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A review of the traditional and modern uses of *Salvadora persica* L. (Miswak): Toothbrush tree of Prophet Muhammad

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Abstract

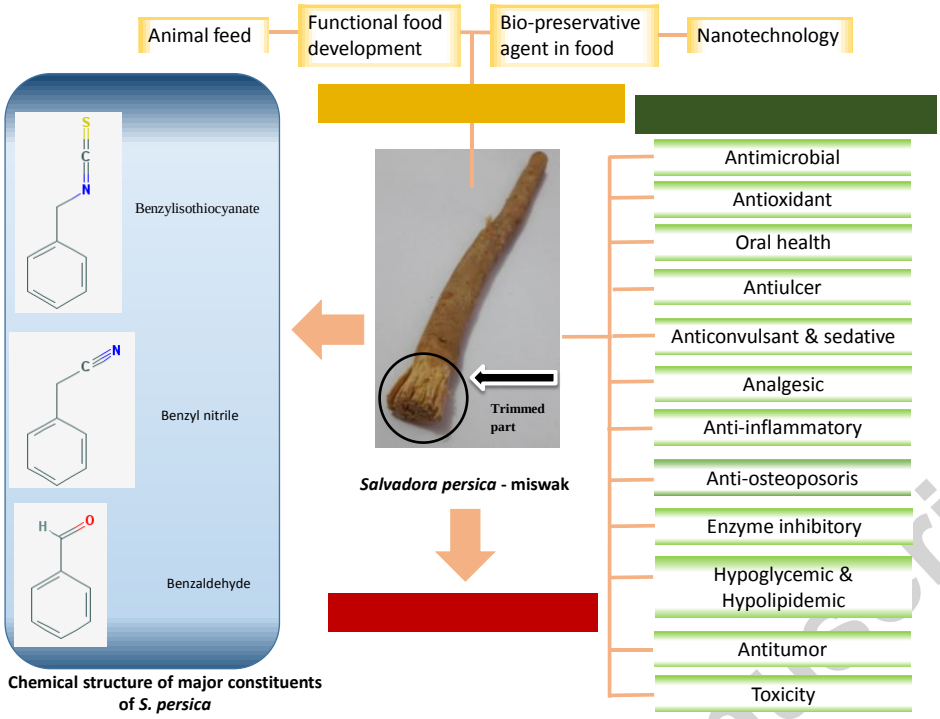
Ethnopharmacological relevance*: Salvadora persica* L., also known as Arak (in Arabic) and Peelu (in Urdu), is the most common traditional source of tooth or chewing stick (miswak) highly recommended by Prophet Muhammad. To date, extensive studies have probed primarily into the validation of its traditional uses in oral care. Nonetheless, there is still a dearth of updated compilation and critical analysis of other potential ethnopharmacological properties of *S. persica*. This review therefore aims to provide an up-to-date detailed structured description of the traditional uses of *S. persica* and a critical analysis of its modern uses, highlighting its phytochemistry, pharmacological properties, and bioapplications.

Materials and methods: Various databases (Science Direct, PubMed, Wiley Online Library, and Google Scholar), books, and relevant primary sources were probed, surveyed, analysed, and included in this review. The literature cited in this review dated from 1979 to 2017.

Results: *S. persica* was found to possess a plethora of bioactive compounds and broad pharmacological properties, including antimicrobial, antioxidant, enzyme inhibitory activity, antiulcer, anticonvulsant, sedative, analgesic, anti-inflammatory, hypoglycemic, hypolipidemic, antiosteoporosis, and antitumor activities. Studies also revealed the potential use of *S. persica* as a natural food preservative and a novel functional food ingredient. In addition, improvement in growth and reproductive performances have been observed by the introduction of *S. persica* in animal feed. Lastly, *S. persica* has also been used in the green synthesis of nanoparticles showing potential biotechnological applications.

Conclusion: *S. persica* showed a wide scope of application and its uses have been extended far beyond the initial traditional uses of its roots, stems, and twigs in oral care. We found a number of other ethnopharmacological uses and potential bioapplications of different parts of *S. persica* that warrants further investigations. Though widely studied using several *in vitro* and *in vivo* models, and tested clinically for oral hygiene mainly, several gaps and research priorities have been identified which needs to be addressed in future.

Graphical abstract



Keywords: *Salvadora persica*; miswak; chewing sticks; traditional uses; phytochemicals; bioapplication; pharmacology; toxicity

***Abbreviations*:** ABTS, 2,2-azinobis (3-ethyl-benzothiazoline-6-sulfonic acid); ACE, angiotensin converting enzyme; Ag-NPs, silver nanoparticles; BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; BITC, benzyl isothiocyanate; CE, catechin equivalent; CFU, colony forming units; CHX, chlorhexidine; CV, crystal violet; DPPH, 1,1-Diphenyl-2-picrylhydrazyl; EDTA, ethylenediaminetetraacetic acid; GAE, gallic acid equivalent; GC-MS, gas chromatography–mass spectrometry; HDL, high-density lipoprotein; LDH, lactic dehydrogenase; L-DOPA, L-3,4-dihydroxyphenylalanine; LDL, low-density lipoprotein; MB, methylene blue; MIC, minimum inhibitory concentration; NPs, nanoparticles; OVX, ovariectomized; SP-HRG-Pd, palladium@graphene nanocomposites; Pd-NPs, palladium nanoparticles; PC, proanthocyanidin content; PE, pyrocatechol equivalent; PTZ, pentylenetetrazol; QE, quercetin equivalent; QS, quorum sensing; RE, rutin equivalent; TC, total cholesterol; TFC, total flavonoid content; TG, triglyceride; TPC, total phenolic content; VLDL, very low density lipoprotein; ZOI, zone of inhibition

Chemical compounds cited in this article: Aniline (PubChem CID: 6115); Benzaldehyde (PubChem CID: 240); Benzylisothiocyanate (Pubchem CID: 2346); Benzyl nitrile (PubChem CID: 8794); Benzylurea (PubChem CID: 10853); Butanediamide (PubChem CID: 8036); N-benzyl-2-phenylacetamide (PubChem CID: 277826); N-benzylamine (PubChem CID: 7504); Caffeine (PubChem CID: 2519); Carvacrol (PubChem CID: 10364); Catechin (PubChem

CID: 9064); α-caryophyllene (PubChem CID: 5281520); β-caryophyllene (PubChem CID: 5281515); Eucalyptol (PubChem CID: 2758); Eugenol (PubChem CID: 3314); Liriodendrin (PubChem CID: 73636); Naphthalene (PubChem CID: 931); Naringenine (PubChem CID: 932); β-pinene (PubChem CID: 14896); Salvadoraside (PubChem CID: 101630443); Salvadoside (PubChem CID: 23664985); Syringin (PubChem CID: 5316860); Theobromine (PubChem CID: 5429); Thymol (PubChem CID: 6989); Trigonelline (PubChem CID: 5570)

1. Introduction

Salvadora persica L., most commonly known as Arak (in Arabic) and Peelu (in Urdu), belong to the family Salvadoraceae. In 1749, the term *Salvadora*, was set forth by Dr Laurent Garcin, in honour of an apothecary of Barcelona, Juan Salvadory Bosca (1598-1681). The term *persica* is used to indicate Persia while the standard author abbreviation L. indicates the father of modern taxonomy, Carl Linnaeus (1707-1778) (Ahmad and Rajagopal, 2013). The common names of *S. persica* used by various countries are summarised in Table 1.

Morphologically, *S. persica* is a large well-branched evergreen tree with soft whitish yellow wood, leaves (3.8-6.3 by 2-3.2 cm), greenish yellow flowers, and red fruit when ripe (Khatak et al., 2010). *S. persica* can survive in extreme conditions and is capable of tolerating very dry environments to highly saline soils. It is found in arid, coastal regions, saline lands, desert flood plains, and grassy savannahs (Haque and Alsareii, 2015). In addition, it shows preference to clays but is also present on loam, sand, and black soils. In different countries, the plant display some variations in its distributional behavior, which may be due to changes in water resources, edaphic variables, climatic factors, and anthropogenic pressures along the elevation gradient (Anthoney and Timothy, 2015).

S. persica is commonly known as miswak tree since it is the most common source of miswak and extensively used among the 182 species of plants used as chewing sticks across the world (Sofrata et al., 2011). Miswak is an Arabic word, also known as miswaak, miswaki, meswak, misswak, mswaki, siwaki, sewak, and siwak in different Arabic dialects and countries, which means tooth cleaning stick. In English, miswak has been referred to as the

"natural toothbrush" (Darout, 2014). Miswak is trimmed at one of the tip forming an exposed end which is then chewed to form a brush (Figure 1).

Figure 1: *Salvadora persica* - miswak

In geographical areas where *S. persica* tree grows, miswak is prepared from that plant itself while in regions where *S. persica* is absent, miswak can be made from other plants, such as *Azadirachta indica* A.Juss. (Neem), *Olea europaea* L. (Zaitoon), *Capparis aphylla* Roth (Khiran), *Acacia arabica* (Lam.) Willd. (Kikar), and others (Almas, 2002; Niazi et al., 2016; Wu et al., 2001). The World Health Organisation (WHO) has also recommened and encouraged the use of these sticks for oral hygiene (WHO, 1984).

Historically, chewing sticks were firstly used by the Babylonians some 7000 years ago and eventually used by Greek and Roman empires. Even now it is used in many parts of the world mainly in Africa and the Middle East (Almas, 2002; Niazi et al., 2016). Recently, there have been considerable interest in exploring the medicinal properties of *S. persica*. Several studies have probed into the biological profile of this plant and a wealth of literature has emerged and published. Nonetheless, there is currently a dearth of updated compilation of available data on its traditional uses, phytochemistry, pharmacological properties, and potential bioapplication in various fields.

In this context, we aimed to provide an up-to-date detailed description of the traditional uses of *S. persica* across the world, and a critical analysis of its phytochemical composition and pharmacological properties. The potential bio-application of *S. persica* in food preservation, functional food development, animal feed, and nanotechnology have also been systematically reviewed. Lastly, possible future directions of research and priority are also discussed.

Table 1: Common names of *S. persica* across the world (Quattrocchi, 2012)

Country/language	Common names
English	mustard tree, saltbush, tooth-brush bush, toothbrush tree
Arabic	arak, miswak, siwak
India	arak, aranmakapicam, aranmakapicamaram, badapilu, bhaara gaangu, brihatpilu, cakantititam, cakuntititam, camarankari, camaratam, cankiciyam, cevvuka, chekkerachettu, chhota-pilu, chhotapilu, chinna-varagogu, chinnavaragogu, chirukalarva, chota-pilu, ciru kalarva, cittuva, cittuvila, cumirtam, darakht-i-misvak, darakht-i-miswak, darakhte-misvak, dhalu, gauli, geya, ghooria, ghunia, gogu, gone, goni, goni chakke, goni-mara, gonia, gonimara, goniya, gonni, gudaphala, gunia, irak, irattakampilucaramakki, irattaputpam, jal, jar, jhai, jhak, jhal, juttueerugamma chettu, kaarugogu, kabbar, kakavallapam, kakham, kalarva, kalawa, kallivira, kankhina, kantacakikam, kantacakikamaram, kareegoni, kargol, kargoli, kari goni mara, karkol, karugogu, khabhar, khakheen, khakhin, kharajal, khari jar, kharjal, kharijal, kharijar, kickin, kickni, kireegoni, kirgonji, kiri gonee mara, kirigoni mara, kodumaavali, kotumavali, kotungo, koyya, kunni, langhupilu, madhupilu, mahaphala, mahapilu, mahavriksha, meeraj, meerajoli, miraj, mirajoli, miriga, mitha jal, mithi-pilu, motijalya, nettuka, nettukamaram, nilavukay, ooghai puttay, opa, pancatipika, paviyam, pedda gogu, peddavara goki, peddavaragogu, peddavaragoki, peddavarajuvenki, peddawaragowenki, peddawaraguwenki, peelu, pelu, pennavaragogu, perungoli, pilu, pilu ka pala, piludi, piluh, piluka, pilva, pilvu, pinna-vera-gogu, pinnavaragogu, piravalapalam, rajapilu, rhakhan, rokacamani, shiru-kalarva, sittuvila, sramsi, surugalarva, tanuka, tanukamaram, tanukonam, thorapeelu, thorapilu, thuraka gogu, tiksna-vrksatphalani, tiksnataru, tiksnavrksa, titcanapalai, titcanapalaimaram, toboto, uba, uga, ughaiputtai, uka, ukai, ukamaram, ukattekku, ukaver, upa, uvay, vagai, varagogu, varagoja, varagoki, varagu, varakari, veda, vedha, velvigai, veragogu, vikkinapalam, virutcanam, vivay, wara gogu, waragogu, waraguwenki, warangu-wenki
East Africa	esekon, mswaki, ol-remit
Kenya	aadde, adde, ade, adhe, adhei, akhai, ashokonyon, asiokon, asiokonion, barsute, cadei, chokow'o, esekon, esokon, hayay, huda, iremito, mjungumoto, mswaki, muezamoyo, mukayau, muswaki, nyaa, nyedhe, olremit, oremit, sogotaiwa, sokotei, sokotu

Namibia	kerriebos (Afrikaans); ozongambu (fruit), otjingambu (Herero); khoris (Nama/Damara); okatunguya, omumkavu (Ndonga); enghadu (Kwanyama); omungavo, omungavu (Mbalantu); omunkavu (Kwambi, Nkolonkadhi, Ngandjera); omgavo, omungavu (Eunda); omungavu (Kwaluudhi)
Nigeria	asawaki, kighir
Somalia	Caday
Southern Africa	omungambu (Herero)
Tanzania	chigombo, iremito, mkayo, mkung'uni, mkunghuni, modee, msaki, mswake, mswaki, mtele, muche, muléwa, muwiga, mwiga, olremit, oremit

2. Methodology

2.1. Procedure for searching information

Relevant literature was retrieved by scrutinising key scientific databases (Science Direct, PubMed, Wiley Online Library, and Google Scholar). Information was also obtained from books and dissertations. The scientific name of the plant was validated using The Plant List (http://www.theplantlist.org/) and The International Plant Names Index (www.ipni.org) as recommended by Rivera et al., 2014. Published review papers on *S. persica* were used as guidelines to design the present study and also to add missing data to ensure a more comprehensive and up-to-date review is obtained. The reference lists of review and research papers were searched for further relevant information. Guidelines proposed by Mullane et al., (2015) were also taken into consideration in the preparation of the manuscript. The literature cited in this review dated from 1979 to 2017. Regarding the search methodology, the following keywords were searched: "*Salvadora persica*" (PubMed=124 search results, Science Direct=374 search results, Wiley Online Library=265 search results), "miswak" (PubMed=119 search results, Science Direct=101 search results, and Wiley Online Library=120 search results). These papers were screened for the respective content in this review e.g. "traditional", "chemical composition", "antimicrobial", "antioxidant", "animal feed", and so on. Google search was also used e.g. "*S. persica* antimicrobial", "miswak antimicrobial, "*S. persica* antioxidant", "miswak antioxidant" and so on. All studies on

traditional uses, phytochemistry, pharmacological properties, and bioapplication were obtained mainly from primary sources. *In vitro*, *in vivo*, and clinical studies were included and literature search was restricted to English language.

2.2. Planning, design, and description of sections

This review consists of five sections (3-7), covering the traditional uses, phytochemistry, pharmacological properties, and bioapplications of *S. persica*. Section 3 highlights the emphasis that Prophet Muhammad placed in the use of *S. persica* in oral health and the method of usage. Section 4 describes the traditional uses of each part of *S. persica* plant. The section was equipped with a table (Table 2), showing the parts of *S. persica* used, method of preparation, and the targeted ailments to provide detailed information of how the plant is used for therapeutic purposes across the world. Section 5 reviews the phytochemical composition of different parts of the plant, displaying the stoichiometry of the major chemicals identified (Table 3). Section 6 provides a detailed and critical analysis of its pharmacological properties in relation to its phytochemistry and traditional uses. A brief introduction on the pathology of each disease has been included before each pharmacological claim for a better understanding of the disease condition, the necessity to explore traditional remedies, and how *S. persica* might be of benefit in the treatment and/or management of such ailments. The detailed antimicrobial activity of *S. persica* has been displayed in the form of table (Table 4), along with a brief summary and analysis of the results. Information on the dose range tested, the minimal active concentration, the model used (*in vitro* or *in vivo* study), controls used, and type of solvent extract used are also reported in the pharmacological studies. Lastly, section 7 provides an overview of the potential applications of *S. persica* in food preservation, functional food development, animal feed, and nanotechnology, which to the best of our knowledge have been compiled for the first time.

3. *S. persica*: Toothbrush of Prophet Muhammad

Natural products have been used in several traditional healing systems, such as traditional Chinese medicine, Ayurveda, Kampo, traditional Korean medicine, and Unani, across the globe (Yuan et al., 2016). Among these systems of healing, there exist a particular type of medicine in Islamic medicine, known as Prophetic medicines, which refers to the sayings, practice, and revelations upon Prophet Muhammad (Peace and blessings of Allah be upon him) regarding medical matters, as well as his way of living, which generated tremendous interest among the scientific community to find out how a man of the desert could make such wonderful statements on medical science. These finally led the scientific community to carry out extensive investigations and it is amazing that not a single statement of Prophet Muhammad on healing is found to be contradictory to science (Bhikha and Dockrat, 2016; Hussain and Hussain, 2016).

In fact, Islam has emphasised the usage of miswak for oral hygiene. Islam teaches the importance of cleanliness of both the body and mind, and thus introduced basic oral hygiene by incorporating it as a religious practice (AbdElRahman et al., 2002). The importance of miswak was highlighted by Prophet Muhammad who preached Islam not only by his words but also through his actions. Regarding *S. persica* (Arak), Prophet Muhammad said: "*Pick the black fruit (fruit of Arak tree), for it is the best*" (Al-Buḫ ārī and Ḫ ān, 1997). In addition, the wife of the prophet, Aishah (may Allah be pleased with her) reported that Prophet Muhammad said: "*Siwak (Miswak) is a mean of purification for the mouth and is pleasing to the Lord*" (An-Nasai, 2007), indicating its role in oral health. Moreover, the Prophet used miswak very often; whenever he would enter his home, when he woke up from sleep, before prayer, indicating the importance of its frequent usage for good oral hygiene. The Prophet also said: "*Were it not that it would be too difficult for my people, I would have commanded them to use the miwak at every time of prayer*." (An-Nasai, 2007). In fact, the use of miswak

was not only the practice of Prophet Muhammad, but all other prophets before him (Peace be upon them), indicating its use as old as mankind's origin on the earth (Mohamed and Tirmidhi, 2007). Even during the last hours of Prophet Muhammad before death, Aishah (may Allah be pleased with her) chewed the miswak and then cleaned the Prophet's teeth with it (Al-Buḫ ārī and Ḫān, 1997). This shows how keen the Prophet was to use the miswak. In addition, the miswak should be used whenever the smell of one's mouth changes, whether this is because of eating food with a strong odour, or because of not eating or drinking for a long time.

The method of usage of miswak has been described previously by Al Sadhan and Almas (1999). Briefly, the length should be convenient to grip, and easy to manipulate in a confined space without breaking it. The miswak should be freshly cut so that it is easily chewed, and still rich in active constituents. About 1 cm of the outer layer from one end of the miswak is peeled to reveal the inner bristles which is then chewed to make it soft. The tip is then soaked in water briefly but not for too long periods which may causes loss of active constituents. Normally, there are two basic holds: three-finger or five finger-grip. It is desirable to hold it with the right hand by putting the thumb under the head of the miswak near the bristle, the little finger under the other end, while the three middle fingers on top of the miswak as shown in Figure 2. Nonetheless, it depends on the user's choice which method is more comfortable. The aim is to ensure a firm but controlled movement of the bristle within the oral cavity, so that all regions of the mouth is reached with relative ease and convenience. The techniques used for brushing is similar to that for a typical toothbrush. The bristle is pressed gently onto the teeth to scrub the front and back surfaces of the teeth and the chewing surfaces of the premolars and molars, ensuring that the bristles is passed between the gaps of the teeth. All other interior parts should be brushed gently, including the gums, palate, tongue, under the tongue, and the surfaces inside of the cheek and lip. After brushing, the bristle tip should be

briefly rinsed to remove any debris and the miswak should be kept in a clean space. When the bristled end of the miswak gets dry, it is cut off and another part is peeled again.

Figure 2: Ideal method of holding miswak as a toothbrush

4. Traditional uses of *S. persica*

Traditionally, *S. persica* have been used for various purposes; in food, fuel, cosmetic, oral hygiene, and and not the least, medicines. For instance, the leaves are cooked as a sauce and eaten as salads or green vegetables (Table 2). The fruits can be eaten in raw, cooked, or dried state. The wood is sometimes used for firewood and charcoal. In addition, the resin that drips from the tree is supposedly useful for making varnish. Crushed leaves of *S. persica* immersed in cow urine are also reported to facilitate the removal of hair with knife. Moreover, the leaves and young shoots are used as fodder for camels, cows, goats, and sheeps, and the leaves are reported to increase lactation in cows and improve the general body weight of animals. The flowers were found to be a good source of nectar for honey bees and it is strongly believed that the honey of *S. persica* have high medicinal value (Orwa et al., 2009; Sher et al., 2011). Interestingly, *S. persica* have been used by several ethnic groups, particularly in Asia and Africa, for medicinal purposes. Different parts of the plants; root,

bark, stem, leaves, seeds, flowers, and fruits, have been used in a wide variety of preparations for internal and external use against various ailments and diseases of the digestive, musculoskeletal, circulatory, glandular, and urinary systems (Table 2).

