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The effectiveness of miswak (*Salvadora persica* L. and *Azadirachta indica* A. Juss.) practices in reducing plaque and gingivitis among adults: A systematic review and meta-analysis

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ABSTRACT

Ethnopharmacological relevance: *Salvadora persica* L. and *Azadirachtaindica* A.Juss. are listed within the most common sources of miswak or chewing stick that widely used among Western Asia and Muslim populations worldwide. Miswak use in conjunction with toothbrush (adjunctive) has become apparent among the adults. Furthermore, miswak has been reported to have mechanical and pharmacological activities, and benefits to the oral health, by many studies.

Aim of the study: To assess the effectiveness of miswak in maintaining periodontal health among adults.

Materials and methods: We searched for randomised controlled trials (RCTs) investigating the effect of miswak published in PubMed, EBSCOHOST (Dentistry & Oral Sciences), SCOPUS, and Cochrane Database for Systematic Review (CDSR) from inception to May 08, 2022. The primary outcomes of interest were changes in the periodontal health measured with plaque and gingivitis scores as well as subgingival bacteria load. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach while the estimates of effect were pooled using a random-effects model.

Results: Ten eligible articles were identified, of which 9 could be analysed quantitatively. The remaining report was included as part of the qualitative analysis. The meta-analysis showed that miswak was comparable with the toothbrush in reducing the mean plaque score (p= 0.08, SMD: 0.39, and 95% CI: −0.05 to 0.83) and mean gingivitis score (p= 0.37, SMD: 0.13, and 95% CI: −0.16 to 0.43). Even higher certainty of evidence for the effect of miswak on mean plaque reduction on labial surface of anterior teeth. However, the adjunctive effect of miswak was significantly more superior for reducing plaque (p= 0.01, SMD: 0.68, and 95% CI: 0.14 to 1.22) and gingivitis score (p= 0.04, SMD: 0.66, and 95% CI: 0.03 to 1.29).

Conclusions: Miswak effectively reduced plaque and gingivitis scores to a level comparable to toothbrush when used exclusively. Adjunctive miswak use was particularly effective in improving periodontal health. However, the included studies inadequately reported on the method of toothbrushing using miswak and the frequency of miswak use. Therefore, further clinical studies are recommended to explore on the advantages and proper method of miswak practice for optima outcome and safety.

1. Introduction

Mechanical plaque removal aims to disrupt and remove any bacteria plaque on the tooth surfaces. Regular mechanical plaque removal by health professionals ensures oral hygiene by local elimination of plaque, as well as supragingival and subgingival calculus. However, daily toothbrushing and other mechanical procedures are still considered the

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Abbreviation

RCTs	Randomised controlled trials
CDSR	Cochrane Database for Systematic Review
GRADE	the Grading of Recommendations, Assessment, Development, and Evaluations
SMD	Standard mean difference
SD	Standard deviation
CI	Confidence interval
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analyses
US	United State
RoB	Risk of bias
RevMan	Review manager
Sp	*Salvadora persica*
TB	Toothbrush
NA	Not applicable
PCR	Polymerase chain reaction
DNA	Deoxyribonucleic acid
WHO	World Health Organisation

most reliable method in controlling plaque, provided that it is performed in a sufficiently thorough manner (Löe, 2000). Moreover, these daily procedures also facilitate long-term plaque control and prevent periodontal disease. The toothbrush is the most common mechanical plaque control device used at home. Ideally, it should be used in combination with fluoridated toothpaste (Kementerian Kesihatan Malaysia, 2019; Mouth Healthy. Brushing Your Teeth, 2021). Despite so, the selection of oral hygiene devices can be associated with personal preference, affordability, and professional recommendations (Laing et al., 2008). As compared to the toothbrush, miswak or chewing stick is considered as a low-cost oral hygiene device that also works effectively in controlling dental plaque and it is often the preferred option among low-income populations (Slots, 2012). Due to its scientific benefits, the application of miswak either individually or as an adjunctive to the toothbrush among various religious and cultural groups of the population has become increasingly popular in recent years (Al-Hammadi et al., 2018; Baharin et al., 2016; Dogar, 2019; Honkala and Al-Ansari, 2005; Idris and Awad, 2016).

