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Review

Miswak and oral health: An evidence-based review

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ABSTRACT

Poor oral health has been associated with several chronic and systemic disease. Currently, the most common method of teeth cleaning is the use of a toothbrush together with dentifrices. However, natural chewing stick such as *S. persica* miswak is still used in many developing countries due to their low cost and availability. The present review aims to summarize the evidences on effectiveness of miswak in promoting oral health. The search was performed using Medline via Ebscohost, Scopus and Google Scholar database to obtain relevant articles published between 2010 to May 2020 using the following set of keywords 1) Miswak OR Salvadora OR persica AND 2) dental OR caries OR plaque OR oral OR orthodontics. Isolated microbial inhibition studies were excluded from the review due to its well-established wealth of literature. Miswak was administered as ten different forms, namely mouthwash, toothpaste, chewing stick, essential oil, aqueous extract, ethanol extract, probiotic spray, dental varnish, dental cement or chewing gum. All studies reported a positive effect of miswak as an anti-plaque, anti-gingivitis, anti-cariogenic, promotion of gingival wound healing, whitening properties, orthodontic chain preservation, and biocompatibility with oral cells. Miswak in its different forms demonstrated positive effect towards oral health maintenance and management.

Contents

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1. Introduction

Poor oral health has a major influence on the general quality of life and well-being (Kassebaum et al., 2017). Several chronic and systemic diseases have been attributed to poor oral health. Diseases such as cardiovascular disease (Kiswanjaya et al., 2017), stroke (Shiraishi et al., 2018), mental illness (Kisely et al., 2015), and diabetes (Nakamura et al., 2016) have recently been associated with the consequences of poor oral health such as chronic oral infections, dental caries and periodontal disease. It is generally accepted that the oral hygiene maintenance through regular removal of dental plaque and food deposits is an essential factor in the prevention of poor oral health.

The use of a toothbrush in combination with dentifrices is one of the most common methods of oral hygiene maintenance. Other notable methods include mouthwash and dental floss (van Leeuwen et al., 2017). In diseased mouth such as the periodontitis, innovative technology such as the biodegradable periodontal chip is used in its management (Al-Bayaty et al. 2013). Use of herbal formulation to positively influence oral health was evident in dentifrices, mouthwash, dental floss and periodontal chip.

In many developing countries, natural methods of tooth cleaning using chewing sticks, selected and prepared from the twigs, stems or roots of a variety of plant species are still being practiced due to their availability, low cost and simplicity (Niazi et al., 2016). Religious and cultural factors also influence the popularity of chewing sticks in these countries (Owens and Sami, 2016). The practice dated back to thousands of years in Asia, Africa, the Middle East and the Americas (Gurudath et al., 2012).

There is approximately 182 species of plants that are used as chewing sticks across the globe. *Salvadora persica* is the most commonly used plant for this practice (Qureshi et al., 2016). *Salvadora persica* plant is commonly known as miswak tree. Miswak, an Arabic word that means tooth cleaning stick, becomes a common name for *Salvadora persica* due its widespread association with the practice (Haque and Alsareii, 2015).

Salvadora persica, belongs to the family *Salvadoracea* with wide geographic distribution ranging from Rajasthan (India), Nepal, and Malaysia in the east through Pakistan, Iran, Iraq, Saudi Arabia, and Egypt to Mauritania in the west. In Africa, they are found in North Africa through Sudan, Ethiopia, and Central Africa to Southwestern Africa (Qureshi et al., 2016).

One end of the miswak stem is trimmed to form an exposed end, which will then be chewed to form a brush. The brush is used to clean the crevices between the teeth to remove any food deposits. World Health Organization encourages the use of chewing sticks following its potential role in the promotion of oral health (Khatak et al., 2010).

Salvadora persica has been reported to comprise wide variety of organic and inorganic compounds within its extract. Among the organic compounds were glycoside, saponins, flavonoids, alkaloids, tannins, benzyl derivatives, phenol compounds, and organic acids. For inorganic compounds, i.e. anionic compounds such as fluoride, chloride, sulphate, thiocyanate and nitrate have been identified (Aumeeruddy et al., 2018).

In terms of oral health, *Salvadora persica* has been reported to be antibacterial (Al-Ayed et al., 2016, Al-Bayaty et al. 2010a), antifungal (Pribadi, Rihansyah and Darusman, 2014), anticariogenic (Ezoddini-Ardakani, 2010), and antiplaque (Varma et al., 2018). Other reported pharmacological properties of *Salvadora persica* include hypolipidemic (El Rabey et al., 2017), antiulcer (Lebda et al., 2018), anticonvulsant (Monforte et al., 2002), antifertility (Darmani et al., 2003), and antioxidant (Mammad et al., 2018).

The aim of the current systematic review is to assess the current update regarding the existing empirical evidences reporting the medicinal properties of *Salvadora persica* and its components, specifically towards promotion of good oral health. This could help pave the way for its use as an alternative for oral health maintenance, particularly in communities with low socioeconomic status, where it is more conveniently and easily obtained.

2. Methodology

Accessible electronic databases were searched to find empirical studies about the reported benefit of miswak in different aspects of oral health published between 2010 and May 2020. The databases used were Medline via Ebscohost, Scopus and Google Scholar. The electronic search was conducted using combination of keywords that represents miswak of the *Salvadora persica* (Miswak OR Salvadora OR persica) and those that represents oral health (dental OR caries OR plaque OR oral OR orthodontics). Isolated microbial inhibition studies were excluded from the review due to its well-established wealth of literature. Selected articles were summarized in Table 1.

3. Anti-plaque properties

Majority of the studies included in this review has shed light on the efficacy of miswak for reducing plaque formation. Plaque is the biofilm layer that formed on the surface of the teeth that comprises components of saliva, bacterial cells and their secretions (Huang et al., 2011). Miswak has been well known to play a role in plaque prevention as an antimicrobial agent that inhibited the growth of many plaque inducing bacteria.

3.1. Mechanical or chemical action of miswak

Mechanical action from tooth brushing together with the appropriate dentifrices has always been prescribed to disrupt the

Table 1
Studies summary of the miswak effect on oral health parameters.