Table 2: Traditional uses of *S. persica* for medicinal purposes

Continent	Country/ ethnic groups/ system of medicine	Part(s) used	Mode of preparation	Ailments / medicinal use	References
Asia	India	Leaf	Leaves are heated and tied up in thin cotton cloth, and then applied	Rheumatism	(Parveen et al., 2007)
			The juice of leaves is given	Scurvy	
			Paste	Rheumatism and scurvy	(Patel and Patel, 2017)
			Paste of 8-10 crushed leaves is taken orally with water	Constipation	(Katewa et al., 2004)
			Decoction, 25 ml taken twice a day orally	Asthma	(Savithramma et al., 2007)
			Decoction	As an expectorant, and given in asthma	(Rabari, 2016)
			Juice of leaves is applied externally to the affected area.	Body pain	(Kosalge and Fursule, 2009)
			NR	Diabetes	(Gunasekaran and Balasubramanian, 2012)
			Paste is applied externally	Scabies, leucoderma	(Mali and Bhadane, 2011)
		Leaf, fruit	Paste	Boils, swelling, piles, constipancy, indigestion	(Kumhar et al., 2017)
		Fruit	NR	Purgative	(Rabari, 2016)
		Root, bark	Paste is applied locally	Blisters	(Katewa et al., 2004)
			Root bark is ground with mustard oil and bandaged on swelling.	Gout	(Bharti, 2015)
		Root bark	Fresh powder	Arthritis	(Patel et al., 2013b)
			Decoction, oral	Fever	(Patel and Patel, 2017)
			NR	Gonorrhea	
		Stem bark	NR	As an ascarifuge and in gastric troubles	
		Young root	As a toothbrush	Toothache	(Patel et al., 2013b)
		Young branch and leaf	Powdered and mixed with honey	Bronchitis	
			Boiled	Seasonal cough and cold	

	Whole plant	NR	Pain of teeth, skin disease	(Patel et al., 2013a)
	Root, shoot, leaves, bark	NR	Used against snake bite, Rheumatism, Tonic	(Sathe et al., 2014)
Ayurvedic system	Fruit, seed oil	NR	As laxative, in rhinitis, hemicrania, intestinal parasites, urinary disorders, and suppurating skin diseases	(Khare, 2004)
	Fresh fruit	Taken with buttermilk	Piles	
Pakistanis residing in Denmark	NR	Use once a day or when doing wudu (ritual washing)	Teeth hygiene	(Ramzan et al., 2017)
Pakistan	Root, soft bark, leaf, Fruit, Seed	Toothbrush, Ash, powder, Extract, Decoction	Toothache, hair remover, skin allergy, constipation, old fever, painkiller, GIT worms, mouth freshener, jaundice, paralysis	(Yaseen et al., 2015)
	Leaf	Decoction, 1 cup decoction of leaves is used for vomiting thrice a day	Malaria symptoms	(Shah and Rahim, 2017)
Jordan	Branch	NR	Cleans and disinfects teeth and gums	(Lev and Amar, 2002)
	Stem	Brushing	Teeth and gum cleansing and treating decays	(Alzweiri et al., 2011)
Saudi Arabia	Leaf, Root	Decoction	As a mouthwash, to cure tooth/gum problems, and as a remedy for joint pain	(Sher et al., 2011)
	Root	Decoction	Epilepsy, gonorrhoea, skin diseases, spleen troubles, and stomach ulcer	
	Seed	NR	Increase fertility. Seed oil is used to treat skin inflammation and rheumatism	

	Unani system	Fruit	Fermented juice is prepared from the fresh fruits	As a strong aphrodisiac agent and a general body tonic	(Sher et al., 2011)
			NR	Diuretic	(Khare, 2004)
		Leaf	NR	Purgative	
		Root bark	NR	Amenorrhoea	
Africa	Kenya	Root, stem	NR	Eye infections, worms, malaria, stomach ache, constipation, tonic, cold, teeth hygiene, respiratory infections	(Kimondo et al., 2015)
		Root	Boil and drink	Upset stomach	(Fratkin, 1996)
			NR	Helminthosis	(Muthee et al., 2011)
			Outer part of root is removed, grinded/crushed, soaked in water, then sieved	Flu/common cold	(Kiringe, 2006)
			Outer cover of root is removed, grinded/crushed, soaked in water, sieved and then some salt and little milk are added	Malaria	
			Outer part of root is removed, soaked in water. Salt is added, sieved, followed by addition of some milk.	Stomachache	
			Outer part of root is removed, soaked/mixed with water	Typhoid	
		NR	NR	Dental caries, relieve tooth ache and gum disease	(Ngaruiya, 2015)
		Root, fruit	NR	Malaria, Gonorrhea, common cold, swollen part	(Tsigemelak et al., 2016)
		Root, stem bark	Boiled and taken as infusion, one glass daily for two weeks. Sometimes taken with soup	Chronic joint pains	(Wambugu et al., 2011)
		Leaf	Infusion in hot water	Veterinary: rinderpest	(Bizimana, 1994)
		Whole plant	Ashes of *S. persica* are mixed in water and given orally	Veterinary: diarrhea	
		Root	Ashes from the root are mixed in water and given orally	Veterinary: trypanosomiasis	

		S. persica root, *Acacia brevispica* Harms root, *Cotyledon barbeyi* Schweinf. ex Baker leaves, stems, and flowers, *Acacia tortilis* (Forssk.) Hayne bark are used. The plants are used one after the other according to availability and until the desired effect is achieved. The plant parts are cut into small pieces, soaked in about 1 litre of water for many hours, and given to cows orally. If urgently needed, the brew can be boiled and given more quickly. However, if the placenta is still retained, one man will try to remove it with his arm washed in the *C. barbeyi* solution.	Veterinary: retained afterbirth	
Mali	Leaf	Decoction of fresh leaves is drunk A porridge is made from the juice from crushed leaves	Influenza Cold and cough	(Hope, 2005)
	NR	Remedy is made from *Boscia senegalensis* Lam. and *S. persica* and then bathes the child three times followed by a massage	Malaria	(Diallo, 2011)
Tanzania	Root bark	The powdered root bark is made into a paste using cooking oil. Topical use, applied locally in the mouth three times daily The powdered root bark is added to porridge, Oral use, one glass is taken three times daily	Oral candidiasis	(Runyoro et al., 2006)
	Root	Decoction, oral	female sterility	(Chhabra et al., 1991)
Namibia	Bark, stem	Bark and stems are crushed, soaked in water and filtered through cloth. Topically applied to treat skin infections in goats	livestock diseases	(Chinsembu et al., 2014)
Ethiopia	Root	Crushed/decoction or boiled with goat meat, Oral	Chest pain, boils, abscess, Chest pain/ Tuberculosis/ coughing with blood, flu, febrile disease, malaria, cancerous swelling	(Teklehaymanot and Giday, 2010)
	Leaf	Leaves are powdered, boiled and drunk after adding sugar	Malaria	(Mesfin et al., 2012)
Egypt	Leaf, fruit, branch	Infusion of the leaves and fruits Young branches chewed	Analgesic Toothache	(Eissa et al., 2014)
	Leaf	Infusion	urinary retention, bilharzia	(Goodman and Hobbs, 1988)

	Root, branch, leaf, fruit	NR	Tooth brush and mouth antiseptic, urinary tract pain, diuretic	(Mahmoud and Gairola, 2013)
Eritrea	Leaf	Fresh leaves are ground and the liquid filtrate is orally administered before meals. There is no precise prescription but a reasonable amount not exceeding one cup per day is recommended	Fever, gonorrhoea, and bronchial asthma	(Ogbazghi and Bein, 2006)
	Twig, Root	Used as chewing sticks	Dental care	
Somalia	Fresh root	The bark is removed from the root and the wood is crushed. A handful is mixed with half a glass of cold water. The extract is applied topically once a day for three days	Against hepatomegaly caused by malaria	(Samuelsson et al., 1993)
	Fresh rootbark	Powdered roots (50 g) are mixed with half a cup of water. The mixture is applied topically and covered with cloth	Against furuncles	
	Fresh or dried root	The roots are powdered and mixed with fresh or fermented cow milk. Two cups twice a day for nine days	Against dysmenorrhoea	
Senegal	Root	NR	As a diuretic and are sometimes used together with kinkeliba leaves for blackwater fever, rheumatism, and venereal diseases	(Oliver-Bever, 1986)
Sudan	Bark	Bark is pulverized and made into a paste with water, which is then applied to the head	In cases of serious febrile diseases	(Oliver-Bever, 1986)
	Dried leaf	NR	Flatulent dyspepsia	
East Africa	Root, bark	NR	livestock diseases: trypanosomosis and abscesses, mange, retained afterbirth, anthrax	(Katerere and Luseba, 2010)
West Africa	Twig	Salt made from twigs is used as an antiseptic of the digestive tract. Method of salt preparation: Twigs are bent down and cut. The cuttings are heaped up and burned in the green state. The resulting ash is then placed on large filters of woven straw. Then water is poured is poured over it and the filtrate is collected in conical vases, followed by heating to	Veterinary: Abdominal disorders	(Bizimana, 1994)

			leave the salt residue		
		NR	NR	Veterinary: poor milk Note: However it is said to give milk a bad taste	
	Sub-Saharan Africa	Root	A two-finger long piece of root is crushed and boiled in 5 litres of water for 1 hour. The decoction is cooled and filtered. The animal that has aborted is then drenched: 2 litres are used to drench one cow. Drench once.	Ethnoveterinary: Brucellosis	(Toyang et al., 2007)
			The surface of an arm-long piece of root is scraped using a knife or sharp stone. The scrapings are crushed and soaked in a calabash (1 litre) of water for 12 hours. The water turns yellow and tastes bitter. The animal is then drenched. The same procedure is repeated the next day if the afterbirth does not come out.	Ethnoveterinary: Retained afterbirth	
NR	NR	Root	NR	Chest disease	(Orwa et al., 2009)
			Pounded and used as a poultice	heal boils	
		Bark	The bark is scratched and the latex is used	Sores	(Orwa et al., 2009)
			Decoction, half a tea-cupful twice daily	Useful in low fever, as a stimulant, and tonic in amenorrhoea	(Panda, 1999)
		Fresh root bark	Bruised and applied to the skin	Act as a stimulant. In some cases, it acts as a vesicant and raises blisters	
		Fruit	Two-three year-old rruits are crushed in water and given orally to induce vomiting	Snakebite	(Trivedi, 2009)
			NR	Aphrodisiac, alexiteric, stomachic, improves appetite, and useful in biliousness	
		Stem bark	NR	Gastric troubles and as an ascarifuge	

	Seed	NR	Purgative, diuretic, tonic and yield fatty oil applied on rheumatic swelling
	Shoot and leaf	NR	Antidote to poisons (Panda, 1999)
	Flower oil	NR	Stimulant, laxative, and beneficial in wind, phlegm, worms, leprosy, gonorrhoea, and headaches. Also applied to painful rheumatic affections.

Abbreviation: NR-Not reported.

5. Phytochemistry of *S. persica*

Several parts (root, leaf, fruit, twig, and stem) of *S. persica* have been profiled. Phytochemical screening of the aqueous extract of *S. persica* leaves revealed the presence of sterols/terpenes, flavonoids, flavone aglycone, saponins, and tannins (Reuben et al., 2011). Gupta et al. (2015) screened various solvent extracts of *S. persica* twig and stem (hexane, chloroform, ethanol, and water extracts) for the presence of phytochemicals including alkaloids, glycosides, tannins, saponins, and flavonoids. All tested phytochemicals were absent in the hexane extract of twig and stem while only alkaloids were present in their chloroform extracts. In addition, the ethanol extract of *S. persica* twig contain all tested phytochemicals while alkaloids and tannins were absent in the ethanolic stem extract. On the other hand, the aqueous extract of stem contain all tested phytochemicals, while only alkaloids were absent in the twig aqueous extract. These variations might be due to difference in polarity of the solvents in extracting phytochemical compounds from the plant. In contrast

to this study, Abdallah and Al-Harbi (2015) did not observe tannin and saponin in the aqueous and ethanolic extract of *S. persica* stem, respectively. This variation among the studies might be due to different extraction techniques since Gupta et al. (2015) employed soxhlet extraction method while Abdallah and Al-Harbi (2015) have used maceration method. Besides the use of different solvents and extraction techniques, other factors can also result in variation in the chemical composition including variations in geographical origin and climatic condition, variety, and agricultural techniques applied.

Chemical study of *S. persica* also indicates the presence of nitrogen-containing compounds in the sticks, including pyrrolidine, pyrrole, and piperidine derivatives (Galletti et al., 1993). From the stems, five lignin glycosides were isolated as sodium 1-O-benzyl-β-D-glucopyranoside-2-sulphate (salvadoside), 5,5'-dimethoxylariciresinol 4,4'-bis-O-β-D-glucopyranoside (salvadoraside), syringin, liriodendrin, and sitosterol 3-O-β-D-glucopyranoside (Ohtani et al., 1992). Additionally, Khalil (2006) reported the presence of four benzyl derivatives identified as (1) butanediamide, N1,N4-bis(phenylmethyl)-2(S)-hydroxy-butanediamide, (2) N-benzylbenzamide, (3) benzylurea, and (4) N-benzyl-2-phenylacetamide. Moreover, Darout et al. (2000b) identified and quantified some anionic components, Cl^-, SO_4^{2-}, SCN^- and NO^{3-} in the aqueous extracts of *S. persica* root and stem. More chloride, sulphate, and thiocyanate were found in the stem extract than the root extract while nitrate concentration was equal in both extracts. In addition, the study of Chabane et al., 2017 revealed 5-O-caffeoylquinic acid and 4,5-O-Dcaffeoylquinic acid as major phenolic compounds in the root while the stem was rich in 5-O-caffeoylquinic acid, 3,5-O-Dcaffeoylquinic acid, catechin and epicatechin. The bark displayed a high content in 5-O-caffeoylquinic acid, naringenine, and some alkaloids including caffeine, theobromine, and trigonelline.

Further comparison of the stem and root was recently investigated by Farag et al. (2017) who studied the chemical composition of three *S. persica* root and one stem samples from different geographical origins (Saudi Arabia and Egypt). The roots contained more amino acids (2-12%) compared to stem (1%), with L-alanine (1-10%) being the major one although other amino acids were found at comparable levels. Total nitrogenous compounds was also present at higher amount in roots ranging from 3.2-5% compared to that of stem (2.86%), with N-benzylamine mostly present in root while urea in stem. On the other hand, stem was more enriched in sugar polyols, such as erythritol and arabitol, while D-fructofuranose, D-allopyranose, and lyxose were the major sugar forms in *S. persica* root. In addition, stem extract was more enriched in fatty acids (18%) compared to roots (1–2%), with palmitic acid (10%) and oleic acid (3%) as major forms. Sterols were also present in greater amount in stem (1.5%) compared to that of roots (0.2%).

In contrast, the organic acid content was much variable ranging from (5-47%) in roots and 24% in stem. Regarding the volatile components, stem contained lower benzyl isothiocyanate content (25%) compared to root (98.9-99.8%). However, benzyl nitrile (34%) and benzaldehyde (12%) were much higher in stem compared to that of roots (0.01-0.33%). Variations observed in the chemical constituents among the three root samples (two from Saudi Arabia and one from Egypt) also provide evidence of differences due to geographical regions. In fact, the study of Al-Ghamdi and El-Zohri (2017) revealed differences in chemical composition of the leaves and roots of *S. persica* from two different habitats (Al-ahsabah valley and Shada Mountain). The south west of Saudi Arabia showed variation in soil quality such that the soil of Al-ahsabah contained higher amount of silt and clay and lower amount of coarse and fine sand, as well as displaying higher pH, moisture, and organic matter than Shada Mountain. In addition, a lower total count of mycorrhizal spores and root colonization percentage was observed in Al-ahsabah. Results showed that carbohydrates, proteins, and

amino acids concentrations in *S. persica* leaves and roots collected from Al-ahsabah valley were significantly higher than those collected from Shada Mountain. An insignificant variation in the composition of phytochemicals was observed, whereby benzene, 1-isocyano-2-methyl- was present only in extract of *S. persica* roots collected from Al-Ahsabah valley, while benzyl nitrile only in *S. persica* roots of Shada Mountain. This explains the necessity to study parameters responsible for the variations observed in the chemical composition of *S. persica* as well as its bioactive properties to obtain better quality extracts with more potent therapeutic activity.

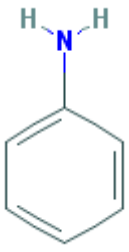
Furthermore, analysis of essential oil from the stems of *S. persica* revealed high amount of benzyl isothiocyanate (52.5%), benzyl nitrile (38.3%), carvacrol (3.3%), benzaldehyde (2.5%), aniline (0.7%), and naphthalene (0.6%) as well as smaller amounts of other chemicals (Noumi et al. (2011). In addition, Alali et al. (2005) identified the major components from the essential oil of *S. persica* stem from Jordan as 1,8-cineole (eucalyptol) (46%), followed by α-caryophyllene (13.4%), β-pinene (6.3%), and 9-epi-(E)-caryophyllene (6.3%). Moreover, GC-MS analysis of the volatile oil from *S. persica* leaves showed the presence of benzyl nitrile (53.96%), eugenol (10.49%), isoterpinolene (<0.50%), thymol (11.37%), isothymol (15.39%), β-caryophyllene (4.72%), and eucalyptol (0.79%) (Alali and Al-Lafi, 2003). The chemical structures of the major chemical constituents of *S. persica* are displayed in Table 3.

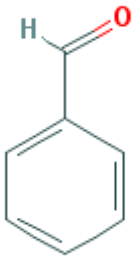
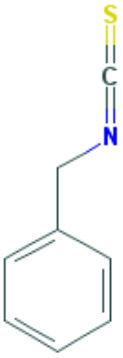
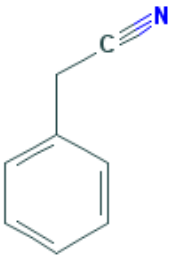
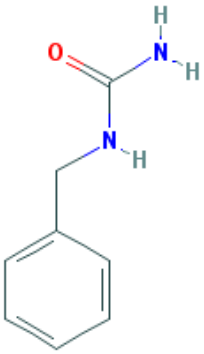
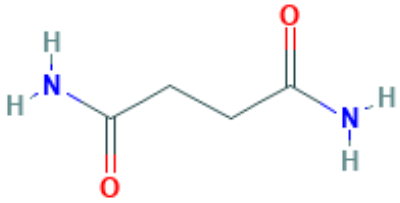
Analysis of the ripen *S. persica* fruit revealed substantial amount of essential nutrients (Kumari et al., 2017). GC-MS analysis indicated high glucose and glucopyranose content (247.62 and 42.90 mg g^{-1} FW, respectively). In addition, HPLC analysis revealed the presence of essential and non-essential amino acids required for healthy body metabolism. Among all amino acids quantified, cysteine was found to be in highest amount (733.69 mg 100 g^{-1} DW), followed by methionine (156.98 mg 100 g^{-1} DW), proline (154.36 mg 100 g^{-1}

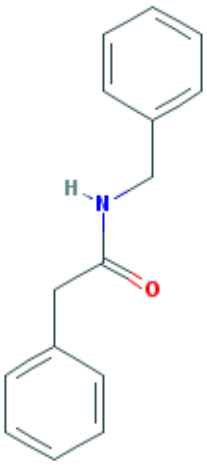
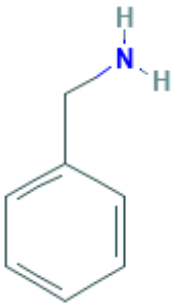
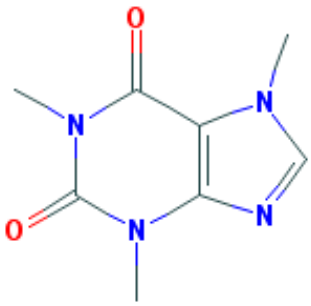
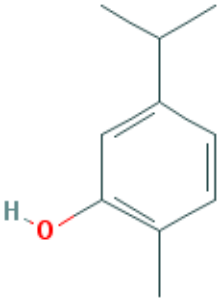
DW), histidine (140.58 mg 100 g^{-1} DW), glutamic acid (107.74 mg 100 g^{-1} DW), phenylalanine (93.57 mg 100 g^{-1} DW), and others in smaller amount. The ascorbic acid and carotenoid content was 67.99 mg 100 g^{-1} DW and 11.37 µg 100 g^{-1} DW, respectively. In addition, essential minerals including Na, K, Ca, Mg, P, Fe, Mn, and Zn were present.

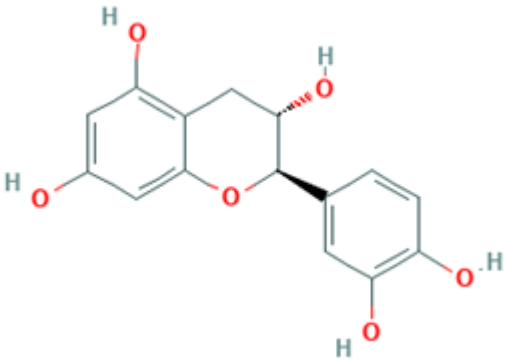
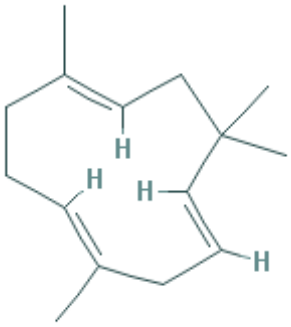
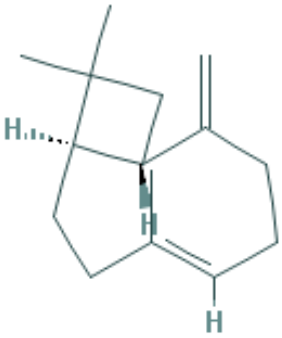
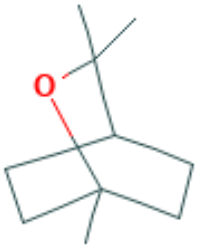
Therefore, it is clear that all parts of *S. persica* appears to be a potential source of pharmaceutically important metabolites which can contribute towards the recommended daily requirement for a healthy human being. The presence of the above-mentioned phytochemicals together with the micro and macronutrients tend to justify both its traditional, biological, and nutritive properties reported in literature. However, future investigation may be geared towards the isolation and characterisation of bioactive compounds from *S. persica* for formulation of new bio-products and/or more potent drugs.