Miswak is obtained from several different plant species such as lime tree (*Citrus medica* L.), orange tree citrus (*Citrus sinensis* (L) Osbeck) and Neem (*Azadirachta indica* A.Juss.). Although Neem is native in India, it is also found in Indonesia, Malaysia, Australia, Sri Lanka, Burma, Pakistan and Africa (Niazi et al., 2016). However, miswak is most commonly harvested from the root, stem, and twig of the Arak tree (*Salvadora persica* L.) (Almas and Al-Lafi, 1995; Al Sadhan and Almas, 1999). The Arak tree is widely distributed in the dry region of Western Asia, Africa, South America, and Asia (Khatak et al., 2010; Wu et al., 2001). Due to the rich content of phloem, the stem and root of the Arak tree become spongy in texture and thus chewable after soaking in water (Wu et al., 2001). Furthermore, the bark can be easily removed when the distal part of the stick is crushed between teeth. As a result, it becomes a brush-like instrument that can be readily used for toothbrushing (Ramli et al., 2016).

In the developing countries, many rural populations use miswak as an oral hygiene tool because of its low price and easy availability (Carneiro et al., 2011; Cheema et al., 2017; Diouf et al., 2013; Ekowmenhenhen et al., 2019; Kalita et al., 2016; Odongo et al., 2011; Quadri et al., 2018). Apart from that, the preference for miswak can also be linked to religious belief (Agbor and Azodo, 2013; Al-Hammadi et al., 2018; Alayan et al., 2017). The small-head feature of miswak provides better control during toothbrushing besides making it easier to reach the posteriorly located teeth (Odongo et al., 2011). Some advocated the positive effects of miswak on oral health such as the lower likelihood of halitosis and oral health problems, and thus, requiring fewer visits to dentists (Agbor and Azodo, 2013). In a 2017 study, all the users of miswak reported oral health improvements and claimed that miswak was more effective in cleaning teeth than a conventional toothbrush (Alayan et al., 2017). In another study, the majority of those who used miswak also reported feeling fresher and having whiter teeth (Al-Hammadi et al., 2018).

In addition, miswak has been shown to contain various bioactive components that promote oral health. For example, silica in miswak is responsible for stain and plaque removal whereas sodium bicarbonate has a mild abrasive effect. Essential oils are linked with antibacterial effects (Haque and Alsareii, 2015; Sawarkar et al., 2020) in which *S. persica* extract was found to inhibit *Prevotella intermedia* and *Peptostreptococcus* spp (Siddeeqh et al., 2016). Besides, benzyl isothiocyanate is a major compound in the essential oil of *S. persica* extract that can effectively destroy Gram-negative bacteria such as *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* that are associated with periodontal disease (Sofrata et al., 2011).

Nevertheless, despite the clinical benefits mentioned, miswak use have been associated with some drawbacks such as clinical attachment loss (Eid et al., 1990, 1991; Darout et al., 2000) and gingival recession (Karia and Kelleher, 2014; Saleh et al., 2017). Improper use of miswak over a long period can result in a risk of oral tissues injury (Ramli et al., 2021). To date, there is a lack of comprehensive evidence-based literature to guide a safe and effective accepted practice that can subsequently be used as oral hygiene instructions for miswak users. Therefore, this systematic review and meta-analysis aimed to critically appraise the available clinical trials of miswak practice on periodontal health. It also aimed to quantify the effectiveness of miswak among adults in terms of plaque and gingivitis score reduction in comparison to the use of the toothbrush.

2. Material and methods

2.1. The review protocol and registration

The protocol for this study was designed according to the guidelines of the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) 2020 (Page et al., 2021a, 2021b). This systematic review was registered on PROSPERO (http://www.crd.york.ac.uk/prospero/) with registration number CRD42021231817.

2.2. Formulated question

The research question was formulated based on the PICO (Population, Intervention, Comparison, and Outcome) strategy (Santos et al., 2007): Is the use of miswak (I) effective in reducing plaque and gingivitis (O) in adults (P) when compared with a toothbrush (C)?

2.3. The systematic searching strategy

The keywords and synonyms for miswak and periodontal health were identified from a list of keywords from previous articles during a scoping search and suggestions from the experts. The search strategy included the keywords using the Boolean operators 'OR' and 'AND', i.e. miswak OR meswak OR siwak OR miswaak OR misswak OR miswaki OR mswaki OR "natural toothbrush" OR "salvadora persica" OR "chewing stick" OR "toothbrush stick" OR "toothbrush tree" AND periodontal OR periodontium OR periodontics OR "periodontal health" OR periodontitis OR "periodontal disease" OR gingivitis OR "dental health" OR "oral health" OR "oral hygiene" OR "dental hygiene" OR "oral disease". The search was performed on electronic databases of PubMed, EBSCOHOST (Dentistry & Oral Sciences), SCOPUS, and Cochrane Database for Systematic Review (CDSR) by using the keywords stated within the title and abstract and keywords from MeSH terms up to May 08, 2022. The

detailed search strategy is described in supplementary materials.