In Vitro					
Articles	Experimental Model	Treatment Intervention	Outcome Measure	Results	Conclusion
Wassel and Sherief, 2019	50 enamel specimen that was subjected to enamel lesion via immersion in demineralizing solution.	1. Ethanolic miswak extract with fluoride (MF; n = 5). 2. Ethanolic miswak extract without fluoride (M; n = 5). 3. Freeze-dried miswak (MFD; n = 5). 4. Ethanolic propolis extract with fluoride (PF; n = 5). 5. Ethanolic propolis extract without fluoride (P; n = 5). 6. Chitosan nanoparticles with fluoride (CSF-NP; n = 5) 7. Chitosan nanoparticles without fluoride (CS-NP; n = 5) 8. Sodium fluoride (NaF; n = 5). 9. Varnish base (n = 5) 10. No treatment (n = 5).	Following application of respective varnishes on the damaged enamel, the following were measured a) Fluoride, calcium and phosphate content released. b) Surface micro hardness (SMH) c) Topography of the enamel specimen	a) Fluoride release from highest to lowest were MF, NaF, MFD, CSF-NP, PF, CS-NP, M, and P.Calcium released from highest to lowest were CSF-NP, CS-NP, MFD, MF, M, P, PF, and NaF. Phosphate release from highest to lowest were CS-NP, CSF-NP, MFD, M, MF, P, PF, and NaF. b) SMH from highest to lowest were CSF-NP, CS-NP, MFD, MF, M, NaF, PF, and P. c) Both CSF-NP and CS-NP resulted in smoother enamel surface, with homogenous amorphous crystals. MFD showed remineralization with smooth homogenous surface. Both MF and M showed partial remineralization which is more pronounced in MF.	Miswak containing varnish was effective in enamel remineralization.
Albabtain et al., 2017	Gingival fibroblasts and oral keratinocytes.	1. Benzyl isothiocyanate (BITC). 2. Miswak essential oil (MEO). 3. Benzyl aldehyde. 4. Benzyl cyanide.	Test compound was supplemented in cell culture media for 24 h.MTT viability assay was used to measure cell viability.	Gingival fibroblast 1. BITC - Toxic dose: 1 μg/ml - Half maximal inhibition (IC_{50}): 3 μg/ml - Stimulating dose: None 2. MEO - Toxic dose: 1.4 μg/ml and - IC_{50}: 3 μg/ml - Stimulating dose: None 3. Benzyl cyanide - Toxic dose: None - IC_{50}: None - Stimulating dose: None 4. Benzyl aldehyde - Toxic dose: 0.8 μg/ml - IC_{50}: 3 μg/ml - Stimulating dose: None- Oral keratinocytes 1. BITC - Toxic dose: None - IC_{50}: None - Stimulating dose: 80 μg/ml 2. MEO - Toxic dose: None - IC_{50}: None - Stimulating dose: 40 μg/ml	Miswak essential oil BITC, benzyl aldehyde, and benzyl cyanide are well tolerated by oral keratinocytes and can be used to formulate a safe mouthwash.
Halib 2017	Extracted human permanent premolar teeth stained with tea and coffee.	1. 0.3% miswak paste. 2. 0.4% miswak paste. 3. 0.5% miswak paste. 4. Commercial toothbrush.	Each stained tooth underwent simulated tooth brushing with frequency of 2 S/second and an applied force of 10 g for 28 min on each buccal and occlusal surface respectively.The whitening effect was evaluated using the VITAPAN® Classical Shade instrument immediately following brushing action.	0.4% and 0.5% extract as well as commercial paste demonstrated changed at an average of two shades compared to one shade in 0.3% extract.	Miswak demonstrated potential as a natural alternative teeth-whitening agent.

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Table 1 (*continued*)

In Vitro					
Articles	Experimental Model	Treatment Intervention	Outcome Measure	Results	Conclusion
Omidkhoda et al., 2015	Closed connector and short connector orthodontic chain	1. Artificial saliva. 2. 0.2% chlorhexidine mouthwash. 3. Miswak mouthwash. 4. 0.05% sodium fluoride mouthwash.	Orthodontic chains underwent 10 thermocycles between 5 and 55° C before they were immersed in different mouthwashes for 1 min daily.The chains were stretched on two post and the force of the chains were measured at initial time point, after 24 h, 1, 2, 3 and 4 weeks.	Orthodontic chains, both short connector and closed connector, experienced significantly reduced force-decay when immersed in miswak compared to all other mouthwashes.	Miswak mouthwash prevents force-decay in orthodontic chain.
Moezizadeh et al., 2015	Human dental pulp stem cell	1. 0.08, 0.18, 0.36, 0.72, 1.43, 2.88, and 5.75 mg/ml miswak water extract 2. 0.08, 0.18, 0.36, 0.72, 1.43, 2.88, and 5.75 mg/ml miswak ethanolic extract	Test compound was supplemented in cell culture media for 24 h.MTT viability assay was used to measure cell viability.	For ethanol extract, cytotoxicity effect was found with the 1.43 to 5.75 mg/ml concentration at 24 and 48 h. For water extract, cytotoxicity was found with the 5.75 mg/ml concentration. Lower concentration of water extract, induces significant cell proliferation.	Low concentrations of miswak water extract induce cell proliferation of human dental pulp stem cell.
Balto et al., 2014	Human gingival fibroblast	1. 0.5 mg/ml miswak ethanol extract. 2. 1 mg/ml miswak ethanol extract. 3. 0.5 mg/ml miswak hexane extract. 4. 1 mg/ml miswak hexane extract. 5. 0.5 mg/ml miswak ethylacetate extract. 6. 1 mg/ml miswak ethylacetate extract.	Different test compound was supplemented in cell culture media for 24 h.MTS, LDH, and crystal violet viability assay was used to measure cell viability.	For ethanol extract, no cytotoxicity effect was found with both 0.5 and 1 mg/ml concentration.For hexane extract, slight cytotoxicity was detected with 1 mg/ml concentration but not 0.5 mg/ml concentration.For ethyl acetate, slight cytotoxicity was detected in 0.5 mg/ml concentration and maximum cytotoxicity was found with 1 mg/ml concentration.	Miswak extracted with different solvent has an acceptable cytotoxicity level that can potentially be used as oral irrigation solution.
In Vivo Studies					
Articles	Experimental Model	Treatment Intervention	Methods	Results	Conclusion
Al-Bayaty et al., 2018	18 male Sprague Dawley rats with tooth extracted.	1. Miswak ethanol extract in a gel (n = 6). 2. Miswak aqueous extract in a gel (n = 6). 3. Gel only (n = 6).	Tooth were extracted from the rats and the extraction socket was filled with treatment. Healing process of the socket was observed macroscopically and histologically for 21 days.	The socket treated with ethanol or aqueous Miswak extract healed faster. Histological analysis showed significantly more mature bone tissue than the control.	Miswak demonstrated a potential for alveolar bone healing.
Dorri et al., 2012	9 male and 9 female Wistar rats with right mandibular first molar extracted.	1. 0.2% chlorhexidine mouthwash (n = 6) 2. 10% miswak mouthwash (n = 6) 3. Tap water (n = 6)	The test mouthwashes were administered twice daily for 7 days before and after extraction of the first molar. Formation of new bone in the mandibular socket was evaluated using histology.	The mean new bone formation was significantly higher in miswak group compared to chlorhexidine group.	Consistent miswak used demonstrated potential to enhance new bone formation following teeth extraction.
Clinical Studies					
Articles	Study Design	Treatment Intervention	Outcome Measures	Results	Conclusion
Albabtain et al., 2018	Double-blind, cross-over arm, randomized controlled trial of 28 patients with mild-to moderate periodontitis, with no previous experience of miswak.	1. Brushing with boiled miswak (chemically inactive) 2. Brushing with non-boiled miswak (chemically active)	At baseline and 3 weeks after the use of chemically active and inactive miswak, the following changes were measured a) Plaque index (PI) b) Visual plaque index (VPI). c) Gingival index (GI) d) Bleeding on probing (BOP).	No significant difference was observed in terms of PI, VPI, GI, and BOP changes after the use of chemically active and inactive miswak.	The chemical effect of Miswak practice on clinical outcome among patients with periodontitis was moderate.
Sobouti et al., 2018	Single-blind, parallel arm, randomized controlled trial of 54 patients who had received 4 months of fixed orthodontic treatment.	1. Miswak mouthwash (n = 18) 2. Chlorhexidine mouthwash (n = 18) 3. Placebo mouthwash (n = 18)	At baseline and after 1 month of using assigned mouthwashes, the following changes were measured a) PI b) GI c) Gingival bleeding index (GBI) d) Pocket probing depth (PPD).	a) PI was significantly reduced with both miswak and chlorhexidine mouthwashes compared to placebo. b) GI was significantly reduced with miswak mouthwash compared to placebo.	Miswak can improve the deteriorating gingival health resulted from orthodontic treatment.