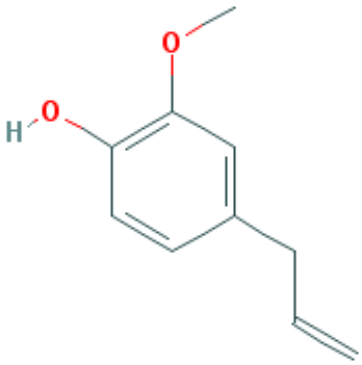
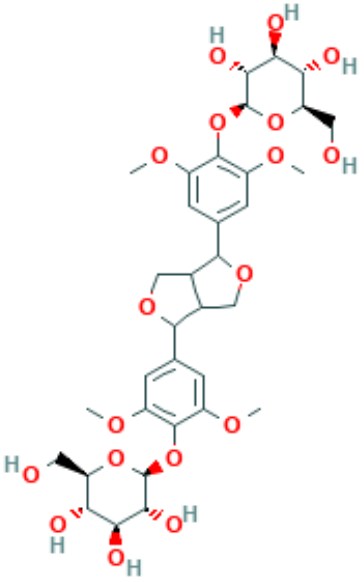
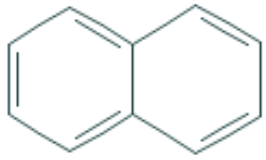
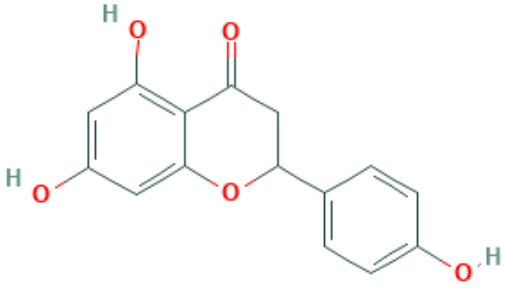
Table 3: Major chemicals identified in *S. persica*

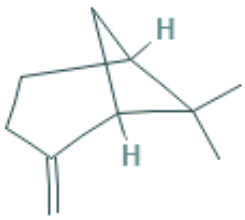
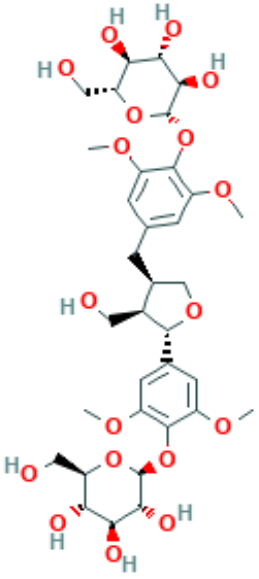
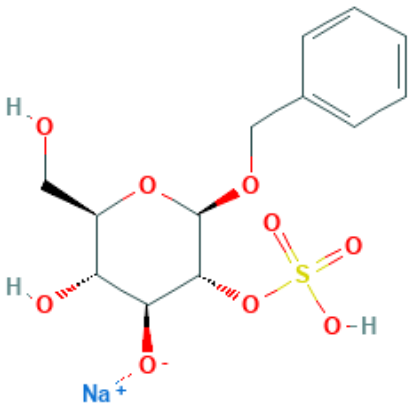
Chemical Name	**PubChem CID**	**Chemical structure**	**Molecular Weight /** g/mol	**Molecular formula**
Aniline	6115		93.129	C_6H_7N or $C_6H_5NH_2$

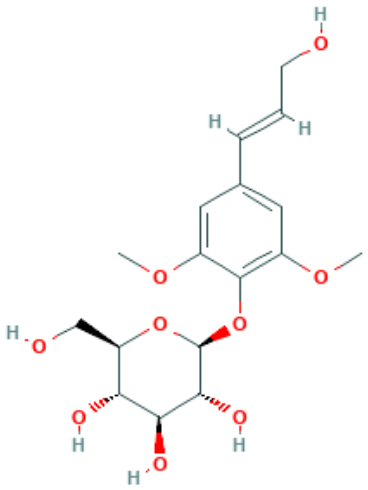
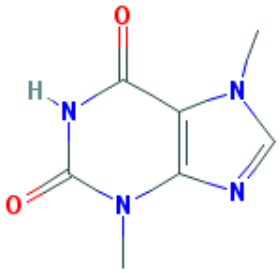
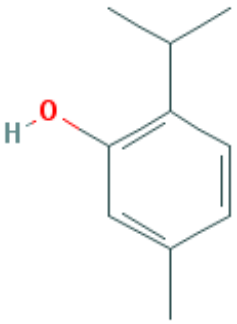
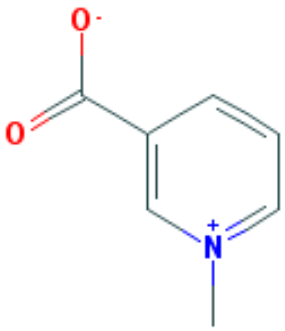
Benzaldehyde	240		106.124	C_7H_6O or C_6H_5CHO
Benzylisothiocyanate	2346		149.211	C_8H_7NS
Benzyl nitrile	8794		117.151	C_8H_7N
Benzylurea	10853		150.181	$C_8H_{10}N_2O$
Butanediamide	8036		116.12	$C_4H_8N_2O_2$

N-benzyl-2-phenylacetamide	277826		225.291	$C_{15}H_{15}NO$
N-benzylamine	7504		107.156	C_7H_9N or $C_6H_5CH_2NH_2$
Caffeine	2519		194.194	$C_8H_{10}N_4O_2$
Carvacrol	10364		150.221	$C_{10}H_{14}O$

Catechin	9064		290.271	$C_{15}H_{14}O_6$
α-caryophyllene	5281520		204.357	$C_{15}H_{24}$
β-caryophyllene	5281515		204.357	$C_{15}H_{24}$
Eucalyptol	2758		154.253	$C_{10}H_{18}O$

Eugenol	3314		164.204	$C_{10}H_{12}O_2$
Liriodendrin	73636		742.724	$C_{34}H_{46}O_{18}$
Naphthalene	931		128.174	$C_{10}H_8$
Naringenine	932		272.256	$C_{15}H_{12}O_5$

β-pinene	14896		136.238	$C_{10}H_{16}$
Salvadoraside	101630443		744.74	$C_{34}H_{48}O_{18}$
Salvadoside	23664985		372.32	$C_{13}H_{17}NaO_9S$

Syringin	5316860		372.37	$C_{17}H_{24}O_9$
Theobromine	5429		180.167	$C_7H_8N_4O_2$
Thymol	6989		150.221	$C_{10}H_{14}O$
Trigonelline	5570		137.138	$C_7H_7NO_2$

6. Pharmacological properties of *S. persica*

6.1. Antimicrobial activity

The global prevalence of infectious diseases coupled with antimicrobial resistance and the associated death toll has become a major public health threat (WHO, 2016). The use of antibiotics has been associated with adverse effects, causing a disturbance in the gastrointestinal flora by reducing the proportion of beneficial microorganisms along with targeted pathogens. This leads to an increased vulnerability of pathogenic microorganisms to colonise the gut, increasing the risk of intestinal infections (Hempel et al., 2012; Jernberg et al., 2010). Consequently, the quest for alternative natural antimicrobials have become an important priority.

Various studies have proved the antimicrobial efficacy of *S. persica* against a broad range of pathogens (see detailed studies in Table 4). However, as expected, the susceptibility of the microorganisms varies among studies depending on the tested concentration of *S. persica*. In addition, variation among studies may also be due to different solvents used for extracting bioactive compounds, extraction techniques, parts of *S. persica* used, geographical origin of *S. persica* tested, and the assays conducted. For instance, Almas et al. (1997) found no activity of the aqueous extract of *S. persica* stick against *S. aureus*, *S. epidermidis*, and *C. albicans* while they were found to be susceptible by other authors (El-Desoukey, 2015; Naseem et al., 2014). In addition, the methanolic stem extract was not effective against *L. acidophilus* and *P. aeruginosa* unlike the aqueous extract (Al-Bayati and Sulaiman, 2008). On the other hand, Al-Ayed et al. (2016) and Kumar et al. (2016) found that the methanol extract of *S. persica* chewing sticks was more effective than the aqueous extract in inhibiting several microorganisms. Another study by Sellami et al., 2013 showed that the hexane extract of *S. persica* bark exhibit greater antibacterial activity compared to the ethanolic and aqueous extracts. Variations observed among these studies indicate that based on polarity, each

solvent extracts different antimicrobial components from *S. persica*. In fact, the antimicrobial activity of *S. persica* can be attributed to its vast diversity of chemical constituents. Benzyl isothiocyanate (BITC), a major component from the roots of *S. persica*, is highly effective against Gram-negative bacteria. BITC has lipophilic as well as electrophilic properties and has been argued that it might infiltrate the outer bacterial membrane and possibly inhibit the bacterial redox systems, thereby disrupting the bacterium membrane potential (Sofrata et al., 2011).

The antimicrobial activity of *S. persica* may also be affected by the pH of extracts. Indeed, the study of AbdElRahman et al. (2002) exposed that among several extracts tested, the most potent extract was the root ethanolic extract showing the lowest pH while the stem water extract showed the highest pH. Moreover, El-Desoukey (2015) observed a greater effectiveness of cold extract of *S. persica* miswak over the hot extract. It can be argued that the loss of the antibacterial activity in boiled miswak stick might be due to the destruction of bioactive compounds. Therefore, further investigations are required to determine the thermal stability of the bioactive compounds of *S. persica*.

Additionally, *S. persica* collected from different geographical regions showed variations in antimicrobial activity. Almas (2001a) showed that *S. persica* from Saudi Arabia was effective against *S. faecalis*, while *S. persica* from Pakistan did not have any antibacterial activity. Moreover, El-Desoukey (2015) revealed that greater zones of inhibition was observed in well-diffusion method compared to disc-diffusion method which may be explained by variation in diffusion pathways of high/low molecular weight phytochemicals through the agar.

Furthermore, studies revealed the antibiofilm activity of *S. persica* extracts, causing significant reduction in biofilm of *Streptococcus* spp. including *S. mutans*, *S. mitis*, *S. sanguinis*, and against high biofilm producers strains of *Staphylococcus* spp. (Al-Sohaibani

and Murugan, 2012; Fatin-Majdina et al., 2014; Halawany et al., 2016; Noumi et al., 2017). It has been argued that the inhibition of quorum sensing (QS) is one approach to manage biofilm forming microorganisms without inducing resistance to antimicrobials drugs (Singh et al., 2017). Interestingly, GC-MS analysis of *S. persica* stick revealed the presence of >28 compounds, of which benzyl (6Z,9Z,12Z)-6,9,12-octadecatrienoate, 3-benzyloxy-1-nitro-butan-2-ol, and 1,3- cyclohexane dicarbohydrazide interacted efficiently with the QS regulators *Streptococcus* OmpP and *Staphylococcus* Lux proteins (Al-Sohaibani and Murugan, 2012). In addition, the methanolic extracts of *S. persica* fruit, leaves, and stems showed significant inhibition of QS-dependent phenomenon such as production of violacein pigment in *C. violaceum*, and swarming motility of *P. aeruginosa* PAO1 (Noumi et al., 2017).

It has also been argued that the combination of *S. persica* with antibiotics revealed significant enhancement in antibacterial activity compared to their individual use (Ahmed et al., 2010, 2012). However, reported studies on the combination of *S. persica* with other antimicrobials do not clearly indicate whether they produce any synergistic activity considering the true definition of synergism. All combinations do not produce synergistic effect and therefore a number of combinations (*S. persica* with antibiotics or with other natural products) are required to be experimented, *via* the use of proper *in vitro* assays (e.g. checkerboard method). It is also important to highlight that no attempt has been made to study the antiviral potential of *S. persica*. Therefore, it is recommended that researchers investigate into the antiviral activity of different parts of *S. persica*.

Table 4: Antimicrobial activity of *S. persica*

Antimicrobial study	**Microorgani**	**Findings**	**References**

	sms		
Comparison of 50% aqueous miswak extract with toothbrush and saline (*in vivo*)	Isolates of *S. mutans* and *Lactobacillus* in saliva	Miswak extract displayed greater reduction in both cariogenic bacteria counts. Reduction of microbial count in females was more for both microorganisms as compared to males.	(Bhat et al., 2012)
Root (in packing), root (without packing), and stem of *S. persica* tree (*in vitro*)	Isolates of *S. aureus*, *S. mutans*, and *C. albicans* from teeth	Root (both packed and unpacked form) exhibited strong antimicrobial activity against all tested microorganisms. Stem did not show any activity.	(Naseem et al., 2014)
Aqueous and methanolic stem extracts of *S. persica* (*in vitro*)	Isolates of *S. aureus*, *S. mutans*, *S. faecalis*, *S. pyogenis*, *L. acidophilus*, *P. aeruginosa*, and *C. albicans*	Aqueous extract inhibited all the microorganisms, showing greater activity on *Streptococcus* species. Methanolic extract was resisted by *L. acidophilus* and *P. aeruginosa*. At highest concentration tested (200 mg/ml), the aqueous extract (ZOI=10.8-22.3 mm, MIC=0.781-6.25 mg/ml) was more efficient than the methanolic extract (ZOI=11.0-17.7mm, MIC=1.56-6.25mg/ml) but were less efficient than the positive control streptomycin (MIC=0.012-0.781 mg/ml) and amphotericin B (MIC=0.195 mg/ml). Both extracts revealed equal MIC against *C. albicans* (MIC: 6.25 mg/ml), although slight differences were seen using the disc diffusion method (aqueous extract: ZOI=12.4 mm, methanol extract: ZOI=11mm) at 200 mg/ml.	(Al-Bayati and Sulaiman, 2008)

Comparison of freshly cut (pH=4.9) and 1-month-old (pH=5.5) miswak (*in vitro*)	*S. mutans*, *S. sanguis*, *S. faecalis*, *S. aureus*, *S. epidermidis*,and *C. albicans*	At 50% (v/v) concentration, the aqueous extract inhibited *S. mutans*, *S. sanguis* and *S. faecalis*, producing an inhibition zone of 1-7 mm. At 5 and 10% (v/v) concentrations, the aqueous extract was effective only against *S. faecalis*. No activity was recorded against *S. aureus*, *S. epidermidis*, and *C. albicans.* No significant difference in antibacterial activity between fresh and 1-month-old miswak was observed.	(Almas et al., 1997)
Miswak pieces (0.14g and 0.17g), without extraction, against oral microorganisms associated with periodontitis and caries tested in two ways: embedded in agar hole or suspended above the agar plate (to test the activity of volatile compounds) (*in vitro*)	*S. mutans*, *L. acidophilus* NCTC 1723, *A. actinomycetemcomitans* HK1519, *P. gingivalis* ATCC 33277, and *H. influenzae* ATCC 49247	Strong inhibitory effect on *P. gingivalis*, *H. influenzae* and *A. actinomycetemcomitans*; less on *S. mutans*, and least on *L. acidophilus.* Miswak pieces (0.14g) were more effective than the corresponding 0.07g. The 0.14g suspended miswak exhibited significantly greater inhibition than the 0.14g miswak embedded in agar on *A. actinomycetemcomitans* and *H. influenzae* but was less effective against *S. mutans.* 0.14g suspended miswak had no inhibitory effect on *L. acidophilus* while the embedded miswak showed mild activity.	(Sofrata et al., 2008)

Bark, pulp, and whole miswak extracts at 1, 5, 10 and 50% concentrations (*in vitro*)	*S. faecalis, S. mutans , S. aureus, S. epidermidis,* and *C. albicans*	All three extracts had no inhibitory effect against *S. aureus, S. epidermidis* and *C. albicans.* All extracts were effective against *S. faecalis* at 10 and 50% concentrations. At 5% concentration, only bark and whole miswak extracts had inhibitory activity against *S. faecalis.* Bark and whole miswak extracts were effective against *S. mutans* at 50% concentration. Whole miswak was more effective compared to bark or pulp separately.	(Almas and Al-Bagieh, 1999)
Comparison of aqueous and ethanolic (60%) miswak extracts with five different toothpastes (*in vitro*)	*S. mutans, L. acidophilus, E. coli, S. aureus,* and *P. aeruginosa*	Ethanol extract (ZOI=3.49-6.06cm) was more effective than the aqueous extract (ZOI=3.11-4.7cm) in inhibiting the tested microorganisms. The aqueous extract did not display any inhibitory effect on *P. aeruginosa*. The miswak extracts showed comparable or slightly stronger activity compared to some toothpastes.	(Mohammed, 2013)
Aqueous extract of seven different types of chewing sticks (including *S. persica*) (*in vitro*)	*S. faecalis, S. mutans, S. aureus,* and *C. albicans*	No activity on *S. mutans, S. aureus*, and *C. albicans* was observed. Peelu (*S. persica* from Pakistan) did not display any antibacterial activity. Arak (*S. persica* from Saudi Arabia) were effective against *S. faecalis* at 50 % concentration.	(Almas, 2001a)
Aqueous and methanolic (95%) extracts of chewing sticks against multidrug resistant (MDR) clinical isolates (*in vitro*)	Isolates of *Methicillin-resistant S. aureus, methicil*	The extracts displayed a concentration dependent activity from 50 mg/ml to 400 mg/ml. At 400 mg/ml, methanol extract (ZOI=7.4-13.6 mm) was more effective than the aqueous extract (ZOI=6-12.3 mm) but less efficient than the positive control vancomycin (30 ??g) (ZOI=18-21 mm) and tobramycin (10 ??g) (ZOI=16-21 mm). The lowest MIC value for the methanolic extract was observed for *E. coli* (0.39 mg/ml), followed by *K. pneumoniae* (0.781 mg/ml). The highest MIC value (6.25 mg/ml) was recorded for methicillin-resistant *S. aureus* (MRSA), *A. baumannii*, and *S. maltophilia.* Methanolic extract showed stronger antibacterial activity against Gram-negative than Gram-positive bacteria.	(Al-Ayed et al., 2016)

	lin-resistant S. epidermidis, S. pyogenes, E. faecalis, E. coli, K. pneumoniae, P. aeruginosa, S. marcescens, A. baumannii, and *S. maltophilia* from patients with nosocomial infections		
Aqueous, ethanolic and hexane extracts of different spices and plants materials, including *S. persica* bark (*in vitro*)	*E. coli* (ATCC 25922), *K. pneumoniae* (ATCC 278	At tested concentration (20 mg/ml), the hexane extract of miswak exerted significant antibacterial effect against all tested bacteria. The MIC of the hexane extract range from 15.62-125 µg/ml. The ethanolic extract showed mild activity while the aqueous extract was ineffective against all bacteria.	(Sellami et al., 2013)