Other additional approaches were used to identify further studies. The reference lists of the included articles were manually screened to identify any eligible studies that might have been missed during the electronic searches. The reviewers also undertook forward citation tracking (using Google Scholar) to identify other eligible studies. Besides, the included studies of recent systematic reviews were also screened. The reviewers also searched in trial registers (US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) to identify registered trials related to the topic. Lastly, corresponding authors of the ten included studies were contacted via email to acquire certain information that was missing in the article.

2.4. Eligibility criteria

The inclusion and exclusion criteria were determined a *priori* and are as follows: 1) full text article written in English and published in academic journals; 2) study designed as randomised controlled trials (RCTs); 3) participants included adults; 4) miswak stick regarded as intervention; 5) toothbrush application as a comparator; 6) the primary outcome included clinical effects on periodontal health such as plaque score and gingival status; 7) the secondary outcomes included the practices of oral hygiene and technique of toothbrushing. Studies were excluded, when 1) recruited participants with orthodontic appliances; 2) used other than miswak stick as intervention; and 3) cellular effect regarded as outcome assessment.

2.5. Screening process

In the first stage, two reviewer authors (HR and TNMD) searched the databases independently. They also categorised each study by grading as eligible/not eligible/might be eligible, based on the titles and abstracts. Subsequently, the full-text article was retrieved and reviewed to shortlist the eligible studies to be included in this review. Any uncertainty and disagreement among reviewers were resolved via consensus in the presence of a third reviewer (SMS).

2.6. Data extraction

The data were extracted by a single author (HR). Second author (TNMD) examined the data independently to ensure accuracy and appropriateness. Any discrepancy was resolved by the third author (SMS). The following data were extracted using a standardised data extraction form: first author, publication year, study design and setting, sample size, description of participant, the intervention and comparison (type of tool, method of toothbrushing, frequency, time, duration of toothbrushing), clinical measurements (plaque indices and gingivitis indices system, plaque stained and microbial assessment), assessment interval and wash-out period.

2.7. Statistical analysis

A meta-analysis was carried out to combine the statistical results of the studies included in this review using the Review Manager software (RevMan 5.4.1). The studies that assessed the effects of miswak on periodontal health were deemed to be highly variable due to the differences in the diagnosis of periodontal disease, participants' characteristics, study methodology, and the intervention or comparison used. Assuming the studies being combined in the meta-analysis were heterogeneous, a random-effect model was used to assess the effect size. Prior to a statistical test for assessing homogeneity was performed to determine whether the results of the different studies could be combined. The extent and impact of between-study heterogeneity or inconsistency coefficient were assessed by obtaining the I^2 statistic from the tau-squared test. Any value of less than 25% is considered as having a strong homogeneity, 50%–75% indicates that the results of such studies are of moderate heterogeneity, whereas a value of more than 75% shows that the studies have high heterogeneity (Higgins et al., 2003). In addition, the 95% CIs (uncertainty intervals) of the tau-squared and I-squared values were also calculated to reflect the confidence of these metrics.

The mean and standard deviation were obtained directly from the paper or requested from the author if the relevant information was not documented in the published paper. Any continuous data presented in different statistical units such as median and interquartile range were recalculated as mean and standard deviation using the excel formula proposed by Wan et al. (2014). The standard deviation and sample size were used to determine the weight of each study and they were included in the meta-analysis of every effect estimate. The mean difference obtained by subtracting post-intervention from the pre-intervention or baseline measurements and standard deviation (SD) of mean difference was calculated based on 95% CI (Higgins et al., 2022). The standard mean difference (SMD) with the 95% CI for continuous data measurement was used to estimate the accuracy and precision. The sensitivity analyses were performed by omitting each study at a time to assess the consistency and stability of the pooled results. Subgroup analysis was performed depending on the characteristics of intervention/comparison such as frequency of toothbrushing (two times and more than two times per day) and type of participants (healthy periodontium and gingivitis patients).