Table 1 (*continued*)

In Vitro					
Articles	Experimental Model	Treatment Intervention	Outcome Measure	Results	Conclusion
				c) GBI was significantly reduced with both miswak and chlorhexidine mouthwashes compared to placebo. d) PPD was significantly reduced with chlorhexidine compared to placebo.	
Varma et al., 2018	Single-blind, crossover arm, randomized controlled trial of 24 healthy individuals.	1. Miswak toothpaste. 2. Tea tree oil toothpaste.	At baseline and 24 h after the use of miswak or tea tree oil toothpaste, changes in PI was measured..	Use of miswak toothpaste demonstrated a significantly greater reduction of plaque compared to the tea tree oil toothpaste.	Miswak was superior to tea tree oil in terms of plaque reduction.
Baeshen 2017	Single-blind, crossover arm, randomized controlled trial of 15 healthy individuals.	1. 0.5% NaF-impregnated miswak. 2. Nonfluoridated miswak. 3. Toothbrush with non-fluoridated toothpaste. 4. Toothbrush with 1450 ppm fluoride toothpaste.	At baseline and 1 week after the use of all 4 interventions, the following changes were measured a) PI b) Salivary fluoride content	a) There was no significant difference in PI between miswak and toothbrush, with or without fluoride. b) Salivary fluoride content was significantly greater with fluoridated miswak compared to the fluoridated toothpaste.	Miswak used is comparable to tooth brushing for plaque reduction. Fluoridated Miswak has greater fluoride release capacity than the fluoridated toothpaste.
Niazi et al., 2018	Double-blind, parallel arm, randomized controlled trial of 80 patients undergoing orthodontic treatment.	1. Chlorhexidine mouthwash (n = 20) 2. Cetylpyridinium mouthwash (n = 20). 3. Miswak extract (n = 20). 4. Neem extract (n = 20).	At baseline and 3 weeks after the use of all 4 interventions, changes in PI was measured.	Miswak mouthwash significantly reduced plaque compared to the chlorhexidine. Reduction in plaque with neem was not statistically significant different to the control.	Miswak can be a good substitute to the synthetic mouthwash in patients with orthodontic treatment.
Kabil et al., 2017	Double-blind, parallel arm, randomized controlled trial of 60 young permanent molars with deep carious lesion from 35 children aged 6 to 9 years old.	1. Glass ionomer cement (GIC) mixed with chlorhexidine gluconate (n = 20).2. GIC mixed with miswak extract(n = 20).3. GIC mixed with deionized water(n = 20).	After 3, 6, and 9 months following restoration of damaged teeth with atraumatic restorative treatment (ART) with assigned GIC, the community periodontal index of treatment needs (CPITN) was measured.	Restoration survival, from highest to lowest were miswak cement, chlorhexidine cement, and basic cement. Differences were significant at 6 and 9 months.	Miswak incorporation in glass ionomer cement increased the chance of restoration survival after ART.
Mustafa et al., 2016	Prospective case-control observation of 240 secondary school children.	1. Miswak users (n = 120) 2. Non-Miswak users (n = 120)	At baseline and after 2 years, participants were evaluated for any decayed, missing or filled tooth and decayed-missing-filled (DMF) index was recorded.	There was significantly more number of teeth that were affected by caries in toothbrush users as compared to miswak users.	Miswak demonstrated cavity prevention in secondary school children.
Rezaei et al., 2016	Double-blind, parallel arm, randomized controlled trial of 76 intubated patient in intensive care unit.	1. Herbal mouthwash containing 10 mg/ml *Salvadora persica* and 940 mg/ml *Aloe vera* (n = 38). 2. 0.2% chlorhexidine mouthwash (n = 38)	At baseline and after 4 days of oral irrigation administered using different mouthwashes every 2–3 h daily, GI was measured	Irrigation with herbal mouthwash resulted in significantly greater GI reduction compared to irrigation with chlorhexidine.	Combination of *Salvadora persica* and *Aloe vera* mouthwash reduces gingivitis among intubated patients in ICUs.
Azaripour et al., 2017	Double-blind, parallel arm, randomized controlled trial of 66 non-smoking patient with gingival inflammation.	1. Miswak extract-containing toothpaste (n = 22).2. Paradontax toothpaste(n = 22).3. Colgate toothpaste(n = 22).	At baseline and after 3 weeks brushing with the assigned toothpaste, the following changes were measured a) Sulcus bleeding index (SBI). b) PI.	a) Reduction of SBI from highest to lowest were Paradontax, miswak and Colgate. b) PI was similar among all intervention.	Miswak showed a similar advantage as the herbal toothpaste Paradontax compared to Colgate and can safely be used for patients with gingivitis.
Farhadian et al., 2015	Single-blind, parallel arm, randomized controlled trial of 72 orthodontic patients with at least two sites of gingival enlargement.	1. Manual toothbrush (1; n = 18). 2. Electric toothbrush (2; n = 18). 3. Manual toothbrush with miswak mouthwash (3; n = 18).	At baseline and after 2 weeks of brushing with the assigned intervention, the following changes were measured a) BOP. b) GI. c) PI.	a) Mean percentage of changes in BOP from highest to lowest were 4, 3, 2 and 1 groups and the differences was significant.	Miswak has similar efficacy as chlorhexidine mouthwash in improving hyperplastic gingiva in orthodontic patients.

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Table 1 (*continued*)