	53), *S. enterica* (ATCC 43972), *E. cloacae* (ATCC 13047), *S. aureus* (ATCC 25923), *S. epidermidis* (ATCC 14990) *and B. flavum* (ATCC 14067) and isolates of *S. xylosus*		
Aqueous stem extract on *Mycobacterium bovis* (*in vitro*)	*M. bovis*	The extract exhibit antibacterial activity on *M. bovis*, with MIC=10 mg/ml.	(Fallah et al., 2015)
Methanol, ethanol, and ethanol/methanol extracts against three isolated and genetically identified oral cavity pathogens (*in vitro*)	*S. aureus* strain KKU-020, *E. faecalis*	All miswak extracts showed high antibacterial activity against all tested pathogens. Maximum activity was observed against *E. faecalis* with the ethanolic extract (ZOI= 40.67 mm).	(Hesham and Alrummman, 2014)

	strain KKU-021, and *K. pneumoniae* strain KKU-022.		
Effect of some herbal ethanol-water (50:50) extracts, including *S. persica* root, against oral pathogens (*in vitro*)	*A. viscosus* PTCC (Persian Type Culture Collection) *1202*, *S. mutans* PTCC 1683, *S. sobrinus* PTCC 1601, *L. fermentum* PTCC 1638, *Lactobacillus casei subsp. case*	*S. persica* extract was more effective against *L. fermentum* and *A. viscosus*, and least effective against *S. sobrinus.* At its most effective concentration (100% w/v), *S. persica* extract was less effective than chlorhexidine (CHX) but showed greater activity than the mouth wash Irsha.	(Vahabi et al., 2011)

	i PTCC 1608, and *E. corrodens* PTCC 1391		
Comparison of ethanolic extract of *S. persica* wood with three commercial mouthwashes containing alcohol, povidine iodine, and fluoride, respectively (*in vitro*)	*C. albicans* isolated from mouth	Miswak wood extracts inhibited *C. albicans* growth but was less effective compared to the three commercial mouthwashes.	(Pribadi E.S., 2014)
Comparison of hot and cold aqueous extracts of *S. persica* miswak and toothpaste containing sodium fluoride (*in vitro* and *in vivo*)	*S. aureus* and *C. albicans* isolated from mouth	Miswak extracts (10%) inhibited both tested microorganisms. ZOI of miswak (25mm/37mm) was greater compared to tooth paste (14mm/29mm) and the positive control (unspecified tested concentration); ciprofloxacin (25mm) and nystatin (16mm). The hot extract exhibit less antimicrobial effect than the cold one. Greater ZOI was observed in well diffusion compared to disc diffusion method. Oral swab cultivated on nutrient agar plate before and after use of both miswak and toothpaste revealed that miswak was more effective than toothpaste in decreasing microbial growth.	(El-Desoukey, 2015)
Crude extracts of *S. persica* roots and twigs using sterile distilled water, 96% ethanol, 2% acetic acid, and ethyl acetate as solvents (*in vitro*)	*S. mutans*, *L. acidophilus*, *Actinobacillus actinomycetemcomitans*, *A. naeslundii*, *P. gingivali*	The most potent extract was the root ethanolic extract while the weakest one was the stem-water extract. Compared with other solvents, the ethanolic extracts showed the strongest activity. The most susceptible strain to all extracts was *S. mutans* while *L. acidophilus* was resistant to all extracts except for the root ethanolic extract. MIC values ranged from 100 mg/ml to 300 mg/ml for the different crude extracts.	(Abd ElRahman et al., 2002)

	s, *P. intermedia* and *C. albicans*		
Combined extract of *S. persica* stem and bark using petroleum ether, acetone, methanol, and water as solvents (*in vitro*)	*S. aureus* (MTCC 1144), *S. mutans* (MTCC 890), *S. sanguinis* (ATCC 10556), *S. sobrinus* (ATCC 33478), *S. salivarius* (MTCC 1938), *L. acidophilus* (MTCC 10307), and *C. albicans* (MTCC 227) and	All solvent-extracts (tested at 200 mg/ml) inhibited the tested microorganisms. Methanol extract was more effective than the other extracts displaying ZOI in the range 14.0-22.3 mm but was less effective compared to the positive control ofloxacin (unspecified tested concentration) (27-35.3mm). The methanolic extract displayed lowest MIC against *S. aureus* (3.12 mg/ml) and highest MIC against *C. albicans* (25 mg/ml).	(Kumar et al., 2016)

	isolates of *S. aureus*, *S. mutans*, *S. sanguinis*, *S. sobrinus*, *S. salivarius* and *L. acidophilus*		
Aqueous and ethanolic extracts of *S. persica* stem (*in vitro*)	*S. enterica* ATCC 5174, *P. vulgaris* ATCC 49132, *K. pneumoniae* ATCC 27736, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *B. cere*	Both aqueous and ethanolic extracts inhibited all tested pathogens. The aqueous extract showed greater activity than the ethanolic extract against *P. vulgaris*, *E. coli*, *P. aeruginosa*, *B. cereus*, and *S. aureus* but was less effective against *S. enterica*. The antibacterial activity of the extracts was comparable or slightly better than penicillin G (10 units/disc), but less effective when compared to gentamicin (10 µg/disc).	(Abdallah and Al-Harbi, 2015)

	us AT CC 10876, *S. epidermidis* AT CC 49461, and *S. aureus* AT CC 25923		
Methanolic (95%) and water extract of *S. persica*, and *Commiphora gileadensis* (L.) C.Chr. stems against some pathogenic bacteria (*in vitro*)	*F. nucleatum*, *Lactobacillus casei*, *S. aureus*, *S. epidermidis*, *S. mutans*, and *S. salivarius*	The methanolic extract of *S. persica* (ZOI=23-29mm) showed greater activity against all tested pathogens compared to the aqueous extract (ZOI=15-21mm). The methanolic *S. persica* extract also showed better inhibitory effect in comparison to *C. gileadensis.* The MIC of *S. persica* methanolic extract ranged from 50-75 µg/ml which was less effective than the positive control ampicillin (MIC= 2-5µg/ml).	(Al-Sieni, 2014)

Extract of *S. persica* dry stems and Tunisian *Juglans regia* L. bark using acetone: water (80:20; v/v), ethyl acetate and methanol as solvents (*in vitro*)	Bacteria: *S. aureus* ATCC 25923, *S. epidermidis* CIP 106510, *M. luteus* NCIMB *8166*, *P. aeruginosa* ATCC 27853, *S. typhimurium* LT2 and *P. aeruginosa* (isolate from oral cavity), Fungi: *C. albicans*, *C. dublinie nsis*, *C. glabrata*, *C.*	All three solvent extracts inhibited all tested bacteria, displaying comparable activity in the range (ZOI=7-10mm). The diluted acetone extract of *S. persica* (300 mg/ml) also showed significant antifungal activity (ZOI=7-11.33mm). Overall, *S. persica* extract showed less antimicrobial activity than *Juglans regia* L. bark extract and the positive control gentamicin (10 µg/disc) and amphotericin B (10 µg/ml).	(Noumi et al., 2011)

	parapsilosis, C. krusei, C. famata, C. kefyr, C. sake, C. holmii, C. lusitaniae, C. intermedia, C. atlantica, C. maritima, Pichia guilliermondii, and *Pichia jardinii*		
Comparison of *S. persica* stick and green tea extracts with conventional irrigation solutions (sodium hypochlorite and chlorhexidine gluconate) (*in vitro*)	*E. faecalis*	*S. persica* extract (5%) (Mean ZOI=11.25 mm) displayed greater inhibitory effects than 5% green tea (Mean ZOI=8.88 mm) but was less effective compared to 5.25% sodium hypochlorite (Mean ZOI=29.88mm) and 2% chlorhexidine gluconate (Mean ZOI=26.13 mm).	(Al-Azzawi, 2015)
Ethanolic extract of *S. persica* roots (*in vitro*)	*P. vulgaris, E. coli, Salmonella typhi, B. cereus,*	The extract showed antibacterial activity against all tested microorganisms (ZOI in the range 27.5-32.8mm) with *E. aerogenes* being the most susceptible at 500 mg/ml of extract.	(Anthoney and Timothy, 2015)

	and *E. aerogenes*		
Antifungal activity of essential oil from *Cuminum cyminum* L. and ethanolic (80%) extract from *S. persica* stick against pathogenic *Candida* strains (*in vitro*)	*C. albicans* ATCC 14053, *C. dubliniensis* ATCC CD60, *C. glabrata* ATCC 90030, *C. krusei* ATCC 6258, and *C. parapsilosis* ATCC 22019	*S. persica* showed inhibitory activity against *C. albicans*, *C. dubliniensis*, and *C. glabrata*, whereas *C. parapsilosis* and *C. krusei* were not susceptible. The MIC and MFC (minimum fungicidal concentration) of *S. persica* extract were 4.9 and 10 mg/ml against *C. albicans* and 20 mg/ml against *C. dubliniensis*, respectively. *S. persica* displayed less antifungal activity compared to *C. cyminum* and the positive control Nystatin (100 units/disc).	(Naeini et al., 2014)
Effectiveness of ethanolic (96%) *S. persica* root extract against a mixture of *E. faecalis* and *C. albicans* after 1 ,6, and 24 hour of exposure, respectively (*in vitro*)	*C. albicans*, *E. faecalis* and a mixture of both	The extract (20%) was effective against *C. albicans* at all tested times. After 1 hour of exposure, the 20% extract was ineffective in inhibiting *E. faecalis* and a mixture of both *E. faecalis* and *C. albicans* but was effective after 6 and 24 hours of exposure.	(Al-Obaida et al., 2010)

Comparison of chlorhexidine (CHX), Persica mouthwash (made of *S. persica*, mint, and yarrow extracts), and miswak extract	*S. salivarius, S. sanguis, Lactobacillus vulgaris*, and *C. albicans*	CHX was more effective than Persica and miswak. CHX was most effective against *S. salivarius*. Persica was most effective against *Lactobacillus*. At concentrations 0.1 and 0.05%, miswak extract was effective against *S. salivarius* and *S. sanguis* but was ineffective against *L. vulgaris.* All three mouthwashes were ineffective against *C. albicans.*	(Moeintaghavi et al., 2012)
Ethanol (10%) and hexane extracts of *S. persica* root against common oral pathogens (*in vitro*)	*S. mutans* ATCC 25175, *S. sanguis* ATCC 10556 and *S. salivarius* ATCC 13419	The extracts showed a concentration dependent activity. Ethanolic extract of *S. persica* showed greater ZOI (16-20mm) against all isolates compared to hexane extract (ZOI=13-16mm) at highest concentration tested (100mg/ml). However, hexane extract displayed lower MIC (2-4 mg/ml) and MBC (4-8mg/ml) value compared to ethanol (MIC=4-8mg/ml; MBC=8mg/ml). After exposure of bacteria to the MBC values for 1-6hr, a greater decline in CFU counts was observed in ethanolic extract compared to the hexane extract. At all tested intervals no viable count was observed for CHX 0.2%.	(Balto et al., 2017)
Aqueous and methanolic extracts of bark of *Colophospermum mopane* (J. Kirk ex Benth.) J. Léonard, roots of *Dichrostachys cinerea* (L.) Wight & Arn. and leaves of *S. persica* (*in vitro*)	*S. aureus* ATCC 33862 and *E. coli* ATCC 25922	*S. persica* aqueous extract (MIC=1.03 mg/ml) showed higher activity than methanol extract (MIC=5.31 mg/ml) against *S. aureus* while the opposite effect was observed against *E. coli*, (MIC=13.6 mg/ml for methanolic extract, MIC=34.3 mg/ml for aqueous extract). Compared to *C. mopane* and *D. cinerea*, *S. persica* was most effective against *S. aureus* but was least effective against *E. coli.*	(Mudzengi et al., 2017)
Crude aqueous and ethanolic extracts of *S. persica* twigs against common oral microbial pathogens causing dental caries and periodontitis (*in vitro*)	Isolates of cariogenic orga	Ethanolic extract showed a significantly higher activity compared to water extract. At highest concentration tested (400µg/ml), the extracts displayed antibacterial activity against the tested bacteria, except that the aqueous extract was not effective against *S. mitis* and *Lactobacilli*.	(Sideeqh et al., 2016)

	nisms such as *S. mutans*, *S. mitis* and *Lactobacilli* and periodontal pathogens such as *Peptostreptococcus* and *P. intermedia* as well as *C. albicans*		
Hexane and ethanol extracts of *S. persica* on a monospecies biofilm model established on orthodontic brackets *(in vitro*)	*S. mutans* (ATCC 25175)	Absorbance values obtained from the MTS reduction assay after exposure to different treatments showed a decline in the bacterial cell viability of the *S. mutans* biofilm. A greater decline was observed using chlorhexidine (+ve control), followed by hexane extract (*S. persica*, 5 mg/ml), ethanol extract (*S. persica*, 5 mg/ml), and saline + 2% DMSO (-ve control). CFU counts were also lowest for chlorhexidine (0.18×10^2), followed by hexane (8.7×10^3) and ethanol (2.9×10^4) extracts. The counts were considerably lower compared to the negative control saline +2 % DMSO (3.6×10^7).	(Halawany et al., 2016)
Evaluation of growth inhibition and antibiofilm effects of various *S. persica* extracts on cariogenic *S. mutans* isolated from samples of dental plaque (*in vitro* and molecular docking studies)	Cariogenic *S. mutans*	The percentage reduction in biofilm inhibition obtained for methanol, ethanol, chloroform, acetone, and aqueous extracts were 87.92%, 85.75%, 72.44%, 61.66% and 58.68%, respectively. GC–MS analyses revealed >28 compounds, of which benzyl (6Z,9Z,12Z)-6,9,12 octadecatrienoate, 3-benzyloxy-1-nitro-butan-2-ol and 1,3- cyclohexane dicarbohydrazide interacted efficiently with the bacterial communication quorum-sensing regulators *Streptococcus* OmpP and *Staphylococcus* Lux proteins.	(Al-Sohaibani and Murugan, 2012)

Antibacterial and antibiofilm potential of *S. persica* methanolic fruit, leaves and stems extracts against oral *Staphylococcus* strains, and their inhibitory activity against quorum sensing-dependent phenomenon such as violacein pigment production in *Chromobacterium violaceum*, and swarming motility of *Pseudomonas aeruginosa* PAO1 (*in vitro*)	Sixteen oral *Staphylococcus* strains representing eight species, including *S. aureus*, *S. capitis*, *S. epidermidis*, *S. haemolyticus*, *S. hominis*, *S. warneri*, *S. xylosus*, *S. saprophyticus*, and *C. violaceum* ATCC 12472, *C. violaceum*	The fruit methanolic extract showed highest anti-*Staphylococcus* activity (MIC=3.125-6.25 mg/ml, MBC=6.25-12.5 mg/ml) compared to the stem extract (MIC=3.125-100 mg/ml, MBC=6.25->100 mg/ml) and leaf extract (MIC=25-100 mg/ml, MBC=50->100 mg/ml). The fruit extract was also more effective than the positive control Ampicilin, tested at 10 mg/ml, (MIC=25-100 mg/ml, MBC=50->100 mg/ml). The tested concentrations (MIC, 2xMIC and 4xMIC) of fruit methanolic extract of *S. persica* showed a concentration dependent anti-*Staphylococcus* antibiofilm activity against high biofilm producers strains on polystyrene and polymethylmetacrylate. *S. persica* exhibited a concentration dependent inhibition (an increase in inhibition from MIC/32: 0.625 mg/ml to MIC: 20 mg/ml) in QS dependent phenotypic production of violacein in *C. violaceum*. At 20mg/ml, the extracts showed 29.23-70.32% inhibition (fruit extract highest activity) in *C. violaceum* ATCC 12472 and 86.09-90.1% inhibition (leaf extract highest activity) in *C. violaceum* CV026. *S. persica* also exhibited a concentration dependent inhibition (an increase in inhibition from 50 to 100 µg/ml) in QS dependent swarming motility of *P. aeruginosa* PAO1, displaying 16.67-29.17 % anti-swarming activity at 100 ??g/ml (stem extract highest activity followed by leaf and fruit, respectively).	(Noumi et al., 2017)

	CV026, *P. aeruginosa* PAO1		
Effect of *S. persica* chewing sticks extract on selected oral bacteria in single-species biofilm in an artificial mouth model simulating before and after meals (*in vitro*)	Clinical isolates of *S. mitis* and *S. sanguinis*, and *S. mutans* ATCC 25175	The population of *S. mitis*, *S. mutans*, and *S. sanguinis* in the respective biofilms for both experiments (before and after meals) involving treatment with *S. persica* extract or Listerine (positive control) was significantly reduced by more than 70% when compared with the negative control (sterile distilled water). Comparing the effect of *S. persica* with Listerine on the bacterial population of the biofilms when used either before or after meal showed that *S. persica* was quite comparable although it was slightly less effective towards *S. sanguinis* before meal and towards *S. mutans* after meal.	(Fatin-Majdina et al., 2014)
Activity of ethanolic (50%) extracts of various parts of 16 medicinal plants, including *S. persica* leaves and bark, against clinical isolates and WHO strains of *Neisseria gonorrhoeae*, including multidrug-resistant (MDR) strains (*in vitro*)	WHO control strains and 11 clinical isolates of *N. gonorrhoeae*	*S. persica* leaves and bark displayed significant antibacterial activity against *N. gonorrhoeae* strains, including strains resistant to penicillin and ciprofloxacin.	(Shokeen et al., 2009)
Potency of *S. persica* bark extracts against 6 multidrug resistant uropathogenic bacteria (*in vitro*)	Isolates of *A. baumannii*, *C. freundii*, *K. oxytoca*, *P.*	*S. persica* bark extracts (30 mg/ml) displayed significant activity against *C. freundii*, *K. oxytoca*, *P. mirabilis*, and *P. vulgaris*, with the ethanolic (80%) extract (ZOI=17-24mm) being more effective compared to the aqueous extract (ZOI=15-22mm). *A. baumannii* and *P. aeruginosa* were resistant to both extracts.	(Rath et al., 2012)

	mirabilis, *P. vulgaris* and *P. aeruginosa*		
Evaluation of antiparasitic and antimicrobial activity of Sudanese *S. persica* stem and leaves (*in vitro*)	*M. violaceum*, *B. megaterium*, *C. fusca*, *P. falciparum* K1, *P. falciparum* NF54, *L. donovani*, *T.b. rhodesiense*, and *T. cruzi*	*S. persica* methanolic (80%) stem and leaf extract (1 mg/ml) displayed mild antimicrobial activity against *M. violaceum* and was ineffective against *B. megaterium* and *C. fusca*. The extracts also showed antiplasmodial activity against *P. falciparum* strain K1 (stem: IC_{50}=1.72 µg/ml, leaves: IC_{50}=2.75 ??g/ml) and strain NF54 (stem: IC_{50}=0.66 µg/ml, leaves: IC_{50}=0.77 µg/ml). IC_{50} value against *L. donovani* was > 30 µg/ml. No activity was observed against *T.b. rhodesiense* and *T. cruzi*.	(Ali et al., 2002)
Activity of eight commercially available non-alcohol mouthrinses and 50% *S. persica* chewing stick aqueous extract (*in vitro*)	Isolates of *S. faecalis*, *S. pyogenis*, *S. mutans*, *C. albicans*, *S. aureus*, *S.*	*S. persica* extract displayed high antimicrobial activity against *S. faecalis* comparable to the most effective mouthrinse, but was mildly effective against *S. mutans*. No inhibitory effect was observed against the remaining microorganisms.	(Almas et al., 2005)

	epidermidis		
Inhibitory activity of the methanolic (20%) extract of *S. persica* bark against oral bacterial strains associated with periodontitis (*in vitro*)	Isolates of *Staphylococcus*, *Streptococcus* and *Lactobacillus*, *Enterococcus* and *Escherichia* from subjects with and without periodontitis	The extract showed a concentration dependent inhibitory activity against all tested strains (increase in activity from 50 mg/ml to 400 mg/ml). The extract at 100-400 mg/ml displayed greater activity (ZOI=3-11mm) compared to ampicillin (10 µg) (ZOI= 2.2-5.1mm) and vancomycin (20 µg) (ZOI=1.4-2.1mm).	(Alireza et al., 2014)
In vitro and *in vivo* antimicrobial activities of methanolic extract of Algerian Hoggar *S. persica* stick on some isolated and identified strains from the oral cavity of subjects with and without caries	Isolates of *S. aureus*, *S. saprophytic us*, *S. epidermidis*, *S. mutans*, *E. coli*, *Lact*	The extract showed a concentration dependent inhibitory activity against all tested strains (increase in activity from 50 mg/ml to 400 mg/ml). At highest concentration tested (400mg/ml), the extract displayed greater activity (ZOI=4.8-12mm) compared to amphotericin B (10 ??g) (ZOI=2-6mm) and streptomycin (20 ??g) (ZOI=1-3mm). In vivo rinsing with Hoggar *S. persica* mouthwash (1ml of sterile methanolic extract at a concentration of 400 mg/ml in 150ml of sterile demineralized water) caused a significant reduction in all tested bacteria after 8 days from 2.79-6.6 log CFU to 0-3.01 log CFU.	(Chelli-Chentouf et al., 2012)

	oba cillu s sp., *C. albi cans*, *Can dida* sp., *Peni cilli um* sp.		
Combined effect of ethanolic *S. persica* stem and leaf extracts and ampicillin (*in vitro*)	*S. aure us*	Both *S. persica* stem (ZOI=18mm) and leaf (ZOI=10.5mm) extract were less effective than ampicillin (ZOI=21.2mm). When used in combination with ampicillin, both extract showed greater activity, with ampicillin + *S. persica* stem extract exhibiting greater inhibitory effect (ZOI=32.3mm) compared to ampicillin + *S. persica* leaf extract (ZOI=29.2mm).	(Ah med et al., 2012)
Combined effect of ethanolic stem and leaf *S. persica* extracts, Tetracycline, and Penicillin (*in vitro*)	*S. aure us*	Both *S. persica* stem (ZOI=18mm) and leaf (ZOI=10.5mm) extract were less effective than tetracycline (ZOI=23mm) although the stem was comparable to penicillin (ZOI= 18mm). Combined effect of tetracycline with penicillin (ZOI= 27mm) was much more effective than when used individually. Combined effect of stem and leaf extracts with the two antibiotics were more effective compared to using the extracts only. Tetracycline + *S. persica* stem extract showed greater inhibition (ZOI=31.5mm) than both tetracycline + leaf extract (ZOI=30mm) and the combination of stem or leaf extract with penicillin (ZOI=16-21mm).	(Ah med et al., 2010)

6.2. Oral health

Despite the variety of existing mechanical cleaning methods such as brushing, flossing, gargling using mouth rinse, and the recent advances in orthodontic materials and techniques, the build-up of dental plaque on teeth and the subsequent progress of enamel decalcification and dental caries around orthodontic appliances remain challenging to manage (Chin et al., 2005; Wang et al., 2015). Being one of the most complex biofilm system, human dental plaque is responsible for a variety of oral infections including dental caries, pulp, and periapical diseases (Wang et al., 2015). A wide range of anti-plaque agents are used to control plaque formation and the development of early periodontal diseases. Chlorhexidine (CHX) has been the most thoroughly studied and has evolved into a gold standard antiplaque

agent in dentistry. However, local side effects such as tooth staining, weakened sense of taste, increased formation of supragingival calculus, occasional mucous membrane irritation, and desquamation are associated with the long term use of CHX mouthwash (Goes et al., 2016; Ilango et al., 2013). Therefore, both consumers and the scientific interests have shifted to safer alternatives, particularly the use of herbal products.