2.8. Risk of bias assessment

The risk of bias for all included articles was assessed using the Cochrane risk of bias tool for RCT (RoB-2) (Sterne et al., 2019; Tawfik et al., 2019). RoB-2 measures three main items, namely methodology, outcome, and result that aim at addressing the five domains of the randomisation process, deviation from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. The characteristics of each study were documented in the standard forms either for parallel or crossover trials before completing the risk of bias assessment. The evaluation of each included study was conducted by two reviewer authors (HR and TNMD) independently. They recorded the supporting information and justifications for judgements of risk of bias for each domain (low/high/some concerns). Any discrepancies in the judgements of risk of bias were resolved in the consensus meeting, with the third author (SMS) acting as mediator. The overall 'risk of bias' judgement (low/some concerns/high) for each specific outcome was derived based on the guidance in RoB 2.0. The details of this evaluation and comments can be found in supplementary materials (excel RoB-2).

2.9. Assessment of the quality of evidence

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach is commonly applied in rating the certainty of evidence in systematic reviews (Granholm et al., 2019; Handbook, 2013). The assessment is made on each outcome measure using the pooled estimate effect of included studies. Each outcome is assessed based on the five domains, namely risk of bias, inconsistency, indirectness, imprecision, and publication bias (Guyatt et al., 2011, 2011a, 2011b, 2011c, 2011d). A summary of findings can be developed in a table format using the GRADEpro GDTsoftware (available at http://www.gradepro.org). In this review, the table was generated to outline the summary effect sizes and certainty of evidence ratings on the effects of miswak or adjunctive miswak on the reduction of plaque and gingivitis (Schünemann et al., 2021) (refer to the supplementary materials).

3. Results

3.1. Study selection

The search strategy retrieved a total of 201 potentially eligible articles published between January 1, 1978 and May 08, 2022 from the four databases of PubMed (26), EBSCOHOST-Dentistry & Oral Sciences (85), SCOPUS (7), and Cochrane Database for Systematic Review, CDSR (72). A further 11 studies were detected among the registered clinical trials at clinicaltrials.gov. From these, 47 duplicates were excluded and another four were excluded for other reasons. The remaining 150 articles were evaluated further. Subsequently, 132 articles were eliminated after the assessment of titles and abstracts. The full texts of the remaining 18 articles were assessed based on the inclusion criteria. Eleven articles were excluded for the following reasons: i) cross-sectional, observational, and analytical studies (n=5), ii) incomplete study (n=5), and iii) participants' age was not stated (n=1). Therefore, only seven articles were included in the systematic review.

Further search from the reference list of the eligible articles identified three more potential articles. One of the referenced articles was not in circulation while the remaining two articles went through a full-text review but only one fulfilled the inclusion criteria. Lastly, the online search identified two recently published articles in which one was eligible for inclusion. Furthermore, another study from a recent systematic review (Adam et al., 2021) was deemed to be qualified to be included. Thus, a total of ten articles were included in the final analysis. The included studies and reports from the systematic searching are summarised in Fig. 1.

3.2. Summary for characteristics of included studies

The characteristics of the included articles are summarised in Table 1. All ten articles were RCTs conducted among adults. The study designs of the RCTs were cross-over (n=5), parallel (n=4), and split-mouth (n=1) respectively. The participants in all the RCTs ranged between 18 and 50 years old. The majority of the studies recruited participants with healthy periodontium, except for three studies that investigated the effects of miswak on those diagnosed with gingivitis (Rifaey et al., 2021; Patel et al., 2012; Dizaye and Othman, 2020). All the included studies compared the effectiveness of two oral hygiene tools on periodontal health based on the measured outcomes of plaque score, plaque distribution, gingivitis score, and bacteria load. The study durations were between one to two months with wash-out period of one week across all the cross-over studies. However, the assessment intervals varied between studies. For example, a parallel design RCT by Patel et al. (2012) reassessed the effects at four time points whereas another split-mouth design study assessed the outcomes after 30, 60, and 120 s of intervention (Batwa et al., 2006).

In the included studies, periodontal health assessment was performed using different types of plaque and gingivitis scores as outcome measures (Table 1). Among the numerous methods employed to determine the plaque score, Turesky modified Quegley-Hein (1970) and Turesky Quegley-Hein were the most used. Meanwhile, the gingivitis index that was most often used in the included studies was the one proposed by Loe and Silness (Löe, 1967). Besides these parameters, three studies (Al-Otaibi et al., 2003; Patel et al., 2012; Batwa et al., 2006) documented stained plaque distribution on the labial or buccal surface