In Vitro					
Articles	Experimental Model	Treatment Intervention	Outcome Measure	Results	Conclusion
		4. Manual toothbrush with 0.2% chlorhexidine (4; n = 18).	d) Hyperplastic index (HI).	b) Mean percentage of changes in GI from highest to lowest were 4, 3, 2 and 1 groups and the differences was significant. c) Mean percentage of changes in PI from highest to lowest were 4, 3, 1 and 2 groups and the differences was significant. d) Mean percentage of changes in HI from highest to lowest were 4, 3, 2 and 1 groups and the differences was significant.	
Malik et al., 2014	Double blind, parallel arm, randomized controlled trial of 50 healthy dental students.	1. Nylon toothbrush with toothpaste (n = 25). 2. Miswak chewing stick (n = 25).	At baseline and after 1 month of brushing with the assigned intervention, the following changes were measured a) PI. b) GI.	a) Miswak significantly reduces PI. b) Both miswak and toothbrush reduces GI but the difference in reduction is not statistically significant between groups.	Miswak reduces plaque better than toothbrush in healthy dental students.
Gupta et al., 2012	Triple-blind, parallel arm, randomized controlled trial of 330 healthy children	1. Miswak containing toothpaste (n = 165). 2. Triclosan polymer and fluoride of 1000 ppm containing toothpaste (n = 165)	At baseline, after 2 and 4 weeks of brushing with the assigned intervention, the changes in PI was measured.	Miswak containing toothpaste demonstrated significantly greater PI reduction compared to the conventional toothpaste.	Miswak has the potential to reduce plaque in healthy children.
Saha et al., 2012	Prospective cohort observation among 297 individuals in Lucknow	1. Miswak users (n = 125). 2. Toothbrush and toothpaste users (n = 93). 3. Miswak, toothbrush and toothpaste users (n = 79).	Interview was conducted to find out patient's oral habit and the following outcome were measured a) Oral hygiene index-simplified (OHI-S). b) GI. c) PI.	Mean PI was significantly lower in combined users of miswak and toothbrush. In terms of GI, miswak users has significantly lower GI compared to toothbrush users. No statistical significant difference found among groups with OHI-S.	Miswak users have lower level of gingivitis and plaque compared to toothbrush user.
Sofrata et al., 2011	Double-blind, parallel arm, randomized controlled trial of 68 regular dental patients.	1. Brushing with boiled miswak (chemically inactive; n = 34) 2. Brushing with non-boiled miswak (chemically active; n = 34)	At baseline and after 3 weeks of brushing with the assigned intervention, the following changes were measured c) PI. d) GI.	a) No significant difference between reductions of PI between groups. b) No significant difference between reductions of GI between groups.	Active and inactive miswak have similar efficacy towards plaque and gingival reduction.
Amoian et al., 2010	Double-blind, parallel arm, randomized controlled trial of 72 female patients with plaque-induced moderate gingivitis.	1. Miswak extract chewing gum with teeth scaling at day 0 and 7 (n = 18). 2. Sugar-free chewing gum with teeth scaling at day 0 and 7 (n = 18). 3. Miswak extract chewing gum without teeth scaling (n = 18). 4. Sugar-free chewing gum without teeth scaling (n = 18).	At baseline, 7, and 14 days of the study, the following changes were measured a) PI b) GI c) Bleeding index (BI).	a) No significant differences in PI was detected between all four treatments. b) Both miswak group with or without scaling shows significant reduction of GI compared to placebo with or without scaling. c) Both miswak group with or without scaling shows significant reduction of BI compared to placebo with or without scaling.	Chewing gum reinforced with miswak extract can improve gingival health even without teeth scaling.
Al-Bayaty 2010a, b	Double-blind, crossover arm, randomized controlled trial of 10 male dental students aged 22 years old.	1. 10% miswak ethanol extract. 2. 0.2% chlorhexidine gluconate solution (Positive control). 3. Distilled water (Negative control).	At baseline and 5 days after the use of all 3 interventions, changes in PI was measured.	a) Miswak ethanol extract demonstrated higher PI compared to chlorhexidine.	Miswak was less effective as mouth rinse compared to chlorhexidine.

long-term accumulation of the dental plaque (Tartaglia et al., 2017). Miswak benefits in dental hygiene could be due to the brushing action of the teeth, its intrinsic chemical properties or both. Sofrata et al. (2011) were the first group to investigate this hypothesis by preparing both fresh and boiled miswak to represent chemically active and inactive chewing stick respectively. Turesky modified Quigley–Hein plaque index was used to assess the plaque status of their 68 patients that were randomized equally into two arms of chemically active and inactive miswak. Both chemically active and inactive miswak were found to have similar efficacy towards plaque reduction (Sofrata et al., 2011). This finding favors the hypothesis of miswak benefit through its mechanical action instead of chemical action.

The hypothesis of chemical action of miswak were also tested by Albabtain et al. (2018) with their periodontitis patients. Periodontitis is an advanced infection of the gums initiated by chronic accumulation of plaque. Reduction in plaque index (PI) was detected in the teeth of 28 periodontitis patients following the use of both chemically active and inactive miswak. Between the treatment arms, no significant difference was observed (Albabtain et al., 2018).

3.2. Miswak chewing stick compared to conventional toothbrush

When compared to the toothbrush, miswak chewing stick was found to be more superior in terms of reducing plaque. A double blind RCT involving 50 healthy dental students was performed to compare the efficacy of nylon toothbrush with dentifrices and miswak chewing sticks. This study revealed that brushing teeth with miswak significantly reduces plaque compared to brushing with a toothbrush (Malik et al., 2014).

Miswak superiority compared to conventional method were further supported by the study conducted by Saha et al. (2012) among 297 individuals in Lucknow. In their study, they found that the mean PI was significantly lower in participants that used both miswak and toothbrush, followed by miswak only users, with toothbrush only users having the highest mean PI (Saha et al., 2012).

On the other hand, Baeshen et al. (2017) in their attempt to incorporate fluoride into miswak chewing stick, reported no significant difference in terms of plaque reduction between the miswak and toothbrush, with or without fluoride, in their single blind, crossover arm, RCT involving 15 healthy individuals. Nevertheless, miswak use was comparable to tooth brushing for plaque reduction (Baeshen et al., 2017).

3.3. Miswak toothpaste

Miswak-incorporated toothpaste can be found prevalently in the market nowadays. In terms of plaque reduction, Gupta et al. (2012) in their triple-blind, parallel arm, RCT of 330 healthy children, compared the efficacy of miswak-incorporated toothpaste and fluoridated toothpaste. They found that significantly greater plaque reduction was achieved with the miswak-incorporated toothpaste compared to the conventional fluoridated toothpaste (Gupta et al., 2012).

Miswak-incorporated toothpaste has also been compared with other herbal toothpaste, namely the tea tree oil-incorporated toothpaste. In a single-blind, crossover arm, RCT of 24 healthy individual, Varma et al. (2018) observed a significantly greater reduction of plaque with miswak toothpaste compared to the tea tree oil toothpaste.

However, this superior effect was not observed among the gingivitis patients. Azaripour et al. (2015) conducted a double blind, RCT of 66 non-smoking patients with gingival inflammation. The patients were randomized into those receiving miswak-containing toothpaste, a herbal toothpaste marketed as Parodontax, and the well-documented fluoride toothpaste Colgate. Although all of the treatment arms resulted in significant reduction of plaque after use, no significant difference between groups was observed (Azaripour et al., 2017).

3.4. Miswak mouthwash

Mouthwash has been established to be an effective method for plaque reduction (Farook and Said, 2018). Chlorhexidine, the cationic chemical agent commonly used in conventional mouthwash due to its potency against plaque, has been reported to cause many side effects such as teeth discoloration, oral mucosal irritation, and an unpleasant taste following its use (Marion et al., 2013). Consequently, the search for natural alternative for mouthwash formulation was needed.

Niazi et al. (2018) conducted a double-blind RCT to compare the efficacy of chlorhexidine, cetylpyridinium, miswak, and neem mouthwash on plaque reduction among 80 patients who underwent orthodontic treatment. Mouthwash formulated with miswak, demonstrated significantly greater plaque reduction effect compared to the two chemical ingredients. Neem mouthwash was not able to demonstrate any significant reduction of plaque when compared to the two chemical ingredients (Niazi et al., 2018).