During the course of the present literature search, it was found that *S. persica* has been mainly studied and validated for oral health (*in vitro* and clinically) and even incorporated in conventional toothpaste. For instance, in a double-blind, cross-over study on 28 healthy human (excluding individuals taking any mouthwashes, on antibiotic treatment, or any treatment from dentist or hygienist), Khalessi et al. (2004) found that Persica™ mouthwash (a commercially available herbal mouthwash containing *S. persica* extracts) improved gingival health and resulted in lower carriage rate of cariogenic bacteria. However, it is to be noted that no significant reduction in dental plaque formation was observed. It can be argued that either a more thorough plaque removal prior to the study or exposing the mouthwash for a longer period of time may ease the reduction of plaque accumulation. Abdulbaqi et al. (2016) showed that the combination of green tea (leafs of *Camellia sinensis* (L.) Kuntze var. *assamica* (J.W.Mast.) Kitam.) and *S. persica* root stick was found to exhibit synergistic anti-plaque activity against primary colonisers of dental plaque *in vitro*. This study indicates the necessity of exploring the combined bioactivity of *S. persica* with other medicinal plants, especially those known to be traditionally used in oral care, which can potentially lead to novel bioactive polyherbal formulations.

In comparison to toothbrush, *S. persica* miswak was found to be more effective in reducing gingivitis compared to tooth brush alone or combined users in an observational descriptive cross sectional study conducted on 528 subjects (63.6% females and 36.4% males) (Shetty et al., 2010). Additionally, in a study conducted in Sudan, comprising of male

miswak (n = 109) and toothbrush users (n =104) with age range 20-65 years, Darout et al. (2000a) found that *S. persica* miswak users showed significantly lower dental calculus and ≥ 4 mm probing depth, higher ≥ 4 mm attachment loss, as well as a tendency to lower gingival bleeding in the posterior sextants compared to toothbrush users. Although these differences were not significant in the anterior sextants, the results imply that the periodontal status of miswak users in Sudanese population was better than that of toothbrush users.

In addition, a clinical study conducted by Gazi et al. (1990) revealed a significant reduction in gingivitis both buccally and lingually after using miswak five times a day compared with conventional toothbrush. Brushing with miswak twice a day showed significant reduction in gingivitis buccally compared with toothbrushing, but the difference was insignificant lingually. In addition, no significant difference was observed in plaque scores between miswak and conventional toothbrush when brushing was continued five times a day. However, when miswak was used only twice a day, plaque scores became significantly higher compared with toothbrushing, specifically on the lingual surfaces of the teeth. Therefore, results from this study tend to indicate that miswak used five times a day may be a suitable alternative to toothbrush for reducing plaque and gingivitis. In fact, taking into consideration the recommended use of miswak at the five daily obligatory prayers by Prophet Muhammad, besides other time mentioned previously in Section 3, this study confirms the importance of the emphasis of Prophet Muhammad on the frequent use of miswak per day in oral care. Moreover, Al-Otaibi et al. (2003) reported that after professional instruction of the proper use of toothbrush and miswak in a sample of 15 healthy Saudi Arabian male volunteers aged 21 to 36 years, miswak was found to be more effective in reducing plaque formation and gingivitis than tooth brush in a single-blind randomized cross-over clinical study. Therefore, it can be suggested that the proper method of use of miswak as discussed above (Section 3) is necessary to ensure all regions of the mouth are cleaned. Interestingly, in

countries where miswak is commonly used, the number of tooth loss in adults has been reported to be quite low (Almas and Almas, 2013).

The difference between toothbrush and *S. persica* miswak can be associated with the frequency and duration of brushing, experiences, and motivation in using miswak (Ezoddini-Ardakani, 2010). In addition to its mechanical cleansing effect, the chemicals released from *S. persica* miswak contain antimicrobial properties that inhibit plaque accumulation. In fact, several studies (see Table 4) have reported that *S. persica* exhibit antimicrobial activity against cariogenic and periodontal pathogens. Moreover, miswak is generally used for longer periods of time than normal toothbrush (Akhtar and Ajmal, 1981). In addition, the enzyme inhibitory properties of *S. persica* miswak may be also involved in deactivating the virulence effects of sub-gingival species that are associated with periodontal disease (Homer et al., 1990; Shetty et al., 2010). In terms of their design, the bristles of *S. persica* miswak is found in the same long axis as its handle and thus can reach the buccal/labial surfaces of the teeth more easily in comparison to a typical toothbrush. The angulation also allows it to adapt more easily to the distal tooth surfaces, especially on the posterior teeth (Tripathi and Tiwari, 2015).

Furthermore, Khalil et al. (2013) studied the differences in oral homeostasis in miswak and tooth brush users. Miswak users showed higher salivary sodium and calcium, and higher dental plaque calcium and inorganic phosphate content when compared to brush users. No difference in saliva and dental plaque pH was observed among the two groups. However, miswak users showed significant negative correlations of pH, with calcium and phosphate, and a positive correlation with dental plaque sodium, suggesting the role of miswak in counteracting the drop of plaque pH. The use of miswak may provide the critical ions needed for remineralisation on frequent acidic exposures. Moreover, Sofrata et al. (2007) found that rinsing with miswak extract raised the plaque pH and stimulated parotid gland

secretion, suggesting a potential role in caries prevention. It can be argued that elevation in plaque pH could be the result of the buffering capacity of the miswak extract, salivary stimulation caused by miswak taste, and/or antibacterial activity against acid producing bacteria (Talha et al., 2013).

Moreover, Balto et al. (2012) found that the ethanolic extract of *S. persica* root was effective in eliminating the smear layer following a root canal procedure at the coronal and middle thirds, with the 5 mg/ml extract being as effective as 17% EDTA in removing the smear layer from the coronal third of the canal wall. However, the *S. persica* extract was less effective than EDTA in removing the smear layer at the apical third. In addition, Almas (2002) showed that CHX gluconate (0.2%) and *S. persica* miswak extract (50%) had similar effects on healthy dentins, with the latter being more effective in removing smear layer than CHX gluconate. Moreover, Almas (2001b) found that healthy and periodontally diseased root dentine, soaked in 25% aqueous *S. persica* miswak extract, resulted in partial removal of smear layer and also, occlusion of dentinal tubules was noticed in dentine specimens polished with miswak solution.

Additionally, Talha et al. (2013) performed a randomised, clinical trial on forty children of both sexes [fluoride group (n = 20) and miswak group (n = 20)] to compare the effect of miswak and fluoride toothpastes on *Lactobacilli* and *S. mutans* counts in dental plaque and their effect on plaque and saliva pH. Both toothpastes were effective against *Lactobacillus*. However, no significant reduction in *S. mutans* CFU count was observed after treatment with miswak toothpaste in contrast to fluoride toothpaste which displayed significant reduction. Regarding pH, only miswak toothpaste was reported to significantly raised plaque pH while no significant effect on saliva pH was observed for both toothpastes. Moreover, Shamshiry and Donyadide (2014) found that a herbal mouthwash of Persica containing three medicinal plants, *S. persica*, Mint, and Yarrow, was effective in reducing

plaque formation and gingival inflammation and had no harmful effects. However, its effects were less than CHX. Therefore, taking into account the usage of *S. persica* miswak in oral hygiene for ages and the validation of its efficacy by extensive *in vitro* and clinical studies, *S. persica* can be considered as an effective and sustainable mean of preventing and minimising oral diseases. Therefore, future studies are required to formulate novel dental products from *S. persica* as well as promoting its global usage in oral care.

6.3. Antioxidant activity

Recently, an alarming increase in death from chronic non-communicable diseases, collectively responsible for about 70% of all deaths worldwide, has been noted (WHO, 2017a). Many of these chronic diseases are associated with an increased oxidative stress caused by an imbalance between excess free radical production and the antioxidant level in the body (Pham-Huy et al., 2008). Interestingly, a vast number of studies have documented the antioxidant potency of *S. persica via* a panoply of standard assays. For instance, Mohamed and Khan (2013) analysed the antioxidant activity of *S. persica* root and observed that the methanol extract demonstrated a concentration dependent scavenging of 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2'-azino-bis (3-ethylbenzo-thiazoline-6-sulfonic acid) (ABTS) radicals, with a free radical scavenging capacity for ABTS radical (IC_{50}= 1.6 µg/ml) three-fold greater than that observed for DPPH radical (IC_{50}= 4.8 µg/ml). In addition, with increasing crude extract content, the total antioxidant activities, based on the reduction of molybdenum (VI) to molybdenum (V), were also increased. However, GC-MS analysis revealed no phenolic and flavonoid compounds or under detected limit in the methanolic extract. After silylation of the extract, furan derivatives (furan-2-carboxylic acid-3-methyl-trimethylsilyl ester, 2-furancarboxaldehyde-5-(hydroxymethyl), and D-erythro-pentofuranose-2-deoxy-1,3,5-tris-O-(trimethylsilyl)), were identified by GC-MS analysis.

These compounds possess hydroxyl groups and may have contributed to its antioxidant activity. In addition, antioxidant enzymes were also detected in the extract with high level of peroxidase (4176 units/g) and low level of polyphenoloxidase (6.1 units/g) and catalase (2.5 units/g). Therefore, these antioxidant compounds and antioxidant enzymes may interact synergistically to contribute to the total antioxidant activity observed for *S. persica*.

In a study by Qasim et al., 2016, it was observed that methanol, ethanol, and water were more effective compared to other solvents (acetone and chloroform) for retrieving antioxidant compounds from *S. persica*. The methanol extract was the most effective (total phenolic content (TPC) = 58 mg GAE g^{-1} DW; total flavonoid content (TFC) = 34 mg QE g^{-1} DW; proanthocyanidin content (PC) =18 mg CE g^{-1} DW) whereas chloroform was the least effective in extracting antioxidant compounds. In addition, the methanolic and ethanolic extract displayed greatest DPPH scavenging activity (IC_{50}= 20.92 µg/ml) and FRAP reducing power activity (6.23 mMol Fe^{+2} g^{-1}), respectively. The highest correlation between polyphenols (TPC, TFC, and PC) and antioxidant activity (DPPH and FRAP) was found in methanol followed by ethanol and water while a weaker correlation was observed in acetone and chloroform extracts. This tend to show the higher extractive capacity of polar solvents over non-polar solvents for active antioxidant phytochemicals from *S. persica*. However, Gupta et al. (2015) showed that the chloroform extract of *S. persica* twig (IC_{50}= 181.33 µg/ml) and stem (IC_{50}= 187.33 µg/ml) displayed higher antioxidant activity, in terms of DPPH free radical scavenging activity, than the ethanolic extract (twig: IC_{50}=197.00 µg/ml; stem: IC_{50}= 35.66 µg/ml) although the extracts were less effective than the positive control ascorbic acid (IC_{50}= 2.03 µg/ml). Additionally, ferulic acid, a potential antioxidant compound present in *S. persica*, was found using high performance thin layer chromatography (HPTLC) ranging in concentration from 0.082% and 0.026% in *S. persica* twig and stem, respectively. It can be argued that the difference observed in the antioxidant activity of the extracts in these

two studies might be a consequence of using *S. persica* from different geographical locations. For instance, Ibrahim et al. (2015) found that the TFC and TPC, was greater in *S. persica* root ethanolic extract collected from southern region compared to that of the central region of Saudi Arabia. In their study, at highest concentration tested (1 mg/ml), the extract from the southern region showed greater percentage inhibition of lipid peroxidation (96.21%), 2,2'-bipyridyl–Fe2+ complex (58.29%), hydrogen peroxide (92.56%), nitric oxide (41.35%), but lower % inhibition of hydroxyl radical (69.42%), and DPPH radical (94.61%) compared to ascorbic acid, tested at 100 µg/ml.

Moreover, higher DPPH free radical scavenging activity and Fe^{3+} reducing power was observed using the ethyl acetate extract of leaves (IC_{50}= 11.8 µg/ml; IC_{50}= 480 µg/ml, respectively) compared to the stem extract (IC_{50}= 7817 µg/ml; IC_{50}= 20124 µg/ml, respectively) from *S. persica* trees grown at Ahaggar in south Algeria. The antioxidant activity were correlated with the higher level of total phenolic, tannin, and flavonoid content found in the leaves (67.32, 39.31 mg PE/g DW and 0.47 mg RE/g DW, respectively) compared to the stem (58.63, 36.83 mg PE/g DW and 0.31 mg RE/g DW, respectively). However, the butanol extract of the stem showed greater antioxidant activity (DPPH: IC_{50}= 14 µg/ml; FRAP: IC_{50}= 3290 µg/ml) compared to the leaves extract (DPPH: IC_{50}= 257 µg/ml; FRAP: IC_{50}= 3660 µg/ml). This discrepancy may be due to the qualitative nature of the phenolic compounds beside their quantity or the presence of antioxidant enzymes which is more easily extracted with butanol (Kholkhal et al., 2010). Therefore, further studies are needed to determine the effect of solvents extractions on the qualitative nature of antioxidant compounds.

Additionally, root extracts of *S. persica* were found to be more effective compared to stem extract in scavenging DPPH, inhibiting lipid peroxidation, and reducing ferric ion in rat brain homogenate. The hydro-alcoholic extracts were the most effective antioxidant in

comparison to alcoholic and aqueous extracts (Hooda and Singh, 2012). Additionally, the methanolic extracts of *S. persica* bark, *S. persica* seedcake, and *S. persica* leaves in two samples, from Gezira (heavy clay soil) and Kordofan (sandy soil) states in Sudan, were significantly effective in inhibiting the oxidation of linoleic acid and the bleaching of β-carotene although they were less effective than butylated hydroxyanisole (BHA) (Mariod et al., 2009). In addition to the leaves, roots, and stem, the fruit of *S. persica* has also been reported as a potential antioxidant based on the observed scavenging activity on DPPH, ABTS, superoxide anion, and hydrogen peroxide radical (Kumari et al., 2017).

Recently, Qasim et al. (2016) found that the antioxidant activity of *S. persica* was higher than that of some medicinally important coastal halophytes and also appeared to be better than synthetic antioxidants (BHA and butylated hydroxytoluene (BHT)). In further comparison to other plant extract such as *Juglans regia* L. walnut bark, diluted acetone extract of *S. persica* was found to display lower DPPH scavenging ability, reducing power, and bleaching of β-carotene (Noumi et al., 2011). Furthermore, Sharma and Ramawat (2013) found that an increase in salinity stress resulted in increased antioxidant activity in *S. persica* callus cultures and proposed that plants grown in these environments may represent a sustainable source of antioxidants.

The observed antioxidant potential of *S. persica* from the above mentioned studies tends to justify its role in the management of several chronic diseases such as inflammation, hyperglycemia, hyperlipidemia, peptic ulcer, epileptic seizures, and cancer. Nevertheless, other *in vitro* and *in vivo* antioxidant approaches are required to establish the complete antioxidant profile and potency of *S. persica* in order to validate its efficacy in the mitigation of oxidative stress and for the treatment and/or management of chronic diseases. It was also observed that different solvent extracts of various parts of *S. persica* exhibit variable antioxidant properties. It was difficult to conclude from the present literature which part and

extraction solvent would exhibit highest activity. Hence, future studies should establish the type of extract and dose of *S. persica* that would be most potent.

6.4. Antiulcer activity

The high prevalence and the associated pain and suffering of ulcer, together with the side effects of anti-ulcer drugs have made it pertinent to study natural products as potential anti-ulcer compounds. Proton pump inhibitors (omeprazole, lansoprazole) have been associated with drawbacks such as nausea, abdominal pain, constipation, and diarrhoea. On the other hand, H2 receptor antagonists (cimetidine) may cause gynaecomastia and loss of libido (Rao et al., 2015; Sahoo et al., 2016; Srinivas et al., 2013). To this effect, the exploration for novel antiulcer with enhanced efficacy and improved safety profile is of fundamental significance.

Various medicinal plants are being studied for the treatment and/or management of ulcer. Nonetheless, few studies have actually probed into the anti-ulcer activity of *S. persica*. Sanogo et al. (1999) confirmed the antiulcer activity of lyophilized decoction of *S. persica* twigs (500 mg/kg body weight) on male Wistar rats weighing 180-200 g each, administered by gavage. Through optical microscopy investigation, it was found that the elements of the gastric mucosa were restored in treated rats. The glands and the lamina propria tended to recover to normal distribution although the epithelium coat was not completely restored.

Another study by Monforte et al. (2001) also investigated the anti-ulcer activity of lyophilized decoction of *S. persica* stems or roots in acetylsalicylic acid-induced ulcer male Wistar rats, weighing 180–200 g each. However, one limitation of this study is that the author mentioned both parts of *S. persica* in their methodology which was confusing to specifically confirm which part was actually tested. In the experiment, *S. persica* decoction was administered by gavage, at 500 mg/kg, dissolved in 0.5% carboxymethylcellulose in water, in

a volume of 0.5 ml/100g b.w. Treating with the lyophilized decoction, once a day for seven days, resulted in significant decrease in the ulcer index (0.9) with respect to control group (11.4). Histologically, the stomach showed considerable regeneration of glandular tissue: the components of gastric mucosa reappeared and tended to recover to normal distribution. In addition, some changes were observed in several organelles of parietal cells following treatment with *S. persica*. For instance, an enlarged lumen was observed in the intracellular canaliculi together with an increase in both the length and number of microvilli, and the mitochondria appeared normal. Nevertheless, in addition to normal zymogenic cells, other cells with dilated reticulum were also observed. These morphological features suggest that the cells tend to recover a moderate secretory activity. It can be concluded that *S. persica* decoction appears to strengthen the mucosal barrier which is the first line of defense against endogenous and exogenous ulcerogenic agents. It can also be suggested that the gastric protective effect of *S. persica* is partly due to an enhancement in the production of mucus. Hence, *S. persica* decoction can be categorised as a cytoprotective agent that warrants further studies before incorporated in clinical practice.

Despite preliminary studies which tend to highlight the gastric protective effect of *S. persica*, it is proposed that more studies be conducted to explore the anti-ulcer activity of *S. persica* and correlated observed biological effects with its phytochemical composition. It is to be noted that none of the above studies have attempted to correlate the anti-ulcer properties of *S. persica* to its phytochemical composition. Additionally, besides ethanol, acetylsalicylic acid, and stress-induced (restraint and cold) gastric ulcer model as used by the two aforementioned studies, other antiulcer testing models could be used (Al-Amin et al., 2012; Choudhary et al., 2013). Studies can further be extended to test the clinical efficacy on other model animals and in human trials to establish therapeutic dose of *S. persica* extracts. Further studies are also required to understand the protective mechanisms of *S. persica*, including the

potential role of their (i) antioxidant activity to chelate free radicals and reactive oxygen species, block lipid peroxidation and prevent damage to the gastric mucosa, (ii) anti-inflammatory activity to prevent inflammation of the gastric mucosa, (iii) cytoprotective activity to increase the production of prostaglandins which promote the secretion of mucus and bicarbonate to protect the gastric mucosal layer, and also restores the damaged epithelial layers of mucosa by causing vasodilation and increased mucosal blood flow, (iv) antisecretory activity to inhibit H^+ K^+ ATPase activity to prevent secretion of gastric acid, (v) antimicrobial activity to prevent *H. pylori* infection, (vi) anticholinergic activity to prevent involuntary movement of smooth muscles present in the gastrointestinal tract, (vii) regulation of small intestinal propulsion to regulate gastric emptying and the secretion of acid and pepsin, (ix) suppression of gastrin and histamine, and other possible mechanisms (Harsha et al., 2017).

6.5. Anticonvulsant and sedative activity

Epilepsy is one of the most common neurological diseases with a global prevalence. It is categorised by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalised) (WHO, 2017b). In a significant percentage of patients, seizures remain inadequately controlled by currently available pharmacological treatments. Additionally, most anticonvulsant drugs are associated with drawbacks such as ataxia, sedation, and cognitive dysfunction at serum concentrations within the therapeutic range for epileptic seizures (de Oliveira et al., 2016). Therefore, exploration of medicinal plants as a source of new antiepileptic drugs are being intensified and *S. persica* has showed promising results in this respect.

For instance, a study by Monforte et al. (2002) confirmed the anticonvulsant activity of *S. persica* stem extracts against pentylenetetrazol (PTZ)-induced convulsion in rats. Pentylenetetrazole is a pharmaceutical agent formerly used to stimulate respiration or as

antidotes to barbiturate overdose. Now it is used in experiments to study seizure phenomenon and to identify anticonsulvant drugs. In the experiment of Monforte et al. (2002), lyophilized decoction of *S. persica* stem (500 mg/kg) was administered to adult male Wistar rats (180-200g) and Swiss mice (20-25g) of both sexes, by gavage, and by i.m. injection, dissolved in isotonic saline solution (NaCl 0.9%, 10 ml/kg). The oral and systemic administration of *S. persica* decoction (500 mg/kg) exhibited protective ability against PTZ-induced convulsion by reducing the number and duration of convulsions, and decreasing mortality. Rats treated with PTZ, at a dose of 75 mg/kg (s.c.), manifested five convulsions (duration 50 s) over a range of 30 min, and a 70% mortality was observed after 20 min. On the other hand, rats treated orally with *S. persica* decoction displayed only two convulsions (duration 20 s), in a range of 30 min after PTZ injection, with a mortality of 20%. Interestingly, rats treated i.m. with *S. persica* decoction showed only one convulsion (duration 15 s). Some rats of this group showed only tremors and jumps but none of the rats died. This study shows variation in the anticonvulsant activity of *S. persica* based on two different routes of administration and hence indicates the need to find the optimal route of administration, in addition to dosage, for better therapeutic activity.