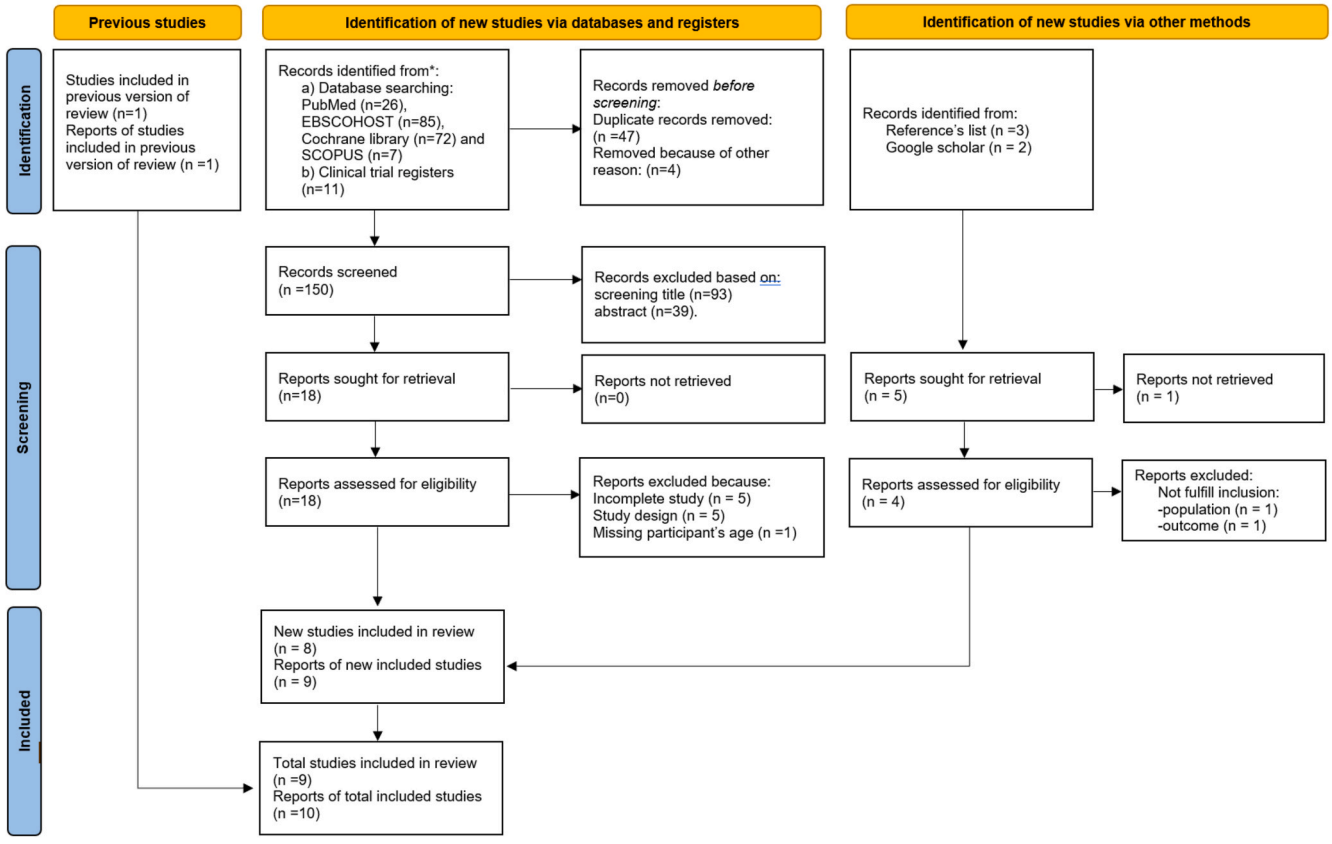

Fig. 1. Flow diagram of systematic literature search.

Table 1
The characteristics of included studies.