Al-Bayaty et al. (2010) conducted a cross over double-blind RCT of 10 dental students aged 22 years old to compare the efficacy of ethanolic extract of miswak compared to chlorhexidine. Distilled water was used as a negative control mouthwash. However, miswak treatment demonstrated higher plaque index when compared to the chlorhexidine group (Al-Bayaty et al. 2010b). Another study that compared miswak and chlorhexidine mouthwash in terms of plaque status following orthodontic intervention also did not observe any difference between the groups. The study was a single-blind RCT of 54 patients who had fixed orthodontic treatment for four months. The plaque reduction effect in both miswak and chlorhexidine was significant in comparison to the placebo mouthwash, suggesting that miswak can serve as a replacement of the synthetic chemical agent, chlorhexidine in orthodontic patients (Sobouti et al., 2018).

Apart from miswak mouthwash, Farhadian et al. (2015) investigated the effect of plaque reduction following the usage of electronic toothbrush. The single-blind, parallel arm, randomized controlled trial of 72 orthodontic patients with at least two sites of gingival enlargement revealed that the use of miswak mouthwash together with electronic toothbrush significantly reduced plaque compared to the use of electronic toothbrush alone.

3.5. Miswak chewing gum

Miswak has also been reinforced into chewing gum. Amoian et al. (2010) investigated the effect of chewing miswak-containing chewing gum with or without teeth scaling. No significant difference was observed in terms of reduction of plaque between all groups.

4. Anti-gingivitis properties

In clinical studies, severity of the gingival inflammation can be quantified by measuring the Lobene modified gingival index (GI) (Safiaghdam et al., 2018). In many studies included in this review, GI was nominated as a secondary outcome following plaque accumulation.

4.1. Mechanical or chemical action of miswak

When comparing chemically active and inactive miswak, both Sofrata et al. (2011) and Albabtain et al. (2018) included gingivitis outcome in their study. Both studies reported no significant differences between groups in GI reduction among regular dental patients and periodontitis patients (Albabtain et al., 2018; Sofrata et al., 2011).

4.2. Miswak chewing stick compared to conventional toothbrush

In terms of chewing stick comparison with toothbrush, Malik et al. (2014) and Saha et al. (2012) also included gingivitis outcome in their study. Malik et al. (2014) reported no significant differences in terms of GI reduction between miswak chewing stick and conventional toothbrush while Saha et al. (2012) reported significantly greater reduction of GI in miswak group compared to the conventional toothbrush among the Lucknow cohort.

4.3. Miswak mouthwash

In terms of miswak mouthwash, Sobouti et al. (2018) and Farhadian et al. (2015) also included gingivitis outcome in their study. Sobouti et al. (2018) reported significantly greater reduction of gingivitis by miswak mouthwash compared to chlorhexidine among their orthodontic patients while Farhadian et al. (2015) reported significantly greater reduction of gingivitis by miswak mouthwash in comparison to the electronic toothbrush intervention among patients with established diagnoses of gingivitis.

Rezaei et al. (2016) compared the gingival index reduction effect of miswak mouthwash and chlorhexidine mouthwash in intubated patients. The study was a double-blind, RCT involving 76 intubated patients in the intensive care unit. Mouthwash was administered for the patient for 4 days every 2 to 3 h daily. It was revealed that GI reduction was most significant with miswak mouthwash in comparison to the chlorhexidine mouthwash.

4.4. Miswak chewing gum

The study of miswak chewing gum by Amoian et al. (2010) also included gingivitis outcome. Use of miswak chewing gum demonstrated significantly greater gingivitis reduction in the presence or absence of teeth scaling.

5. Anti-cariogenic properties

Dental caries is the lesion on the enamel surface of the teeth, typically as a result of prolonged plaque accumulation. Several restorative techniques were available to restore damaged teeth such as glass ionomer cement and dental varnishes. Success of dental caries restoration is dependent on the prevention of further bacterial colonization to the caries site and enhancement of remineralization of the enamel surface. Fluoride, phosphate, and calcium are the three components of the hydroxyapatite crystal that form the teeth structure. Miswak has been reported to possess these three minerals, suggesting its potential to enhance dental caries restoration (Wassel and Sherief, 2019).

Moreover, in a prospective case-control observational study conducted by Mustafa et al. (2016) between miswak user or non-user, the prevalence of dental caries was found to be significantly greater in the non-user. The study was performed on 240 school students that were evaluated for their decayed-missing-filled (DMF) index over the period of two years. The lower prevalence of dental caries among miswak users suggest potential of miswak in dental caries prevention (Mustafa et al. 2016).

In a double-blind RCT of 60 teeth with deep carious lesions, Kabil et al. (2017) restored the teeth with glass ionomer cement (GIC) that was incorporated either with miswak or chlorhexidine. GIC incorporated with distilled water was used as a control. Restoration survival, defined by the shrinking of the defects after 3, 6, and 9 months were evaluated. The differences between groups were statistically significant at 6 and 9 months with the highest degree of restoration survival was found with the use of miswak cement, followed by chlorhexidine cement, and finally the control cement. This finding reinforced the hypothesis of remineralization effects of miswak following dental caries.

Wassel and Sherief, (2019) investigated the efficacy of teeth varnishes incorporated with chitosan, miswak, and propolis in enhancing remineralization of damaged enamel. By introducing enamel lesion following its immersion in demineralizing solution made from 0.05 M acetic acid, 2.2 mM NaH_2PO_4, and 2.2 mM $CaCl_2$, pH was adjusted to 4.4 by 1 M KOH) for 96 h, teeth varnishes incorporated with respective natural product were applied to the damaged enamel and its remineralization was measured. Chitosan and miswak demonstrated significantly higher remineralization compared to the control varnish, thus, revealing the potential of miswak in remineralization of damaged enamel.

6. Gingival wound healing properties

Following tooth extraction, the remaining socket could get infected from bacterial colonization and this will delay the healing process. Bacterial colonization prevention with antimicrobial agent would enhance the wound healing process. Miswak is a well-established antimicrobial agent of the oral cavity which may enhance the gingival wound healing process. Thus, its effect on the gingival wound healing process has been investigated in some of the studies included.

Al-Bayaty et al. (2018) fabricated a gel that could filled up the gingival pocket following tooth extraction. This gel was made of 2 ml of 4% pectin and 2 ml of hydroxypropylmethyl cellulose (HPMC). Two ml of either ethanol or aqueous extract of miswak were incorporated into the gel. The gel without miswak was used as a control. Socket filled with miswak gel, both aqueous and ethanol extract, demonstrated healing as early as one week. From the histological analysis, significantly more mature bone tissue was found in the miswak treated socket compared to the control.

Dorri et al. (2012) prepared their intervention in the form of mouthwashes. A 10% *persica* mouthwash was compared against 0.2% chlorhexidine mouthwash and tap water. The test mouthwashes were administered twice daily for 7 days before and after extraction of the first molar. Rats were sacrificed at day 14 of the experiment and wound healing indicators, namely extraction socket surface epithelialization, intertrabecular connective tissue development and maturation, and subperiosteal bone formation were observed. Although there was no statistically significant difference between the groups could be shown, there was a trend that favored the miswak mouthwash as compared to chlorhexidine mouthwash (30). Taken together, miswak has the potential to enhance wound healing in gingival socket following tooth extraction.

