.*, carried out a study at the Institute of Odontology, Karolinska University Hospital at Karolinska Institutet, Sweden. Photogrammetric techniques giving measurements in an interval scale were used to obtain the measurements of the plaque area [161-163]. The *S. persica* was found as effective as a conventional toothbrush in reducing plaque in all of cleaning periods, i.e., after 30, 60 and 120 seconds. The clinical part also confirmed the experimental findings were in agreement with earlier reports that chewing-sticks was equally effective compared to toothbrushes in children and adults [164,165]. The results obtained are illustrated in Table-5. Some other investigators have also found that chewing-sticks were effective in reducing plaque and gingival inflammation.

Solaiman A. Amro, (Asst. Prof., Periodontology & Oral Medicine, Al-Azhar University), *et al.*, assessed all subjects using Simplified Oral Hygiene Index (OHI-S), Gingival Index, Pocket depth and Gingival Recession Measurement to nearest mm and concluded that apart from gingival recession that might be encountered in *S. persica* users as a result of improper technique, the *S. persica* exhibited a significantly higher improvement in gingival and periodontal conditions compared to toothbrush [14]. When properly used, *S. persica* had been reported to be as effective as tooth brushing [100,116,117,123,157]. However, some other investigators disagreed and reported that there were more plaque formation and gingival bleeding in individuals who used chewing-sticks with comparison to toothbrush users [143,166].

A study reported that about 22% of the Saudi schoolchildren with gingival recession used Miswak [167], but this group had minimal calculus deposits which may be attributed to the use of *Miswak*. It was further reported that *Miswak* users had significantly more sites of gingival recession than did the toothbrush users. In addition, the severity of the recession was significantly more pronounced in the *Miswak* users than that in the toothbrush users [168], which might be due to poor techniques.

**Table 5: Comparative Mean Plaque Level After Brushing with *S. persica* & Toothbrush (Brushing Time & Maxillary Anterior & Posterior Regions)** [100]

<table>
<thead>
<tr>
<th>Location</th>
<th>Brushing Time (Sec)</th>
<th><em>Salvadora persica</em></th>
<th>Toothbrush</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean %</td>
<td>95% Cl</td>
<td>Mean %</td>
<td>95% Cl</td>
</tr>
<tr>
<td>Maxillary Anterior</td>
<td>0</td>
<td>53.4</td>
<td>40.9, 65.8</td>
<td>53.9</td>
<td>41., 66.7</td>
</tr>
<tr>
<td>Region</td>
<td>30</td>
<td>22.5</td>
<td>13.0, 32.0</td>
<td>24.3</td>
<td>15.0, 34.4</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>13.1</td>
<td>7.4, 18.7</td>
<td>14.5</td>
<td>8.2, 20.7</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>6.9</td>
<td>4.2, 9.6</td>
<td>6.6</td>
<td>3.3, 9.8</td>
</tr>
<tr>
<td>Maxillary Posterior</td>
<td>0</td>
<td>55.5</td>
<td>42.4, 68.3</td>
<td>64.6</td>
<td>53.8, 75.4</td>
</tr>
<tr>
<td>Region</td>
<td>30</td>
<td>20.7</td>
<td>15.2, 26.3</td>
<td>25.0</td>
<td>16.5, 33.5</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>12.2</td>
<td>7.9, 16.5</td>
<td>13.4</td>
<td>8.8, 18.0</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>6.5</td>
<td>4.2, 8.8</td>
<td>8.6</td>
<td>4.7, 12.5</td>
</tr>
</tbody>
</table>

Some toothpastes produced from *S. persica* plant extract commercially available in the Middle East, South Asia, Southeast Asia, Europe and North America are Sarkan Toothpaste (UK), Quali-Miswak Toothpaste (Switzerland), Miswak Özel (Turkey), Dentacare Miswak Plus (Saudi Arabia), Epident Toothpaste (Egypt), Siwak-F Toothpaste (Indonesia), Miswak Herbal Dental Gel (Australia), Jaris Miswak Toothpaste (Singapore), Isha Ayurveda Misvak (China), Fluroswak Miswak (Pakistan), Miswak Hamdard
Peelu Toothpaste (India), *Meswak* Dabur Toothpaste (formerly owned by Balsara Hygiene, India), etc. [169,170].

4.2 Mouthwashes

*S. persica* extract is being used as an ingredient in the mouthwashes [2,12]. Mustafa, *et al.*, found a reduction in plaque formation by *S. persica* based mouthwash [171]. Several other studies indicate that *S. persica* extract is somewhat comparable to other mouthwashes or oral disinfectants and anti-plaque agents, like *triclosan* (C₁₂H₇Cl₃O₇) and *chlorhexidine gluconate* (C₃₄H₅₄Cl₂N₁₀O₁₄), if used at a very high concentration [13,169]. At physiologic pH, *chlorhexidine* and *triclosan* dissociate and release positively charged cations. The bactericidal effect is a result of binding of these cationic molecules to the negatively charged bacterial *enoyl-acyl* carrier protein reductae (ENR) enzyme, which is encoded by the gene Fabl. This binding increases the enzyme’s affinity for *nicotinamide adenine dinucleotide* (NAD⁺) and appears *bacteriostatic* targeting bacteria by formation of a stable complex (ENR-NAD⁺- *chlorhexidine* / *triclosan*), which at low concentrations primarily inhibits fatty acid synthesis that is necessary for building and reproducing cell membranes; but at high concentrations acts as biocides with multiple cytoplasmic and membrane disruptions causing the death of bacterial cells [172-174]. Since humans do not have ENR enzyme are not affected by this mode of action.

Some of the nonalcoholic mouth-rinse preparations commercially available in market are Listerine Miswak Mouthwash, Siwak-F Mouthwash (Indonesia), Jaris Miswak Mouthwash (Singapore), Dabur Miswak Mint Fresh/Germ Kill Mouthwash (India), Himalaya Miswak Pomegranate Mouthwash (India), etc. [123,131].

4.3 Endodontic Irrigation Solution

Due to the *antimicrobial* characteristics, *S. persica* extract has been reported to be utilized as an ingredient in endodontic irrigation solution [2,12]. Abo Al-Samh, *et al.*, evaluated, *in vitro*, the effect of different concentrations of *S. persica* extract on L929 cell-line in tissue culture and compared the results with *sodium hypochlorite* (NaOCl) and found a concentration-dependent morphological change in L929 cell-line when exposed to both *S. persica* extract and NaOCl, the former showing inhibition effects at much higher concentrations than NaOCl; and suspected the recovery of the cells after a 4-h exposure period to different *S. persica* extract concentrations [98,125,175-177].

5. SUPPLEMENTARY THERAPEUTIC APPLICATIONS

Apart from cleaning both the teeth and the tongue and treating toothache, *S. persica* has various other therapeutic applications also, which require further clinical investigations. These are its functional aspects of chewing as a jaw exerciser following *traumatic* injuries to the jaw and *temporomandibular* joint, a reflex induction of copious saliva or *Sialogogue*, which is beneficial to the oral hygiene, general health and development of *dentition* during eruption of the wisdom teeth [28], improving appetite and regulating *peristaltic* movements of the *gastro-intestinal tract* [2,12,178].

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