In the same experiment, Monforte et al. (2002) also explored the sedative effect of *S. persica*. A sedative or hypnotic drug reversibly depresses the activity of the central nervous system, and is used mainly to induce sleep and to allay anxiety (Rampalli et al., 2013). In the study, rats were treated (i.m.) with lyophilized decoction of *S. persica* stem, at doses of 500, 700, and 1000 mg/kg, dissolved in NaCl 0.9% aqueous solution, in a volume of 10 ml/kg body weight. Organic extracts (chloroform, diethyl ether, and ethyl acetate), obtained from the lyophilized *S. persica* decoction, were injected (i.m.) at doses corresponding to 500 mg/kg of lyophilized decoction. 30 min later, the rats received sodium pentobarbital (an anesthetic and sedative agent) at a dose of 50 mg/kg, i.p. in physiological saline. The

administration of *S. persica* stem decoction displayed potentiation of the hypnotic effects of sodium pentobarbital, showing a decrease in the sleep-induction time (from 333 sec to 148-153 sec) and an enhancement in the sleeping time (from 93 sec to 179-189 sec), but the effects were not dose dependent. Additionally, of the organic extracts, the most active was the chloroform extract (sleep-induction time: 84 sec; sleeping time: 228 sec). This study shows that *S. persica* can be an alternative potential source of bioactive drugs for alleviating insomnia, which is a persistent difficulty in falling or staying asleep that affects daytime function and can induce significant psychological and physical disorder (Rout and Kar, 2013). At the same time, the use of *S. persica* might eliminate the side effects of sedative drugs. Actually, insomnia can be caused by psychological (stress, anxiety and depression), dietary, medical (such as cough, chronic pain, apnea, circadian rhythm disorders, neural diseases, etc.), environmental (excess cold, heat), and drug related causes. Prescribed drugs including benzodiazepines, zolpidem, zopiclone, and zaleplon help to calm the nerves, reduce anxiety, and decrease awareness of one's surroundings. Despite clinical success, these drugs can easily lead to dependency, addiction, and other side effects such as deterioration of cognitive functioning, psychomotor impairment, confusion, excitement, aggression, and anterograde amnesis (Edewor-Kuponiyi, 2013; Rout and Kar, 2013).

6.6. Analgesic activity

Despite recent developments in pain therapies, the need for safe, effective, and potent analgesic drugs for the treatment of different unbearable painful conditions which causes discomfort and suffering is of major importance (Diravidamani et al., 2012). Due to physical dependency, tolerance, addiction, and associated side effects to currently available synthetic analgesics, the tendency of exploring natural products as potent analgesics has attracted much interest (Abbott and Fraser, 1998).

Although *S. persica* has been used traditionally as a painkiller (Table 2) by Indians (Kosalge and Fursule, 2009), Pakistanis (Yaseen et al., 2015), Kenyans (Wambugu et al., 2011), and Ethiopians (Teklehaymanot and Giday, 2010), the need to scientifically validate its effective doses is necessary. For instance, Sulaiman et al. (1996) found that *S. persica* root decoction lowers mice's response to chemical and thermal stimuli in a dose dependent manner, showing more effectiveness against thermal stimuli, and therefore was assumed to be more effective against peripheral pain than visceral pain. In their study, miswak decoction was injected intraperitoneally into mice (male MFI mice, 30-140 g) in dose volumes of 0.3-12.5 ml/kg 15 min before the three analgesic tests (writhing reflex, hot plate, and tail flick). Mice injected with *S. persica* root decoction showed lower writhes reflex (5-16 writhes/min), longer latency period (9.6-20.5 sec in hot plate test, and 8.5-20.5 sec in tail flick test) than those injected with an equivalent volumes of saline (13-20 writhes/min, latency period of 8-13 sec in hot plate test and 6-14 sec in tail flick test). The effective dose 50 (ED_{50} values) for *S. persica* decoction were 5.5, 3.5, and 0.4 ml/kg for writhing reflex, hot plate, and tail flick tests, respectively. Moreover, the analgesic effects of *S. persica* root decoction in the three tests were antagonised by prior treatment with Naloxone (0.4 mg/kg) which was performed to examine the relevance of opiate's system to *S. persica* root action. Results of the writhing reflex, hot plate, and tail flick test revealed that the ED50 for *S. persica* decoction in the presence of Naloxone was increased by 1.45, 0.71, and 2.25 folds, respectively, which was higher than that of mice treated with *S. persica* alone. It was speculated that this analgesic effect could be due to interaction with central and/or peripheral opiated pathway. This assumption is in agreement with early findings in which *S. persica* extracts was found to lower the spontaneous locomotor activity in mice (Sulaiman et al., 1986). The conclusion is consistent with the notion that opiates produce immobility or decrease locomotor activity (Browne et al., 1979).

Furthermore, Hoor et al. (2011) observed that the crude ethanolic extract of *S. persica* displayed a significant dose-dependent analgesic activity in mice (albino Wistar mice of both sexes weighing on average 26 g each) at tested doses of 500 and 700 mg/kg body weight, orally. However, one limitation of this study is the lack of specification in the methodology pertaining to the part of *S. persica* that was tested. Results from their study showed a significant increase (about 40-50% on an average) in tail flick latency period in *S. persica* treated mice as compared to the control group and were comparable with the standard drug aspirin (tested at the same doses of extract). The analgesic activity of the extract and aspirin were increased gradually and were found to be maximum at 120-150 min and then started to decline. In addition, Rajesh et al. (2010) studied the analgesic effect of the ethyl acetate extract of *S. persica* leaves, based on the tail immersion method by measuring the reaction time to lift the tail from hot water, using albino mice of either sex, weighing between 16-22 g body weight. They found that the extract (500 mg/kg body weight, i.p.) showed significant analgesic activity (reaction time of 6.54 sec, 7.89 sec, 5.46 sec, measured at 45 min, 60 min, and 120 min, respectively) when compared to the control group (reaction time of 4.09 sec, 4.09 sec, 3.54 sec, measured at 45 min, 60 min, and 120 min, respectively). Nevertheless, the extract was slightly less effective compared to the standard drug pentazocine, tested at 10 mg/kg body weight, i.p. (reaction time of 8.31 sec, 8.82 sec, 7.08 sec, measured at time 45 min, 60 min, and 120 min, respectively). Further research focussed towards evaluating the activity of other parts, identifying the bioactive phytomolecules and mechanism of action for the observed analgesic effects of *S. persica* decoction would be beneficial in future drug development programmes.

6.7. Anti-inflammatory activity

Inflammation is a part of the complex biological response of living tissues to harmful stimuli, such as pathogens, damaged cells or irritants and is characterized by redness, swollen joints, joint pain, joint stiffness and loss of joint function (Kumar et al., 2013). It involves a complex assortment of enzyme activation, release of mediators, extravasation of fluid, cell migration, tissue breakdown, and repair (Okémy Andissa et al., 2015). The developments of effective anti-inflammatory drugs with reduced side effects from medicinal plants are now under limelight of the scientific community. In fact, over 300 compounds isolated and identified from plants have demonstrated anti-inflammatory activity (Perez, 2001).

Rajesh et al. (2010) showed that the ethyl acetate extract of *S. persica* leaves (500 mg/kg body weight, orally) showed significant anti-inflammatory activity against carrageen induced paw edema in rats (Wistar albino rats of either sex, weighing between 150-210 g), and was comparable or slightly less effective compared to the standard drug indomethacin (10 mg/kg body weight, orally). The inhibition of paw edema exhibited by the extract were 13.24%, 45.16%, 33.32% and 12.69% at 1, 2, 3 and 4 hr, respectively, compared to indomethacin (inhibition of 23.53%, 51.61%, 44.44%, and 33.33% at 1, 2, 3 and 4 hr, respectively). In addition, Hoor et al. (2014) found that the crude ethanolic extract of *S. persica* stick (diluted in 1 ml of water in a dose of 700 mg/kg body weight, orally) significantly decreased the paw volume of carrageenan induced edema (4.32 ml) in rats (albino rats of both sexes, weighing 400 g on average) after five hours, compared to the control group (5.42 ml), and was comparable with the standard drug aspirin (4.49 ml), tested at the same dose of extract (700 mg/kg body weight, orally).

Furthermore, Ibrahim et al. (2011a) found that the crude ethanolic extract and ethyl acetate fraction (100 mg/kg, orally) of *S. persica* stick significantly reduced the thickness of edema in rats (adult male Sprague Dawley rats, weighing between 150-180 g) in a time dependent manner. At the first hour, *S. persica* extracts didn't show any significant reduction

in oedema as compared to the vehicle control group or reference drug indomethacin. After 4hr, the inhibition percentage was 17.59% for crude ethanolic extract and 27.08% for ethyl acetate fraction, which was comparable to the inhibition level of the standard drug indomethacin (27.31%), tested at 20 mg/kg, orally. The ethyl acetate extract was also found to significantly reduce the secretion of inflammatory mediators, including interleukin-1β, interleukin-6, tumor necrosis factor-α, and transforming growth factor-β1 in serum, displaying an inhibition % of 38, 19.5, 28.9, 39.1, respectively, which was comparable to the drug indomethacin, tested at 20 mg/kg (inhibition % of 44.2, 19.6, 32.2, 40.9, respectively). It can be argued that the anti-inflammatory activity of *S. persica* may be attributed to flavonoids identified in the ethyl acetate extract. For instance, three major flavonoids were isolated from the extract and were identified as apigenin rhamnoglucoside, rutin, and luteolin glucoside. In fact, several mechanisms have been proposed for the actions of bioflavonoid in reducing inflammation (Ibrahim et al., 2011a).

From the aforementioned studies, it can be deduced that *S. persica* showed significant anti-inflammatory activity. Further studies should be carried out to study the potential activity of other parts of the plant as well as using other *in vitro* and *in vivo* models to validate its safe use as an anti-inflammatory agent. Also, it can be speculated that the reported anti-inflammatory activity might be attributed to the antioxidant potential of *S. persica* but the mechanism still need to be clarified by further in-depth studies.

6.8. Anti-osteoporosis

Osteoporosis represents a major worldwide public health burden which is characterised by low bone mass, compromised bone tissue, disruption of bone microarchitecture, and reduced bone strength. It also results in an increased risk of fractures causing disability and mortality. The pharmacotherapies for osteoporosis include calcium and

vitamin D supplements, and currently FDA-approved drugs such as bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid), calcitonin, estrogen agonist/antagonist (raloxifene), estrogens and/or hormone therapy, tissue-selective estrogen complex (conjugated estrogens/bazedoxifene), parathyroid hormone 1-34 (teriparatide), and Receptor Activator of Nuclear Factor kappa-B Ligand (RANKL) Inhibitor (denosumab) (NOF, 2014). However, due to their associated side effects, the pursuit for effective and safe agents to improve upon existing therapies still represents a definite need.

A recent study by (Fouda and Youssef, 2017) investigated the effectiveness of *S. persica* stick extract on ovariectomized (OVX) (i.e. estrogen deficient) rat model of osteoporosis. The extract was administered orally at doses of 50, 150, and 300 mg/kg, dissolved in 0.5 ml distilled water/100 g of body weight, to OVX rats (3-month-old female Sprague-Dawley rats weighing 200-220 g) every morning for 16 weeks. Results showed that the extract displayed a dose-dependent protective action (increase in activity from 50 mg/kg/d to 300 mg/kg/d). *S. persica* dose-dependently attenuated the OVX-induced rise in bone turnover markers as indicated by decreased serum osteocalcin (11.12-9.88 nmol/L), bone specific alkaline phosphatase levels (201.44-148.17 U/L), and urinary deoxypyridinoline/creatinine ratio (75.12-60.32 nmol/mmol) compared to the OVX vehicle control group (serum osteocalcin: 13.34 nmol/L, alkaline phosphatase: 227.87 U/L, urinary deoxypyridinoline/creatinine ratio: 84.76 nmol/mmol). Additionally, the extract dose-dependently prevented the urinary loss of calcium and phosphorus indicating that *S. persica* down-regulated the rate of bone resorption.

Moreover, at doses of 150 and 300 mg/kg/d for sixteen weeks, *S. persica* extract dose-dependently improved bone mineral density and prevented the decrease in mechanical indices of the femoral bone such as the maximum stress (178.4-192.9 MPa), energy to failure (56.8-58.9 N.mm) and Young's modulus (5984-6224 MPa) compared to the OVX vehicle control

(maximum stress: 145.7 MPa, energy to failure: 41 N.mm, Young's modulus: 4367 MPa). Rats treated with 150 and 300 mg/kg/d of *S. persica* extract also demonstrated restoration of the OVX-induced depreciation of bone microarchitecture as indicated by a dose-dependent increase in the trabecular bone volume fraction (0.3089-0.3787), trabecular number (2.9195-3.766 /mm^2), trabecular thickness (0.1036-0.1045 mm), and reduction of trabecular separation (0.2655-0.1888 mm) compared to the OVX vehicle control group (trabecular bone volume fraction: 0.2254, trabecular number: 2.3561 /mm^2, trabecular thickness: 0.0714 mm, trabecular separation: 0.3987 mm). Overall, *S. persica* extract at 300 mg/kg/d was found to be comparable or slightly less effective compared to the OVX + 17β-estradiol (25 µg/kg/d) treated rats.

This preliminary study is the only report which showed the promising antiosteoporotic activity of *S. persica* stick, though not traditionally documented by indigenous population. Further research should explore the potential antiosteoporotic activity of other parts of *S. persica*, and attempts should be made to identify bioactive compound/s in *S. persica* responsible for this effect.

6.9. Enzyme inhibitory activity

Enzyme inhibition in drug discovery has become a fundamental approach to manage pathologies such as diabetes, obesity, hypertension, and Alzehimer disease. Research on the enzyme inhibitory activity of medicinal plants has therefore recently been intensified. Few studies have actually reported the enzyme inhibitory activity of *S. persica*. For instance, Muddathir et al. (2017) studied the antityrosinase activity of the methanolic extract of *S. persica* leaves and stems. Tyrosinase is a key enzyme in melanin biosynthesis. Moreover, tyrosinase is also responsible for the undesired enzymatic browning of fruits and vegetables by catalyzing the oxidation of phenolic compounds (Pintus et al., 2015; Ya et al., 2015).

Therefore, prevention of this browning reaction has always been a challenge to food scientists and the interest in finding tyrosinase inhibitors from natural sources is increasing.

In the study of (Muddathir et al., 2017), the methanolic extract of *S. persica* leaf, at highest concentration tested (500 μg/ml), caused a greater percentage inhibition (68% and 47%) compared to the stem extract (42% and 33%), using L-tyrosine and L-DOPA as substrates, respectively. Although being less effective than the positive control Kojic acid (inhibition level of 99.65% and 94.40% against L-tyrosine and L-DOPA, respectively, at 500 μg/ml), *S. persica* displayed greater antityrosinase activity than some tested plant extracts including *P. aculeata* L. leaves, *L. inermis* L. leaves, *N. sativa* L. seeds, *L. sativum* L. seeds, *C. carvi* L. fruits, and others. Therefore, *S. persica* displayed promising antityrosinase activity and its further exploration may lead to novel skin whitening agents, anti-browning substances for application in the cosmetic, food, and pharmaceutical industry.

Furthermore, a study by (Nyman et al., 1998) revealed that the water, ethanol, and acetone extracts of unripe seed of *S. persica* (tested at 0.33 mg/ml) displayed greater angiotensin converting enzyme (ACE) inhibition (55%, 36%, 24%) compared to the leaf extracts (21%, 19%, 14%), respectively. ACE is a Zn-metallopeptidase which plays an important role in regulating blood pressure in the renin-angiotensin-aldosterone system. ACE catalyse the conversion of Ang-I (a decapeptide) to Ang-II (an octapeptide), a potent vasoconstrictor, which interacts with the Ang-II type 1 receptor (AT1) to stimulate the secretion of aldosterone. This enhances sodium and water re-absorption in the nephron and elevates blood pressure by increasing the intravascular fluid volume. The use of ACE inhibitors has proven to be an effective strategy in the prevention and treatment of hypertension which is considered as one of the major risk factors for cardiovascular disease (Geng et al., 2015). ACE inhibitors currently available on the U.S. market are benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and

trandolapril. Five of them; captopril, enalapril, lisinopril, ramipril, and trandolapril, have been tested in large scale trials and have been proven to decrease mortality and morbidity in heart failure and post-infarction (Furberg and Pitt, 2001). However, due to lack of large-scale trials of other drugs, concern over long term safety, and lack of regulatory claim in their labelling, natural alternatives are being explored. *S. persica* can be one alternative but needs more studies to validate its efficacy as a promising ACE inhibitor.

Further research can be carried out to study the inhibitory potential of *S. persica* against key physiological enzymes involved in diabetes (α-amylase, α-glucosidase, and pancreatic lipase), skin aging (collagenase and elastase), and neurodegenerative disorders (acetylcholinesterase), cardiovascular diseases (pancreatic cholesterol esterase) and other enzymes implicated in chronic diseases. In addition, the potential of *in silico* methodologies could be explored in further studies to elucidate the enzyme inhibitory properties of *S. persica*. *In silico* studies on isolated compounds from *S. persica* could also provide additional insights into the possible mechanism of action and binding mode of active compounds against the above mentioned metabolic key enzymes.

6.10. Hypoglycemic and hypolipidemic activity

Diabetes mellitus is a metabolic disease characterised by hyperglycemia (increased blood glucose) and is caused by insulin secretion deficiency or ineffectiveness of the insulin produced (Sajeda et al., 2017; WHO, 2017c). Currently available therapy for diabetes includes insulin and various oral hypoglycemic agents including sulfonylureas, metformin, glucosidase inhibitors, and troglitazone amongst others. However, these are reported to be associated with side effects such as in the event of excess dosage-fatal hypoglycaemia or other serious adverse side effects (Mamun-or-Rashid et al., 2014; Tanko et al., 2008; Dangi and Mishra, 2010; Selmi et al., 2015).

S. persica has been studied as a potential hypoglycemic and hypolipidemic agent by several researchers. For instance, the first study by Galati et al. (1999) showed that the lyophilized decoction of *S. persica* stem (at a dose of 500 mg/kg by gavage, dissolved in aqueous vehicle, in a volume of 0.5 ml/100 g of body weight) displayed significant hypocholesterolemic activity and provides considerable protection against insurgence of diet-induced hypercholesterolemia in adult male Wistar rats weighing 180-200g. Administration of *S. persica* decoction once daily from the 15th to 30th day, in rats fed with a hypercholesterolemic diet for 30 days, significantly reduced cholesterol and low density lipoprotein (LDL), by 10% and 18%, respectively. On the other hand, administration of *S. persica* decoction simultaneously with the hypercholesterolemic diet for 30 days displayed greater reduction on cholesterol and LDL. Nonetheless, the authors reported no change in high-density lipoprotein (HDL) and triglyceride (TG) concentrations, although we notice a slight decrease in TG (11%) and increase in HDL (9%) in their results during the simultaneous administration of *S. persica* decoction with the hypercholesterolemic diet for 30 days. In the third treatment in triton-induced hypercholesterolemia rats, *S. persica* decoction was inactive at 18 hr after administration, but significantly reduced cholesterol and LDL plasma levels at 27 hr.

On the other hand, Khan et al. (2014) observed changes in HDL and TG concentrations in male albino Wistar rats (150-200 g). They found that among several tested *S. persica* root extracts (Indian *S. persica* v/s Arabian *S. persica*, at doses of 250 and 500 mg/kg), the aqueous root extract of Arabian *S. persica* at 500 mg/kg dose level, when administered orally (p.o.) as aqueous suspensions (3% v/v with Tween 80 in water) once per day from the 7th to 21st day after the first 7 days of streptozotocin treatment (60 mg/kg), displayed greater reduction (77%) in blood glucose, comparable to the standard drug glibenclamide (79%), tested at 5 mg/kg/day, p.o. Biochemical measurement at the end of the

4th week, in Arabian *S. persica* (500 mg/kg) treated rats, also revealed significant reduction in TG, total cholesterol (TC), LDL, very low density lipoprotein (VLDL), and increase in HDL, compared to the diabetic control rats. In addition, TG level in Arabian *S. persica* treated rats (75.40 mg/dl) was better compared to the normal (non-diabetic) control rats (87.34 mg/dl) and VLDL level was comparable in both groups (Arabian *S. persica* treated rats: 22.78 mg/dl, normal control: 21.55 mg/dl). On top of that, the extract was comparable or slightly less effective compared to the standard drug glibenclamide, tested at 5 mg/kg/day, p.o, showing reduction in TG, TC, LDL, VLDL, and increase in HDL level compared to the diabetic control. In addition, the Arabian extract (at 500 mg/kg) caused acceleration of β-cell regeneration in experimental animal's pancreas (number of β cells= 32.6) in comparison to diabetic control animal's pancreas (number of β cells= 8.1) at the end of 28th day, which was slightly less effective compared to the standard drug glibenclamide (number of β cells= 39.3).

Furthermore, Hooda et al. (2014) showed that the hydro-alcoholic extract of *S. persica* root (extracted with 70% ethanol) reduced blood glucose level in diabetic adult Wister albino rats. In streptozotocin-induced diabetic rats, the blood glucose levels was increased from 281.25 to 323.25 mg/dl after 21 days, which was considered as severe diabetes. In the extract (400 mg/kg) and glibenclamide (5 mg/kg) treated rats, blood glucose level significantly decreased from 285.50 to 150.25 mg/dl and from 281.50 to 106 mg/dl after 21 days, respectively. However, values did not return to normal control (92.5 mg/dl). In addition, measurement of lipid profile in the root extract (400 mg/kg) treated rats on the 21st day revealed significant decrease in TC, TG, LDL, VLDL, and increase in HDL, compared to diabetic control rats. Moreover, HDL (26.5 mg/dl) and VLDL level (19 mg/dl) in extract treated rats were found to be close to the normal (non-diabetic) control (HDL: 28.5 mg/dl, VLDL: 17.5 mg/dl). Nonetheless, glibenclamide (5 mg/kg) treated rats showed greater decrease in TC, TG, LDL, VLDL, and increased HDL level, than the extract when compared

to the diabetic control. Besides, streptozotocin-treated rats (diabetic rats) showed reduced body weight (from 218.25 g to 198.25 g) compared to normal control rats which displayed increased body weight (from 220.50 g to 247.25 g) after 14 d of treatment. However, streptozotocin-induced lower body weight was significantly reversed by the *S. persica* extract (from 218.25 g to 209.25 g after 7 d of treatment, and from 209.25 g to 217 g after 14 d of treatment.