7. Whitening properties

Tooth discoloration can occur with food that contain tannins. Tannins allow substances to adhere to the tooth and promote discoloration. Tooth discoloration was often corrected with abrasive material such as hydrated silica, calcium carbonate, aluminium oxide, dehydrated calcium phosphate and perlite. Silica was also found in miswak and is thought to act as a natural abrasive agent.

Thus, the potential of miswak as a tooth whitening agent has been investigated in one study in this review.

Halib et al. (2017) investigated the tooth whitening potential of miswak with extracted human permanent premolar teeth stained with tea and coffee. Each stained tooth underwent simulated tooth brushing with frequency of 2 S/second and an applied force of 10 g for 28 min on each buccal and occlusal surface respectively. The whitening effect was evaluated using the VITAPAN® Classical Shade instrument. Miswak at different concentration, has no significantly different whitening effect compared to the commercial whitening toothpaste used as a positive control in this study. The study with combination of probiotic and miswak spray by Nasry et al. (2018) reported greater reduction in staining index with miswak compared to the control. However, the difference was not statistically significant.

8. Orthodontic chain maintenance

Orthodontic chains are used by orthodontists to apply retraction forces to the teeth for orthodontic correction intervention. One concern about orthodontic chains, particularly the one made with elastomeric materials, is the force degradation that reduces its effectiveness overtime. The force degradation may be due to the exposure to the intraoral environment.

Omidkhoda et al. (2015) investigated the effect that miswak incorporated mouthwash on the maintenance of force within the tested orthodontic chains. Orthodontic chains underwent 10 thermo cycles of 5 and 55^{0} C before they were immersed in different mouthwashes for 1 min daily. Mouthwashes used included 0.2% chlorhexidine, 13.65% miswak ethanolic extract, and 0.05% sodium fluoride mouthwash. The chains were stretched on two post and the force of the chains were measured at initial time point, after 24 h, 1, 2, 3 and 4 weeks. The force decay percentage of the orthodontic chains were the lowest when immersed in *persica* mouthwashes. The difference was significant when compared to other mouthwashes.

9. Biocompatibility with oral cells

Following the use of miswak on various application for promoting oral health, evaluating its cytotoxicity effect against cells of the oral cavity is paramount. Balto et al. (2014) evaluated the safety of miswak oral irrigation solution, prepared using three different extraction method, namely ethanol, hexane and ethylacetate. The cell viability of human gingival fibroblast exposed to low (0.5 mg/ml) and high (1 mg/ml) concentration of miswak extract was evaluated using three different cell viability tests. The three assays used were 3-(4,5-Dimethylthiazol-2-yl)- 2,5-diphenyltetrazolium bromide, a tetrazole (MTS), lactic dehydrogenase (LDH), and crystal violet (CV) cell viability assay.

For ethanol extract, cell viability was maintained following exposure at both low and high concentration. For hexane extract, cell viability was maintained following exposure at low concentration while a slight cytotoxicity was detected with the high concentration. For ethyl acetate, slight cytotoxicity was detected with low concentration and maximum cytotoxicity was found with the high concentration. Taken together, cytotoxicity towards human gingival fibroblast were absent with miswak extracted with ethanol and hexane at low concentration, revealing its potential to be used as a safe oral irrigation solution.

Albabtain et al. (2017) investigated the cytotoxicity effect of miswak essential oil and chemical constituents of miswak including benzyl isothiocyanate (BITC), benzyl aldehyde, and benzyl cyanide in both gingival fibroblasts and oral keratinocytes. BITC at the concentration of less than 1 μg/ml, miswak essential oil concentration of less than 1.4 μg/ml, benzyl aldehyde concentration of less than 0.8 μg/ml, and all concentration of benzyl cyanide demonstrated maintenance of the gingival fibroblast cell viability. In oral keratinocytes, viability was intact with 5 to 100 μg/ml BITC and miswak essential oil with higher concentration improves its viability.

Finally, Moezizadeh et al., (2015) investigated the cytotoxicity effect of different concentrations of miswak ethanol and aqueous extract on human dental pulp stem cell. For ethanol extract, cytotoxicity effect was found with the 1.43 to 5.75 mg/ml concentration at 24 and 48 h. For water extract, cytotoxicity was found with the 5.75 mg/ml concentration. Lower concentration of water extract, induces significant cell proliferation. Taken together, the cytotoxicity level of different constituents of *Salvadora persica* can be beneficial in planning for optimal dosing to achieve the best efficacy and safety.

10. Conclusion

In the present review, existing empirical evidences reporting the medicinal properties of *Salvadora persica* or miswak and its components, specifically towards promotion of good oral health were identified. Clinical effects of miswak include anti-plaque, anti-gingivitis, anti-cariogenic, promotion of gingival wound healing, whitening properties, orthodontic chain preservation, and biocompatibility with oral cells.

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References

Al-Ayed, M.S.Z., Asaad, A.M., Qureshi, M.A., Attia, H.G., AlMarrani, A.H., 2016. Antibacterial activity of *Salvadora persica* L. (Miswak) extracts against multidrug resistant bacterial clinical isolates. Evid. Based Complement Alternat. Med. https://doi.org/10.1155/2016/7083964.

Al-Bayaty, F.H., Zaidi, W.I., Abdullah, M.N., Emad, O., Al-Obaidi, M.M., 2018. Effect of Salvadora persica (Miswak) on alveolar bone healing after tooth extraction in rat. J. Int. Dent. Med. 11 (3), 770–777.

Al-Bayaty, F.H., Kamaruddin, A.A., Ismail, M., Abdulla, M.A., 2013. Formulation and evaluation of a new biodegradable periodontal chip containing thymoquinone in a chitosan base for the management of chronic periodontitis. J Nanomater 2013, 397308.

Al-Bayaty, F.H., Abdulla, M.A., Hassan, M.I.A., Roslan, S.N.B., Hussain, S.F. and Said, H. B.B., 2010, December. Effect of mouthwash extracted from Miswak (Salvadora Persica) on periodontal pathogenic bacteria an in-vitro study. In 2010 International Conference on Science and Social Research (CSSR 2010) (pp. 178-181). IEEE.

Al-Bayaty, F.H., Al-Koubaisi, A.H., Ali, N.A.W. and Abdulla, M.A., 2010b. Effect of mouth wash extracted from Salvadora persica (Miswak) on dental plaque formation: a clinical trial. J Med Plant Res, 4(14), 1446-54.

Albabtain, R., Ibrahim, L., Bhangra, S., Rosengren, A., Gustafsson, A., 2018. Chemical effects of chewing sticks made of Salvadora persica. Int. J. Dent. Hyg. 16 (4), 535–540. https://doi.org/10.1111/idh.12359.

Albabtain, R., Azeem, M., Wondimu, Z., Lindberg, T., Borg-Karlson, A.K., Gustafsson, A., 2017. Investigations of a possible chemical effect of Salvadora persica chewing sticks. Evid. Based Complement Alternat. Med. 2576548. https://doi.org/10.1155/2017/2576548.