Similarly, the trend in the restoration of blood glucose and lipid profile was also observed by other studies. For instance, Saini and Yadav (2013) found that the ethanolic extract of aerial parts (stem and leaves) of *S. persica*, in 1% w/v suspension of carboxymethylcellulose (vehicle) at a dose of 2 g/kg body weight, orally, lowered blood glucose in normal and diabetic rats (adult albino Wister male rats weighing between 160-200g), and was comparable to the standard drug tolbutamide (at a dose of 0.5g/kg b.w) after 21 days. The level of TG, TC, LDL, and VLDL were significantly lowered and HDL level was also improved. In another fairly similar study, Iyer et al. (2012) also found that oral administration of chloroform fraction of *S. persica* stems, suspended in distilled water plus Tween 80 at doses of 200 and 400 mg/kg body weight, dose-dependently reduced TC, TG, LDL, and increased HDL level in Triton loaded Swiss albino rats of either sex, 6 - 8 weeks old and weighing 100-120 g, and was more effective than the ethanolic extract. More importantly, Iyer and Patil (2012) found that Stigmast-5, 22-dien-3β-ol, isolated from *S. persica* stems (suspended in distilled water plus Tween 80 at an oral dose of 200 mg/kg) significantly restored lipid profile in Triton-induced hyperlipidemic albino rats of either sex, 6-8 weeks old and weighing 100-120 g. The isolated compound lowered TC, TG, LDL, and increased HDL level, after 5 days of treatment, which was better compared to the chloroform extract, ethanol extract, and the standard drug beta-sitosterol in reducing TG and LDL and increasing HDL. In addition, the isolated Stigmast-5, 22-dien-3β-ol was comparable to the

extracts in reducing TC (11%) although it was less effective than beta-sitosterol (18%), all tested at 200 mg/kg.

From the above results, *S. persica* was found to display a dose-dependent hypoglycemic and hypolipidemic activity. Despite showing positive outcome *in vivo*, extracts of *S. persica* can be screened in other antidiabetic *in vitro* model e.g. in the inhibition of key carbohydrate hydrolyzing enzymes such as α-glucosidase and α-amylase to delay digestion of carbohydrates, reduce the rate of glucose absorption and consequently a suppression of postprandial hyperglycemia (Trinh et al., 2016). Moreover, besides the observed regenerative effect of *S. persica* on pancreatic β cells by Khan et al. (2014), further research need to clarify the exact mechanisms by which *S. persica* induces hypoglycemic effect including their potential role in protecting and restoring pancreatic β-cell function, increasing insulin secretion from β-cells, improving insulin sensitivity, reducing carbohydrate absorption from the small intestine, enhancing glucose uptake by tissues, and inhibiting gluconeogenesis (Vahid et al., 2017). Researchers can also study the antioxidant property of *S. persica* as a protective mechanism in diabetes-induced oxidative damage caused by reactive oxygen species. Therefore, it is evident from these studies that *S. persica* exhibit significant hypoglycemic and hypolipidemic activity based on *in vivo* models but needs further clinical validation.

Additionally, up to now, no study have clarified the mechanisms by which *S. persica* improve the lipid profile. Proposed mechanisms include the inhibition of cholesterol absorption in the intestine, interference with lipoproteins, enhancement of cholesterol degradation, increase of cholesterol excretion in the form of bile acids or other sterols (Galati et al., 1999), lowering of LDL level due to the presence of flavonoids which cause a significant increase in LDL receptor mRNA levels, which in turn, increase hepatic uptake and degradation of LDL (Saini and Yadav, 2013; Wilcox et al., 2001). Therefore, further works

are required to clarify the hypolipidemic mechanisms of *S. persica*. Researchers can also explore the inhibitory activity of *S. persica* against key enzymes and transporters involved in the aetiology of hyperlipidemia, including lipases, HMG-CoA reductase, N-terminal Niemann-Pick C1-like protein 1 receptor (NPC1L1), proprotein convertase subtilisin/kexin type 9 (PCSK9), microsomal triglyceride transfer protein, cholesteryl ester transfer protein (CETP), diacylglicerol O-acylotransferase 1 (DGAT-1), Acyl-CoA cholesterol acyltransferase (ACAT), squalene synthase, carboxylase Ac-CoA, phospholipase A2, and the activation of intracellular receptors peroxisome proliferator-activated receptors alpha (PPAR alpha) (Okopień et al., 2016).

6.11. Antitumor activity

Chemotherapy, radiotherapy, and surgery are three major existing modes of treatment and management in modern medicine for cancer. Chemotherapy is still a major challenge to cancer patients because such highly potent drug can be toxic and damage healthy cells and tissue. In addition, the associated cost, side effects, and resistance towards drug remain a major problem (Sayeed et al., 2014). In contrast to chemotherapy which is designed to destroy cancer after it appears, chemoprevention is another strategy, using pharmacological, biological, and nutritional interventions, to prevent, reverse or delay carcinogenesis and can also be used as adjuncts to current cancer therapies (Aggarwal et al., 2004; Guilford and Pezzuto, 2008). In recent times, the trend in cancer research has shifted towards identifying novel anticancer drugs from natural resources.

Interestingly, *S. persica* has showed promise in this field. For instance, Iyer and Patil (2012) investigated into the antitumor activity of the ethanolic extract, chloroform fraction, and Stigmast-5, 22-dien-3β-ol, isolated from *S. persica* stem, in hybrid mice (C57BL strain + Swiss albino strain). Mice were injected daily with the test compounds at a dose of 50 mg/kg

body weight i.p. for 10 consecutive days. The mice were then observed for the growth of tumor after injection of B16F10 melanoma cells into their dorsal skin. They found that compared to the extract and fraction, Stigmast-5, 22-dien-3β-ol caused a greater delay in tumor growth in hybrid mice, by displaying a greater increase in volume-doubling time and growth delay. Better mean survival time was also observed compared to the control. Furthermore, Ibrahim et al. (2011b) observed that among several extracts of *S. persica* sticks and bark (crude ethanolic (70%) extract, and petroleum ether, chloroform, and ethyl acetate fractions), the petroleum ether fraction was the most potent, displaying IC_{50}=43.6 µg/ml against human hepatocellular carcinoma cell line-HepG2, IC_{50}= 44.3 µg/ml against human breast carcinoma cell line-MCF7, IC_{50}= 19.87 µg/ml against lung carcinoma cell line-A549 and IC_{50}= 10.2 µg/ml against colon carcinoma cell line-HCT116, which is significantly lower than the concentration which was cytotoxic to the normal green African monkey kidney cells (VERO) (IC_{50}= 379 µg/ml). In addition, two isolated triterpenes from the petroleum ether extract of *S. persica* (ursolic acid and oleanolic acid) were also tested and showed better cytotoxic effect than the petroleum ether fraction against HePG2 and MCF7, but were also more cytotoxic against VERO (IC_{50}= 57 µg/mL and 104 µg/mL for ursolic acid and oleanolic acid, respectively). Moreover, Hammad et al. (2014) found that the cytotoxic effects of aqueous extracts of *S. persica* on both oral squamous cell carcinoma (PE/CA- PJ15) and oral epithelial dysplasia (DOK) cell lines were significant at a concentration (11.25, 13.50 and 15.75 mg/ml) lower than the concentration which is significantly cytotoxic to the normal periodontal ligament fibroblast cell line (13.50 mg/ml). The highest concentration tested in the study was 15.75 mg/ml.

These studies therefore suggest the therapeutic cancer preventive potentials of *S. persica*. In addition to isolated chemical from *S. persica* such as Stigmast-5, 22-dien-3β-ol, which contribute to its antitumor activity as observed by Iyer and Patil (2012), the antitumor

activity of *S. persica* may also be attributed to its antioxidant properties. Nonetheless, the protective mechanisms of *S. persica* against free radicals involved the aetiology of cancer still need to be clarified. Moreover, the observed efficacy of *S. persica* against the aforementioned cancer cell lines indicates its potential activity against other cell lines yet to be studied. In addition, taking into consideration the widespread use of *S. persica* in oral care, it can be potentially used in the prevention and/or treatment of oral cancer which must be validated by future studies. Researchers can also investigate the potentiating effect of *S. persica* extracts or their isolated lead compound on chemotherapeutic drugs as well as understanding their different mechanism of actions for greater clinical effectiveness.

6.12. Toxicity

The conviction that natural products are much safer than synthetic or conventional drugs has resulted in an exceptional growth in its use by consumers as both prophylactic and for treating human ailments. Despite plants being a rich source of bioactive compounds with potent pharmacological properties, some of them may be toxic and induce adverse effects to humans (Celik, 2012; Nondo et al., 2015).

Concerning the toxicity of *S. persica*, Al-Samh et al. (1997) found that the higher the concentration of ethanolic extract of *S. persica* root, the greater the morphological changes of L929 cell line *in vitro*. After a two-hour exposure of cultured cells to 100% *S. persica* extract, the cells became round in shape and the cell surface was covered with blebs. Upon exposure to lower level (25%) of *S. persica* extract solution, these morphological changes were reduced; the blebs became smaller in size and the smooth cell wall surface were covered by few microvilli. Increasing exposure time of cultured cells to 4 hrs still resulted in some morphological cell changes. However, microvilli and ruffles reappeared even when the cells were exposed to higher concentrations of *S. persica* root extract (50%), indicating that

cellular changes which were observed in the two-hour exposure may be reversible. Therefore, the recovery of cells after exposure to *S. persica* extracts should be further studied before a final conclusion concerning its toxicity could be reached.

Additionally, Tabatabaei et al. (2015) found that the water extract of *S. persica* chewing sticks showed cytotoxic effect only at 5.75 mg/ml and caused significant cell proliferation at 1.43-0.08 mg/ml at 24 h. At 48 h, only 0.17 mg/ml and 0.08 mg/ml concentrations caused significant cell proliferation. On the other hand, the ethanolic extract showed severe cytotoxic effects at 5.75-1.43 mg/ml on human dental pulp stem cells at 24 and 48 hr. Moreover, Balto et al. (2014) studied the cytotoxic effect of *S. persica* root extracts on human gingival fibroblast cells *in vitro*. Ethanol extract of *S. persica* at 0.5 mg/ml and 1 mg/ml and hexane extract at 0.5 mg/ml showed no sign of cytotoxic activity. However, at 1 mg/ml, the hexane extract displayed some cytotoxicity with cell survival of 86% in lactic dehydrogenase (LDH), and 88% in crystal violet (CV) assays. Similarly, at 0.5 mg/ml, the ethyl acetate extract of *S. persica* maintained cell viability of 81% in LDH, and 80% in CV assays. Maximum cytotoxicity against human gingival fibroblast cells was exhibited by the ethyl acetate extract of *S. persica* (1 mg/ml) with cell survival of 40% in LDH, and 66% in CV assays. In addition, the cytotoxicity of *S. persica* root extracts was also evaluated using another assay. However, because of a confusion in their methodology, of the dye (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (MTT) with MTS, which is actually (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium), we did not report the result to avoid any confusion on which cytotoxicity assay was actually used.

Furthermore, acute toxicity studies of the hydro-alcoholic extract of *S. persica* root (extracted with 70% ethanol) in fasting mice revealed no lethality or toxic reaction of the extract at doses up to the highest tested concentration, 1200 mg/kg body weight, orally, until

the end of the study period (48 hr) (Hooda et al., 2014). All the animals were alive, healthy, and active during the observation period. Moreover, Monforte et al. (2002) evaluated the toxicity of lyophilized decoction of *S. persica* stem (at doses of 10, 100 and 1000 μg/ml) on brine shrimp (*Artemia salina* Leach) and LC_{50} was determined after 24 hr. Acute toxicity was also determined on Swiss mice. Results demonstrated that *S. persica* decoction did not display toxicity. The LC_{50} was >1000 μg/ml and LD_{50} was >2g/kg. Additionally, behavioural analysis was performed according to Irwin's test. The lyophilized decoction was administered, by gavage, at doses of 500, 700 and 1000 mg/kg, dissolved in water, in a volume of 0.5 ml/100g body weight and i.m. at the same dose, dissolved in NaCl 0.9%. Results showed that oral administration of *S. persica* decoction, at doses of 700 and 1000 mg/kg, desensitized the rat to external stimuli, which became even more evident after 2 hr. However no effect was observed at lower doses. On the other hand, administration of 500 mg/kg, i.m., produced head-tremors, mouth stereotipy movements, piloerection and vibration of the ears and whiskers after 20 min. After 30 min, the *S. persica* decoction induced passivity in the rats. These responses were dose-dependent and were pronounced at 700 mg/kg. Maximal behavioural changes was observed at the highest dose (1000 mg/kg). Nonetheless, the animals appeared normal 24 hr after treatment.

Therefore, it is important that more toxicity studies be carried out on the common traditional method of usage of *S. persica* including infusion, maceration, and decoction to confirm the doses required to limit potential toxicity and side effects. Indeed, we found no supportive data to reach a final conclusion on the toxicity effect of *S. persica* in humans. To this effect, further studies on various human cells using different toxicity models are recommended together with *in vivo* toxicological analysis in an endeavour to establish safety doses that when used medicinally, would not induce side effects in humans.

7. Bioapplications

7.1. Bio-preservative agent in food

Food safety is a major challenge to public health worldwide. Processing of food can lead to increased lipid oxidation and microbial growth, which are the primary factors affecting the safety, shelf life, and quality of food products (Hawashin et al., 2016). Therefore, proper preservation techniques play an important role in the safety, shelf life, and quality of food products (Kim et al., 2016). For the last decades, incorporation of natural antimicrobial compounds has gained much momentum in preventing microbial growth without imparting the desirable characteristics of food products (Woraprayote et al., 2016). Due to the growing concern of consumers on the toxic effects of synthetic preservatives such as BHT, BHA, sulphites, benzoate, bromates, butylates (Mohamed and Mansour, 2012; Sharma, 2015), there have been an increasing trend towards the use of natural preservatives.

Abou-Zaid et al. (2015a) investigated the effect of aqueous *S. persica* root extracts (root macerated for 24 hr and 48 hr in water) as a natural food preservative agent on chicken burger by studying its effect on the chemical composition, microbial profile, and the organoleptic characteristics. The 48 hr extract caused a greater decrease in the total viable count in chicken burger compared to the 24 hrs extract, showing a concentration dependent activity. The most effective treatment was the 48 hr extract (50%). Moreover, the growth rate of coliform bacteria group in chicken burger was also reduced as the concentration level of extract was increased from 12.5% to 50%. However, with increasing level of extract, a lighter color of chicken burgers was observed with slightly higher L (whiteness) and Yellow (b) values, and slightly lower values of redness (a). In terms of the gross chemical composition of chicken burger**,** crude fats, crude protein, and carbohydrates content of the treated chicken burger were decreased while moisture and ash were increased. Moreover, the sensory scores of the most evaluated organoleptic quality characteristics of cooked chicken burger were

slightly decreased or not affected with increasing concentration up to 50% extract (24 hr) or 25% extract (48hr). The chicken burger showed good sensory quality and acceptability. However, cooked chicken burgers containing 50% of extract (48 hr) exhibited a slight reduction in the judging scores of the organoleptic quality characteristics; especially odor, flavor and color. It was concluded that the 50% extract (24 hr) or 25% extract (48 hr) may be added to the chicken burger as a natural food preservative to benefit from its preservative effect without negative influences on the sensory quality characteristics.

A similar study by Abou-Zaid et al. (2015b) was performed on the effectiveness of the aqueous stem extracts of *S. persica* as a bio-preservative agent for beef sausage products. Fairly similar results were obtained except that the color characteristics were not tested in this study. It was concluded that the aqueous extract of *S. persica* stem possesses good antibacterial effect and may be added to beef sausage components at amounts approximately 50% to benefit from its preservative effect. Furthermore, Zommara et al. (2007) investigated the antifungal effect of water, acetone, and ethanol extracts of several herbs and spices, including *S. persica* miswak, on the predominant fungal strains isolated from Ras cheese surface. The observed antifungal activity of *S. persica* miswak extracts against the tested stains indicate its potential as an alternative to the use of synthetic chemicals in the prevention of cheese surface spoilage by prohibiting fungal growth on Ras cheese surface.

Based on these results, *S. persica* can therefore be recommended as a safe and economical natural food preservative. Further research may study the application of *S. persica* in other food system such as other meat products, as well as fruits and vegetables. Further studies can also explore the preservative effect of the essential oil extracted from *S. persica*. Essential oils are known to be responsible for the odour, aroma and flavour of spices and herbs and therefore can be added to improve the sensory characteristics of food. In addition, due to their extensive bioactivity (especially antioxidant and antimicrobial

properties), they can protect against various food spoilage and pathogenic microorganisms as well as reducing lipid oxidation, hence preserving the safety and quality of food (Prakash and Kiran, 2016). Furthermore, an alternative to direct application of *S. persica* extracts on food is to incorporate it into edible films and coatings made from bio-based polymers including collagen, corn zein, casein, whey protein, alginate, dextrin, pectin, chitosan, starch, and cellulose derivatives. Due to the gradual release of active agents from the coating to the food surface for an extended period of time, this strategy may be more advantageous than direct incorporation into foods. In addition to their low cost and biodegradability, these novel packaging systems can offer biocompatibility, edibility, aesthetic appearance, barrier to the passage of oxygen and water, thereby slowing oxidation reactions and retaining moisture (Bourtoom, 2008; Sánchez-Ortega et al., 2014; Šuput et al., 2015).

7.2. Animal feed

The ethnoveterinary practice of *S. persica* has been reported in the treatment of diseases such as gastrointestinal disorders and to increase milk production in goats, cows, and camels in Saudi Arabia (Sher and Alyemeni, 2011). In Namibia, the bark and stems are crushed, soaked in water, filtered through cloth, and topically applied to treat skin infections in goats (Chinsembu et al., 2014). Interestingly, various scientific studies have proved the potential of *S. persica* as a feed additive to promote animal growth. For instance, El-Kholy et al. (2010) evaluated the effect of 0.1%, 0.2%, and 0.3% *S. persica* root as feed additive on the performance of pre and post-sexual maturity of Black Baladi rabbit males aged 30 days and weighing 570 g on average. Several reproductive traits were recorded at the age of maturity. Growth performance (daily weight gain, final body weight, and feed efficiency) was improved. In terms of reproductive performance, both the weight of sexual-accessory glands and plasma testosterone concentration were increased with increasing *S. persica* root levels which can be attributed to the increase in the activity of sexual accessory gland. Moreover, as

dietary proportion of *S. persica* root was increased, puberty age was found to decrease while testicular index increased linearly and quadratically. The improvement in puberty age could be related to the improving effect of *S. persica* root on testosterone level which causes faster maturity. In addition, the increase in testicular index also reflects testosterone production and spermatogenesis. Nonetheless, it was found that addition of *S. persica* root had no effect on weight at puberty or scrotal circumference. Besides, sexual desire, mating activity, advanced-sperm motility, semen-ejaculate volume, total-sperm output, and sperm-cell concentration were both linearly and quadratically increased by *S. persica* root inclusion. The increase in ejaculate volume could be because of the increase in sexual accessory gland weight in *S. persica* treated rabbits, since the accessory glands and spermatogenesis are controlled by the testosterone level, which was higher in treated rabbits. Importantly, acrosomal damage was reduced which could be due to the antioxidant activity of *S. persica*, mainly attributed to flavonoids, which can protect the plasma membrane surrounding the acrosome and tail.

Furthermore, El-Neney et al. (2013) analyzed *S. persica* root as natural feed additive (at 0.50 %, 0.75 % and 1.0 %) on the productive and reproductive performance of Dokki $_4$ (local strain) laying hens at 37 weeks of age. Feeding basal diet supplemented with *S. persica* root (0.50 %, 0.75 %, and 1.0 %) resulted in significant increase in body weight gain, final body weight, egg mass, and egg production, while egg weight was significantly increased only at 0.5 % and 0.75 %. Moreover, feed conversion ratios was significantly improved, unlike feed intake. On top of that, digestibility coefficient values of crude protein and crude fat were significantly improved using *S. persica* root (0.75 % and 1.0 %). Addition of *S. persica* root (0.75 %) to diet also significantly increased egg shape index, shell thickness, albumen percentages, and decreased yolk percentage and Haugh unit. However, no effect on shell weight and shell percentage was observed. On the other hand, both fertility and total hatchability percentages of total eggs were increased at all tested levels of *S. persica* root.

Furthermore, live body weight, giblets and spleen percentage, and total edible parts were significantly higher with diets supplemented with *S. persica* root (0.75 %). Significant increase was also observed in plasma components such as total plasma protein, globulin, hormones (T3 and T4), albumen, and total plasma antioxidants capacity. In addition, cholesterol, plasma total lipids, and plasma uric acid were significantly decreased at all tested levels of *S. persica*. With regards to immunity, leukocytes counts and mainly lymphocytes were increased significantly. Importantly, the net revenue and relative economic efficiency values were found to be maximised on addition of *S. persica* root at the recommended level of 0.75 % in diets.