Amoian, B., Moghadamnia, A.A., Barzi, S., Sheykholeslami, S., Rangiani, A., 2010. Salvadora persica extract chewing gum and gingival health: improvement of gingival and probe-bleeding index. Complement Ther. Clin. Pract. 16 (3), 121–123. https://doi.org/10.1016/j.ctcp.2009.11.002.

Aumeeruddy, M.Z., Zengin, G., Mahomoodally, M.F., 2018. A review of the traditional and modern uses of Salvadora persica L. (Miswak): Toothbrush

tree of Prophet Muhammad. J. Ethnopharmacol. 213, 409–444. https://doi.org/10.1016/j.jep.2017.11.030.
Azaripour, A., Mahmoodi, B., Habibi, E., Willershausen, I., Schmidtmann, I., Willershausen, B., 2017. Effectiveness of a miswak extract-containing toothpaste on gingival inflammation: a randomized clinical trial. Int. J. Dent. Hyg. 15 (3), 195–202. https://doi.org/10.1111/idh.12195.
Baeshen, H., Salahuddin, S., Dam, R., Zawawi, K.H., Birkhed, D., 2017. Comparison of fluoridated miswak and toothbrushing with fluoridated toothpaste on plaque removal and fluoride release. J. Contemp. Dent. Pract. 18 (4), 300–306. https://doi.org/10.5005/jp-journals-10024-2035.
Balto, H.A., Al-Manei, K.K., Bin-Mohareb, T.M., Shakoor, Z.A., Al-Hadlaq, S.M., 2014. Cytotoxic effect of Salvadora persica extracts on human gingival fibroblast cells. Saudi Med. J. 35 (8), 810–815.
Darmani, H., Al-Hiyasat, A.S., Elbetieha, A.M., Alkofahi, A., 2003. The effect of an extract of Salvadora persica (Meswak, chewing stick) on fertility of male and female mice. Phytomedicine. 10 (1), 62–65.
Dorri, M., Shahrabi, S., Navabazam, A., 2012. Comparing the effects of chlorhexidine and persica on alveolar bone healing following tooth extraction in rats, a randomised controlled trial. Clin. Oral Investig. 16 (1), 25–31. https://doi.org/10.1007/s00784-010-0474-y.
El Rabey, H.A., Almutairi, F.M., Al-Sieni, A.I., Al-Seeni, M.N., Al-Duais, M.A., Sakran, M.I., Elbakry, M.A., 2017. The antioxidant, antidiabetic and antilipidemic activity of Salvadora persica twig in alloxan diabetic male rats. Indian J. Biochem. Biophys. 54, 314–322 http://nopr.niscair.res.in/handle/123456789/43361.
Ezoddini-Ardakani, F., 2010. Efficacy of miswak (Salvadora persica) in preventing dental caries. Health. 2 (5), 499–503.
Farhadian, N., Bidgoli, M., Jafari, F., Mahmoudzadeh, M., Yaghobi, M., Miresmaeili, A., 2015. Comparison of electric toothbrush, persica and chlorhexidine mouthwashes on reduction of gingival enlargement in orthodontic patients: a randomised clinical trial. Oral Hlth. Prev. Dent. 13 (4), 301–307. https://doi.org/10.3290/j.ohpd.a33443.
Farook, F.F., Said, K.N., 2018. A review of the effectiveness of antiseptic mouth rinses for oral health. J. Oral Hyg. Health. 6, 246. https://doi.org/10.4172/2332-0702.1000246.
Gupta, P., Agarwal, N., Anup, N., Manujunath, B.C., Bhalla, A., 2012. Evaluating the anti-plaque efficacy of meswak (Salvadora persica) containing dentifrice: A triple blind controlled trial. J. Pharm. Bioallied Sci. 4 (4), 282. https://doi.org/10.4103/0975-7406.103238.
Gurudath, G., Vijayakumar, K.V., Arun, R., 2012. Oral hygiene practices: ancient historical review. J. Dent. Orofac. Res. 2 (4), 225–227. https://doi.org/10.5005/jp-journals-10026-1047.
Halib, N., Nuairy, N.B., Ramli, H., Ahmad, I., Othman, N.K., Salleh, S.M., Bakarudin, S. B., 2017. Preliminary assessment of Salvadora persica whitening effects on extracted stained teeth. J. Appl. Pharm. Sci. 7 (12), 121–125. https://doi.org/10.7324/JAPS.2017.71217.
Haque, M.M., Alsareii, S.A. A review of the therapeutic effects of using miswak (Salvadora Persica) on oral health. Saudi Med. J. 36(5), 530-543. http://dx.doi.org/10.15537/smj.2015.5.10785.
Huang, R., Li, M., Gregory, R.L., 2011. Bacterial interactions in dental biofilm. Virulence. 2 (5), 435–444. https://doi.org/10.1177/0022034509346811.
Kabil, N.S., Badran, A.S., Wassel, M.O., 2017. Effect of the addition of chlorhexidine and miswak extract on the clinical performance and antibacterial properties of conventional glass ionomer: an in vivo study. Int. J. Paediatr. Dent. 27 (5), 380–387. https://doi.org/10.1111/ipd.12273.
Kassebaum, N.J., Smith, A.G., Bernabé, E., Fleming, T.D., Reynolds, A.E., Vos, T., Murray, C.J., Marcenes, W., GBD 2015 Oral Health Collaborators, 2017. Global, regional, and national prevalence, incidence, and disability-adjusted life years for oral conditions for 195 countries, 1990–2015: a systematic analysis for the global burden of diseases, injuries, and risk factors. J. Dent. Res. 96(4), 380-387. http://dx.doi.org/10.1177/0022034517693566.
Khatak, M., Khatak, S., Siddqui, A.A., Vasudeva, N., Aggarwal, A., Aggarwal, P., 2010. Salvadora persica. Pharmacogn. Rev. 4 (8), 209–214. https://doi.org/10.4103/0973-7847.70920.
Kisely, S., Baghaie, H., Lalloo, R., Siskind, D., Johnson, N.W., 2015. A systematic review and meta-analysis of the association between poor oral health and severe mental illness. Psychosom. Med. 77 (1), 83–92. https://doi.org/10.1097/PSY.0000000000000135.
Kiswanjaya, B., Boel, T., Priminiarti, M., Iskandar, H.H., 2017. The relationship between oral health condition and systemic disease in healthy Indonesian population. J. Int. Dent. Med. 10, 465–469.
Lebda, M.A., El-Far, A.H., Noreldin, A.E., Elewa, Y.H., Al Jaouni, S.K., Mousa, S.A., 2018. Protective effects of miswak (Salvadora persica) against experimentally induced gastric ulcers in rats. Oxid. Med. Cell Longev. 2018, 6703296. https://doi.org/10.1155/2018/6703296.
Malik, A.S., Shaukat, M.S., Qureshi, A.A., Abdur, R., 2014. Comparative effectiveness of chewing stick and toothbrush: A randomized clinical trial. North Am. J. Med. Sci. 6 (7), 333–337. https://doi.org/10.4103/1947-2714.136916.
Mammad, Z., Hsaine, S., Djassinra, T., Ounine, K., 2018. The antibacterial and antioxidant effect of Salvadora persica on antibiotic resistant strains. Am. J. Plant Sci. 9 (7), 1478–1485. https://doi.org/10.4236/ajps.2018.97108.
Marion, J., Pavan, K., Arruda, M.E., Nakashima, L., Morais, C.A., 2013. Chlorhexidine and its applications in endodontics: a literature review. Dental Press Endod. 3 (3), 36–54.
Monforte, M.T., Trovato, A., Rossitto, A., Forestieri, A.M., d'Aquino, A., Miceli, N., Galati, E.M., 2002. Anticonvulsant and sedative effects of Salvadora persica L. stem extracts. Phytother. Res. 16 (4), 395–397. https://doi.org/10.1002/ptr.977.
Mustafa, M., Al Jeaidi, Z., Al Aajam, W.H., Dafaalla, M.K., 2016. Study of caries prevalence among miswak and non-miswak users: a prospective study. J. Contemp. Dent. Pract. 17 (11), 926–929.
Nakamura, M., Ojima, T., Nakade, M., Ohtsuka, R., Yamamoto, T., Suzuki, K., Kondo, K., 2016. Poor oral health and diet in relation to weight loss, stable underweight, and obesity in community-dwelling older adults: a cross-sectional study from the JAGES 2010 project. J. Epidemiol. 26 (6), 322–329. https://doi.org/10.2188/jea.JE20150144.
Nasry, S., Elgamily, H., El-Refai, I., Mehanna, N., 2018. The clinical efficacy of a probiotic miswak oral spray in patients with gingivitis. J. Int. Dent. Med. 11 (2), 433–440.
Niazi, F.H., Kamran, M.A., Naseem, M., Al Shahrani, I., Fraz, T.R., Hosein, M., 2018. Anti-plaque efficacy of herbal mouthwashes compared to synthetic mouthwashes in patients undergoing orthodontic treatment: a randomized controlled trial. Oral Hlth. Prev. Dent. 16 (5), 409–416. https://doi.org/10.3290/j.ohpd.a40983.
Niazi, F., Naseem, M., Khurshid, Z., Zafar, M.S., Almas, K., 2016. Role of Salvadora persica chewing stick (miswak): A natural toothbrush for holistic oral health. Eur. J. Dent. 10 (2), 301–308. https://doi.org/10.4103/1305-7456.178297.
Omidkhoda, M., Rashed, R., Khodarahmi, N., 2015. Evaluation of the effects of three different mouthwashes on the force decay of orthodontic chains. Dental Res. J. 12 (4), 348–352. https://doi.org/10.4103/1735-3327.161453.
Owens, J., Sami, W., 2016. The role of the Qur'an and Sunnah in oral health. J. Religion Health. 55 (6), 1954–1967. https://doi.org/10.1007/s10943-015-0095-5.
Pribadi, E.S., Rihansyah, H.P., Darusman, H.S., 2014. *In vitro* growth inhibition of Candida albicans caused by antifungal properties of miswak *(Salvadora persica* Linn.) ethanolic extract and commercial mouthwash. J. Oral. Health Dent. Manag. 13 (4), 1048–1051.
Qureshi, A.A., Qureshi, A.A., Dohipoide, A., Jamadar, N.N., 2016. Effects of Miswak-Salvadora persica on oral health. Al Ameen J. Med. Sci. 9 (4), 215–218.
Rezaei, S., Rezaei, K., Mahboubi, M., Jarahzadeh, M.H., Momeni, E., Bagherinasab, M., Targhi, M.G., Memarzadeh, M.R., 2016. Comparison the efficacy of herbal mouthwash with chlorhexidine on gingival index of intubated patients in Intensive Care Unit. J. Indian Soc. Periodontol. 20 (4), 404–408. https://doi.org/10.4103/0972-124X.194269.
Safiaghdam, H., Oveissi, V., Bahramsoltani, R., Farzaei, M.H., Rahimi, R., Medicinal plants for gingivitis: a review of clinical trials. Iran. J. Basic Med. Sci. 21(10), 978-991. http://dx.doi.org/10.22038/IJBMS.2018.31997.7690.
Saha, S., Mohammad, S., Saha, S., Samadi, F., 2012. Efficiency of traditional chewing stick (miswak) as an oral hygiene aid among Muslim school children in Lucknow: A cross-sectional study. J. Oral Biol. Craniofac. Res. 2 (3), 176–180. https://doi.org/10.1016/j.jobcr.2012.10.009.
Shiraishi, A., Yoshimura, Y., Wakabayashi, H., Tsuji, Y., 2018. Prevalence of stroke-related sarcopenia and its association with poor oral status in post-acute stroke patients: implications for oral sarcopenia. Clin. Nutr. 37 (1), 204–207. https://doi.org/10.1016/j.clnu.2016.12.002.
Sobouti, F., Rakhshan, V., Heydari, M., Keikavusi, S., Dadgar, S., Shariati, M., 2018. Effects of fixed orthodontic treatment and two new mouth rinses on gingival health: A prospective cohort followed by a single-blind placebo-controlled randomized clinical trial. Int. Orthod. 16 (1), 12–30. https://doi.org/10.1016/j.ortho.2018.01.027.
Sofrata, A., Brito, F., Al-Otaibi, M., Gustafsson, A., 2011. Short term clinical effect of active and inactive Salvadora persica miswak on dental plaque and gingivitis. J. Ethnopharmacol. 137 (3), 1130–1134. https://doi.org/10.1016/j.jep.2011.07.034.
Tabatabaei, F.S., Moezizadeh, M., Javand, F., 2015. Effects of extracts of Salvadora persica on proliferation and viability of human dental pulp stem cells. J. Conserv. Dent. 18(4), 315-320. http://dx.doi.org/10.4103/0972-0707.159740..
Tartaglia, G.M., Kumar, S., Fornari, C.D., Corti, E., Connelly, S.T., 2017. Mouthwashes in the 21st century: a narrative review about active molecules and effectiveness on the periodontal outcomes. Expert Opin. Drug Deliv. 14 (8), 973–982. https://doi.org/10.1080/17425247.2017.1260118.
Van Leeuwen, M.P., Rosema, N.A., Versteeg, P.A., Slot, D.E., Hennequin-Hoenderdos, N.L., Van der Weijden, G.A., 2017. Effectiveness of various interventions on maintenance of gingival health during 1 year–a randomized clinical trial. Int. J. Dent. Hyg. 15 (4), e16–e27. https://doi.org/10.1111/idh.12213.
Varma, S.R., Sherif, H., Serafi, A., Fanas, S.A., Desai, V., Abuhijleh, E., Al Radaidah, A., 2018. The antiplaque efficacy of two herbal-based toothpastes: A clinical intervention. J. Int. Soc. Prev. Community Dent. 8 (1), 21–27. https://doi.org/10.4103/jispcd.JISPCD_411_17.
Wassel MO, Sherief DI. Ion release and enamel remineralizing potential of miswak, propolis and chitosan nano-particles based dental varnishes. Pediatr. Dent. J. 29 (1), 1-10. http://dx.doi.org/10.1016/j.pdj.2018.12.004