Another fairly similar study was performed by El-Dein et al. (2014) who investigated into the possible use of *S. persica* miswak as a natural alternative antibiotic in comparison to Neomycin in Dokki $_4$ chickens at 18 weeks up to 36 weeks of age. The influence of different concentrations of miswak (0.50 %, 0.75 %, and 1.0 %) on laying hen's performance, egg quality, immunity, some blood plasma constituents, as well as semen traits of Dokki $_4$ chickens strain was also studied. In addition to the similar trend in results obtained by El-Neney et al. (2013) as mentioned previously, El-Dein et al. (2014) found that feeding miswak (1.0 %) to laying hens enable them to reach sexual maturity earlier. Supplementing both miswak at level (1.0 %) and Neomycin (25 mg/kg diet) also induce significant immune response against Primary Newcastle Disease Virus (ND1), Secondary Newcastle Disease Virus (ND2), Avian Influenza (AI), and Sheep Red Blood Cells (SRBCs). Moreover, in addition to the blood components analysed by El-Neney et al. (2013), El-Dein et al. (2014) found a gradual increase in red blood cells, hematocrit, and hemoglobin with increasing dietary levels of *S. persica* miswak while no effect was observed in traits aspartate transaminases and alanine transaminase which is in accordance to the findings of El-Neney et al. (2013). With regards to semen quality, El-Dein et al. (2014) found that supplementing

diets with *S. persica miswak* significantly increased sperm concentration, semen ejaculate volume, total sperm/ejaculate, live sperm percentage, sperm motility, and total live sperm/ejaculate while abnormal sperm percentage and total abnormal sperm/ejaculate were decreased. The author concluded that 1.0 % *S. persica* miswak has the potential to be used as an alternative to neomycin in laying hen diets.

Therefore, taking into account the reported traditional use of *S. persica* in livestock management and the positive effects observed by various studies on animal performance, it can be argued that *S. persica* can be used as an animal feed. Researchers can further study the effect of a broader range of doses of *S. persica* in different livestock animals to obtain optimum growth performance. Further research can be carried out in formulating novel natural livestock feed using *S. persica* mixed with other plant extracts which can be more beneficial in terms of taste and growth performance. Researches can also investigate into the potential prebiotic effect of *S. persica* on the beneficial gut microbiota of livestock. On top of that, the extensive pharmacological properties of *S. persica*, as reviewed above, indicates that it can be further explored in veterinary uses as a potential alternative to antibiotics in the treatment and/or management of diseases in animals.

7.3. Functional food development

Recently, there have been a surge in consumer's interest towards the role of food in health besides satisfying hunger, appetite sensation, and basic nutritional requirement, in order to improve their quality of life and prevent the risk of diseases (Siró et al., 2008). In response to this concern, the food industry is continuously developing a variety of new functional food products, which turns out to be quite a challenging process to meet consumers' expectation, acceptance, and demands (Winger and Wall, 2006; Thompson and

Moughan, 2008). For a food to be considered functional, it must offer health benefits through a meaningful physiological effect on the body that is over and above simple nutrition.

Taking into account the scientific validation of the biological properties of *S. persica* as witnessed by a vast number of studies, novel functional food products can be developed by incorporating different parts of *S. persica* into functional dairy and fruity beverages, yogurt, and cereals. In fact, the oral use of different parts of *S. persica* have been traditionally practiced for the treatment and/or management of several ailments as reported in Table 2. For instance, juice prepared from leaves are taken to treat scurvy (Parveen et al., 2007). Decoction of the leaves are used to treat asthma and malaria (Mesfin et al., 2012; Savithramma et al., 2007; Shah and Rahim, 2017). Infusion of the leaves are also taken in the treatment of urinary retention and bilharzia (Goodman and Hobbs, 1988). In addition, decoction of the roots is taken to treat female sterility (Chhabra et al., 1991). Powdered roots are also mixed with fresh or fermented cow milk for the treatment of dysmenorrhoea (Samuelsson et al., 1993). Therefore, considering the oral traditional use of different parts of *S. persica* together with their reported bioactivities, *S. persica* can be incorporated in functional food products together with other tasteful ingredients to make it acceptable by consumers.

Furthermore, the probiotic market has emerged out to be one of the prime revenue to the functional food industry (Gadhiya et al., 2015). Research on probiotics has thus been intensified to validate their efficacy, and so far, has demonstrated beneficial effects on human health (Kechagia et al., 2013; Nagpal et al., 2012). In fact, a study by (Moustafa et al., 2016) found that a *Bacillus endophyticus* strain, isolated from the inner tissue of *S. persica* stem, displayed antagonistic effect against a pathogenic strain of *S. aureus* which was resistant to 9 out of 10 antibiotics. Therefore, researchers might explore the different parts of *S. persica* as well as its rhizosphere for novel probiotic strains, and evaluate their probiotic potential in

terms of their acid and bile salts tolerance, survival in gastrointestinal tract, their bioactivities, and more importantly, their safety assessment. Further studies can also be carried out to study the effect of *S. persica* on the viability of probiotics, as well as exploring for potential prebiotic activity of extracted polysaccharides from *S. persica*. In fact, the use of synbiotics, where probiotics and prebiotics are used in combination, can enhance the survival of probiotics in the gut. Indeed, probiotics have limited ability to survive food processing factors (ingredients, humidity, temperature, pH, oxygen), as well as digestive process (gastric acidity, bile salts, enzymes), in order to reach the intestine (Gadhiya et al., 2015).

7.4. Nanotechnology

Nanotechnology can be considered as one of the most demanding field of research in the present scientific world. Although nanoparticles (NPs) can be synthesised by physical and chemical methods, the method of green synthesis is the most demanding and affordable process (Neelima et al., 2016). Since plant extract-mediated synthesis of NPs is cheap, easy to use, does not need toxic chemicals, solvents, and sophisticated laboratory facilities, it may facilitate the large scale biosynthesis of metallic NPs (Khan et al., 2017). Among various metallic NPs, silver nanoparticles (Ag-NPs) have drawn considerable attention of researchers and scientists because of their wide range of applications in the progress of new technologies in various fields. However, the morphology, size, and size distribution of NPs are important parameters which define their biological fate, toxicity, and specific targeting ability. Therefore, controlling these parameters is important during the plant extract mediated synthesis of NPs (Shaik et al., 2016).

For instance, Shaik et al. (2016) studied both the chemical and green synthesis of Ag-NPs, using an aqueous solution of *S. persica* root extract as a bio-reductant. The extract alone (10–300 μg/ml) did not display any antibacterial activity. The role of the aqueous extract was

largely as a reductant for the synthesis of NPs since the concentration used for the synthesis was too low to show its own antibacterial activity. However, the extract exerted significant effects on the antibacterial property of the green synthesised Ag-NPs. This study shows the influence of the volume of plant extract on the size and the dispersion qualities of NPs.

Furthermore, Barzegar et al. (2017) synthesised Ag-NPs using the ethanolic extract of *S. persica* leaf. These green-synthesised NPs were found to display greater antifungal activity against *Penicillium digitatum* and *Aspergillus niger* compared to the ethanolic extract of *S. persica* leaf. Moreover, Neelima et al. (2016) synthesized Ag-NPs from *S. persica* miswak twig extracts which were tested against *P. gingivalis*, a causative agent of peridontitis. Ag-NPs produced from freshly prepared extracts displayed greater antibacterial activity than those from 1 month old extracts. On the other hand, the miswak extract itself exhibited a mild antibacterial effect which was less compared to the Ag-NPs synthesized from the extract. Similarly, the study of (Miri et al., 2016) revealed that Ag-NPs, synthesized from the aqueous extract of *S. persica* bark, displayed significant antibacterial activity, with MIC of 100 and 400 µg/ml against *E. coli* and *S. aureus*, respectively, and MBC of 200 µg/ml against *E. coli*.

In addition to antimicrobial activity, Tahir et al. (2015) studied the photo degradation of methylene blue (MB) by green synthesised Ag-NPs from *S. persica* stem extract. The photo degradation of MB was rapid and decomposed 96% in 80 min. This strong photo catalytic activity of the synthesized Ag-NPs confirmed their potential utilization in water purification by removing MB which is of great importance for the environment. Many industries release a variety of organic compounds including dyes which cause adverse effects on the environment. Among these dyeing agents, MB is a stable water soluble organic compound with a large heterocyclic aromatic molecular structure. This complex structure may play a role in its strong resistance to heat and light, and therefore its degradation require

severe conditions. Therefore, the use of NPs to degrade these waste products would be of great significance.

Furthermore, Khan et al. (2017) demonstrated the catalytic activity of green synthesized palladium nanoparticles (Pd-NPs) using an aqueous solution of *S. persica* root extract as a bioreductant. During the preparation, highly crystalline, spherical-shaped Pd-NPs were obtained without the use of any harmful chemical reagents as reducing or capping agents. It was found that the polyphenolic phytomolecules present in the root extract not only facilitated the reduction of $PdCl_2$, but was also helpful in functionalising the surface of Pd-NPs by behaving as stabilisers.

Another study by Al-Marri et al. (2016) described a green approach for the synthesis of catalytically active palladium(Pd)@graphene nanocomposites (SP-HRG-Pd) using *S. persica* root extract as a bio-reductant. The phytomolecule content of the *S. persica* extract not only facilitated the reduction of graphene oxide and $PdCl_2$, but also ensured the homogeneous binding of the Pd-NPs on the surface of graphene, facilitated the stabilisation of the surfaces of SP-HRG-Pd nanocomposite and enhanced its dispersibility. As a result, the as-prepared SP-HRG-Pd nanocomposites also demonstrated excellent catalytic activity toward the oxidation of various aromatic alcohols.

These studies showed the potential application of metallic NPs synthesized from *S. persica* in various fields. Future research should determine the complete biological profile of these green synthesized NPs as well as incorporating bioactive components of *S. persica* on NPs. In fact NP-bound drugs are reported to have an extended half-life *in vivo* and longer circulation times. In addition, the size and surface characteristics of NPs can be modified to achieve a desired delivery characteristics. Moreover, since NP-bound drug is not able to circulate broadly, its side effects can be minimised and a high localised concentration can be achieved to the target site. On top of that, NP-bound drugs are able to penetrate deep in

organs and tissues since they are easily suspended in liquids (Mittal et al., 2013). In fact, many diseases originate from alterations in biological processes at the molecular or nanoscale level. Various molecules and infectious agents are nanometers in size and might be found in biological systems which are protected by nanometer-size barriers (Kim et al., 2010). Further studies are needed to determine the toxicity profile of green synthesised NPs from *S. persica* on cellular environment and beneficial gut microbiota. Future studies should also be designed to evaluate their stability during gut transit which may be affected by extreme pH and ionic shifts in the stomach and intestines, mucus, and bile acids secreted within the gut or by interactions with food or medications.

8. Research gaps and future perspectives

During the course of preparation of this review, we observed several gaps in current knowledge of the ethnopharmacology of *S. persica* which warrants due attention in future studies. These are summarised below:

Despite occupying a strong place in the traditional system in some Asian, Arabian Peninsula, and African countries, it is necessary to carry out more detailed and comprehensive ethnomedicinal studies of *S. persica* in these countries. Indeed, we found that some studies from these regions have not properly documented specific information on the method of preparation and administration, doses, frequency of usage, whether used alone or as adjunct to conventional therapy, and if improvement in health and/or side effects were experienced when *S. persica* was consumed. Proper documentation and detailed ethnomedicinal uses and paying due attention to taxonomic nomenclature (Rivera et al., 2014) are necessary steps because traditional knowledge provides base line information for further scientific investigation. Recent guidelines proposed for conduct of field studies could also be taken into account (Heinrich et al., 2018) for future studies.

Globally, it was found that *S. persica* twigs, roots, and stems, have been traditionally appraised mainly as a chewing stick. Pharmacological studies of *S. persica* also tend to be skewed more towards its validation in oral care such as its antimicrobial potential observed against a range of pathogens, particularly related to oral infections, and plaque formation (Table 4). However, it was found that the scope of application of *S. persica* can extend far beyond its initial traditional practice in oral care and can be exploited for other pharmacological studies. For instance, *S. persica* root was found to possess antimicrobial, antioxidant, antiulcer, analgesic, hypoglycemic, and hypolipidemic activities. In addition to these bioactivities, the stem was studied more compared to the root and found to exhibit other pharmacological activities such as anticonvulsant, sedative, and antityrosinase. Interestingly, the leaves have also received much attention traditionally in the treatment of rheumatism, scurvy, constipation, asthma, pain, and malaria amongst others (see Table 2). In fact, pharmacological investigation of the leaves revealed significant bioactivities including antimicrobial, antioxidant, analgesic, anti-inflammatory, antityrosinase, and ACE inhibitory activities. However, it is to be noted that not all parts of *S. persica* have received much pharmacological validation. For instance, to the best of our knowledge, *S. persica* fruit has only been investigated for its antimicrobial (Noumi et al., 2017) and antioxidant potential (Kumari et al., 2017) while the seed was only evaluated as an ACE inhibitor (Nyman et al., 1998). No study was conducted on the flower of *S. persica*, though traditionally appraised for its medicinal value (Panda, 1999). Therefore, it is of prime importance that future pharmacological studies be geared towards validation of reported traditional uses (Table 2) of each part of *S. persica* not yet scientifically confirmed.

Furthermore, we found that results recored from certain studies were not consistent. For instance the zone of inhibition against same strain of bacteria tend to vary. This could be due to differences in extraction techniques, or due the sample of *S. persica* collected from

different geographical regions with variable soil and climatic conditions, and agricultural techniques applied. However, only few studies have aimed to investigate into these factors (Al-Ghamdi and El-Zohri, 2017; Almas, 2001a). In addition, we found a shortage of genuine comparative data from the literature to compare the bioactivity of each part which could serve as a guide to both consumers and the scientific community. Therefore, future research priorities should address these gaps and attempts be made to study factors responsible for such variation(s) based on phytochemical composition and bioactive properties. Additionally, we observed that researchers tend to evaluate lyophilized water decoctions and organic-solvent extracts of *S. persica* using mainly maceration technique, followed by concentration *in vacuo*. It is proposed that other extraction methods can be further explored, including recent extraction technologies such as microwave-assisted, ultrasound-assisted extraction, and supercritical fluid extraction, which are aimed to increase yield of bioactive compounds at lower cost. In addition, it is important to note that no study was done on its exact traditional method of use, such as paste, extracted juice, infusion, or decoction without concentrating the extract (Table 2). Indeed, the process of drying plant and concentration *in vacuo* to obtain a crude extract can lead to loss and/or destruction of some bioactive compounds. Therefore, there is a need to compare and authenticate the traditional method of preparation of *S. persica* and attempts should also be made to confirm these traditional methods clinically.

S. persica roots were found to be extensively used in many countries. This led to speculate on the sustainability of such traditional practice from a conservation point of view, particularly when the raw materials are harvested from the wild. Indeed, several reports tend to emphasise the high medicinal, economic, and ecological values of *S. persica* in arid and semiarid ecosystems in Africa, Arabian Peninsula, and some Asian countries which pose serious threat to the survival of this species in the wild. It was observed that the conservation

status of *S. persica* is highly threatened in some of the above countries (Sher et al., 2010). Hence, future studies should also provide additional data on the detailed ethno-ecological behaviours of this plant in an attempt to conserve remaining population and possible loss of valuable medicinal plant germplasm. Future investigations should also study the possible threats of wild harvesting on the survival of *S. persica* and other demographic variables such as increasing population size, urbanisation, modernisation of agriculture, and climatic change.

It is imperative to highlight that most of the reported pharmacological properties were mainly conducted using *in vitro* models (antibacterial, antioxidant, and cytotoxicity using cell lines amongst others). As highlighted above, the only exception has been the extensive clinical evaluation of *S. persica* as a toothbrush and tooth paste (Section 6.2). It has been argued that *in vitro* models inherently bear limitations and fail to replicate the precise cellular and metabolic conditions of an organism. For instance, the positive *in vitro* ACE inhibitory property (Nyman et al., 1998) does not guarantee the blood pressure regulating potential of *S. persica* extracts if ingested. In addition, the potent *in vitro* antioxidant potential of *S. persica* extracts (Section 6.3) does not confirm its clinical use to delay the onset or mitigation of chronic diseases. Also, *in vitro* antitumor and toxicity assays using cells lines (Sections 6.11 and 6.12) cannot mimic the complexity of a living organism where cells are assembled in organs, under the influence of different systems; hormonal, immunological, nervous, and circulatory (Garattini and Grignaschi, 2017).

Future research could also be geared towards the study of the synergistic bioactivity of *S. persica* with other natural products particularly where *S. persica* has been reported to be used as part of a polyherbal formula. It is to be noted that few studies have proved the potentiating effect of *S. persica* on conventional drugs such as antibiotics (Ahmed et al., 2010; 2012) and the sedative drug sodium pentobarbital (Monforte et al., 2002). Therefore, the possibility of *S. persica* to potentiate conventional drugs should be high on the research

agenda, particularly where modern medicine fails. If a synergistic effect is observed, research can be further extended to find out the compatible relationship between their compounds and the proper ratio in which they should be used. It is to be emphasized that even though many phytocompounds have been isolated and identified from *S. persica* (Section 5), only few of them have been subjected to pharmacological evaluations (Ibrahim et al., 2011b; Iyer and Patil, 2012; Sofrata et al., 2011). Although phytochemical studies of the essential oil from stem and leaves of *S. persica* revealed significant bioactive compounds (Alali and Al-Lafi, 2003; Alali et al., 2005; Noumi et al., 2011), we found no pharmacological study of the essential oil fraction of *S. persica*. To this effect, it is proposed that future studies be designed to validate the bioactivity of isolated phytochemical(s) and essential oils from different parts of *S. persica*, either individually or in combinations. Future investigations are also required to study their mechanism of actions by which they exert their therapeutic effects, thereby serving as valuable starting points for drug discovery and developments.

We also found that almost all *in vivo* studies (hypoglycemic, hypolipidemic, analgesic, and anti-inflammatory activity) of *S. persica* were conducted on rats. However, we observed certain limitations which warrant further attention. For instance, some studies did not specify the precise age of rats, while some of them mentioned the term "adults" (Galati et al., 1999; Hoor et al., 2011; Rajesh et al., 2010). Only few studies have specified the health status of the animals used for *in vivo* experiments (Hooda et al., 2014; Saini and Yadav, 2013). In addition, *in vivo* studies conducted on rats were mainly tested at a concentration of 500 mg/kg body weight (Monforte et al., 2001, 2002; Rajesh et al., 2010; Sanogo et al., 1999), although few studies extended to 1200 mg/kg body weight (Hoor et al., 2011, 2014). We observed that most *in vivo* studies on *S. persica* tend to follow the same dose level (500 mg/kg). However, using similar doses as previous studies should ensure similar tolerance between animal species and strains, sources, or ages, which may differ in the way they

respond to tested extracts (Robinson et al., 2009). It is also important to highlight that findings from some studies were comparable or slightly less effective compared to the positive control (Hoor et al., 2011, 2014; Ibrahim et al., 2011a; Khan et al., 2014; Rajesh et al., 2010). Therefore, it can be recommended that future studies can explore the possibilities of administration of a higher dose which might give a better response to the positive control. The above argument can be supported based on two previously published toxicological studies of *S. persica*, where no toxicity was observed at highest dose tested [1200 mg/kg body weight (Hooda et al., 2014), and LD_{50} value of more than 2 g/kg as observed by (Monforte et al., 2002)]. Nonetheless, the maximum tolerated dose should be determined by testing increasing doses until the highest dose with acceptable side effects is reached. In addition, the duration of single or repeated dosing also need to be taken into consideration (Robinson et al., 2009) and the time interval between repeated dosing ought to be determined by the onset, duration, and severity of toxic signs (OECD, 2001).

Another important issue in *in vivo* testing is the route of administration of *S. persica* extract. Data gathered in this review showed that most *in vivo* studies involve oral administration of *S. persica*. It is to be noted that the study of (Monforte et al., 2002) found that administration of lyophilized decoction of *S. persica* i.m. displayed better anticonsulvant effect compared to oral administration. Therefore, it would be interesting that future studies explore the response of other routes of administration of *S. persica*, such as subcutaneous and intravenous injection, inhalation, topical, transdermal, and intranasal route, at the same time evaluating the physicochemical, pharmacokinetic, and pharmacodynamic properties of the extract. It is also recommended that future *in vivo* research be carried out on other animals beside rats, including those more closely related to humans, together with precise specification of experimental design, health status, weight, sex, quantity, age (Mullane et al.,

(2015), as well as the duration of treatment, use of wider range of doses, and analysing any possible side effects experienced.

Last but not least, the current application of *S. persica* in food preservation, animal feed, and nanotechnology indicates its possible applications in other fields which need to be further explored. For instance, the traditional oral administration of *S. persica* infusion and decoctions indicates its possibility as a functional beverage ingredient. The use of *S. persica* in animal feed can be further explored as an alternative antibiotics in ethnoveterinary medicine.

9. Conclusion

The present review provides an updated and structured compilation of studies on *S. persica*. It is to be noted that there has been earlier attempts to summarise the medicinal potential of *S. persica*, even though with a different or a less broad ethnopharmacological focus. However, this review can be considered as the first attempt to broaden and critically assess scientific evidence on the ethnopharmacology of *S. persica*. It is obvious from this review that *S. persica* can be regarded as an important traditionally used medicinal plant harboring a panoply of bioactive compounds, pharmacological properties, and modern applications in emerging fields of interest. It is anticipated that this review article will open new avenues for research and stimulate further studies that will fill research gaps highlighted above.

Conflict of interest

The authors declare no conflict of interest or commercial interest.

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