Reference	Year	Study design	Sample size	Participant	Type of siwak	Type of toothbrush (TB)	Intervention				Comparison	Clinical parameters			Subgingival plaque sample	Duration of study and assessment interval	Wash-out period
				Range age/ mean age (years old)			Siwak only	Siwak with toothbrush	Sp mouthwash and TB	Chlorhexidine mouthwash and TB	Control	Plaque index	Gingival index	Plaque stained (Digital photograph)	Bacterial count		
Al-Otaibi et al.	2003	Single blind (examiner), randomized controlled trial. Cross over.	15	21–36 years old. Healthy periodontium	*Salvadora persica*	Regular and straight handle	✓	NA	NA	NA	Manual TB without toothpaste	Turesky modified Quegley-Hein	Loe & Silness	labial surface upper incisors	No	3 weeks	1 week
Al-Otaibi et al.	2004	Single blind (examiner), randomized controlled trial. Cross over.	15	21–36 years old. Healthy periodontium	*Salvadora persica*	Regular and straight handle	✓	NA	NA	NA	Manual TB without toothpaste	Turesky modified Quegley-Hein	Loe & Silness	No	Yes (Bacteria subgingival plaque count: Checkerboard DNA-DNA hybridisation)	3 weeks	1 week
Baeshen et al.	2017	Single blind (examiner), randomized controlled trial. Cross over.	14	Mean age 28.8 ± 4.7 yrs. Healthy periodontium	*Salvadora persica*	Regular, straight handle and soft bristle	√ (Flouridated or non-flouridated)	NA	NA	NA	Manual TB with toothpaste (Flouridated or non-flouridated)	O' Leary 1972	No	No	No	1 week	1 week
Rifaey et al.	2020	Single blind (examiner), randomized controlled trial. Cross over	20	Mean age of 24 ±3.0 years. Mild or moderate gingivitis	Not reported	Not reported	NA	✓	NA	NA	Manual TB with toothpaste	Loe & Silness	Loe & Silness	No	Yes (Bacteria supragingival plaque count: Quantitative real time PCR)	2 weeks	1 week
Patel et al.	2012	Single-blind (clinical investigator), randomized controlled trial. Parallel.	30	18–35 years old. Mild to moderate gingivitis	*Salvadora persica*	Regular, straight handle and medium/ soft bristle	✓	✓	NA	NA	Manual TB without toothpaste	Turesky modified Quigley-Hein	Loe & Silness	labial surface of upper central incisor	No	2,4,6,8 weeks	NA
Malik et al.	2014	Double blinded (examiner and trial statistician), randomized controlled trial. Parallel.	50	18–22 years old (mean SD: 20 ± 0.66 years). Healthy periodontium	Azadirachta indica	Regular and soft bristle	✓	NA	NA	NA	Manual TB with toothpaste	Turesky Quigley Hein (1962)	Loe and Silness (1962)	No	No	4 wks (1 month)	NA
Batwa et al.	2006	Single blinded, randomised controlled trial. Split mouth design.	15	20–50 years (mean SD: 35.2±8.6). Healthy periodontium	*Salvadora persica*	Regular and straight handle	✓	NA	NA	NA	Manual TB without toothpaste	No	No	plaque on buccal surface of canines, premolars, first and second molars of maxillary left and right quadrants.	No	within same day	NA

(*continued on next page*)

Table 1 (*continued*)

Reference	Year	Study design	Sample size	Participant	Type of siwak	Type of toothbrush (TB)	Intervention				Comparison	Clinical parameters			Subgingival plaque sample	Duration of study and assessment interval	Wash-out period
				Range age/ mean age (years old)			Siwak only	Siwak with toothbrush	Sp mouthwash and TB	Chlorhexidine mouthwash and TB	Control	Plaque index	Gingival index	Plaque stained (Digital photograph)	Bacterial count		
Bhambal et al.	2011	Single blind (examiner), randomized controlled trial. Cross over.	30	18–25 years old. Healthy periodontium	Azadirachta indica	Regular	✓	NA	NA	NA	Manual TB without toothpaste	Turesky Quigley Hein (1962)	Loe and Silness (1964)	No	No	3 weeks	1 week
Dizaye et al.	2020	Randomised controlled trial. Parallel.	50	20–50 years old (mean SD: 33±11.1). Mild to moderate gingivitis	*Salvadora persica*	Regular	✓	✓	✓	✓	Manual TB with toothpaste	Plaque index created by Greene and Vermillion.	Gingival Index according to Löe and Silness.	No	No	4 weeks	NA
Riasat et al.	2021	Randomised controlled trial. Parallel.	80	18–45 years old (mean SD: 25.54±6.004). Healthy periodontium	*Salvadora persica*	Not reported	✓	NA	NA	NA	Manual TB with toothpaste	Turesky modified Quegley-Hein	No	No	No	4 weeks	NA

Abbreviation: Sp: *Salvadora persica*; NA: not applicable; TB: toothbrush.

of at least the anterior maxillary teeth using a digital photograph and computer software (UTH SCSA Image Tool [IT version 2]). Furthermore, another outcome measure, bleeding on probing (BOP) was recorded in one study (Rifaey et al., 2021). Al-Otaibi et al. (2004) reported quantitative analysis of subgingival plaque whereas Rifaey et al. (2021) reported the results of supragingival plaque analysis.

A standard toothbrush with a straight head, with or without toothpaste was applied as the control in all studies. As for the intervention, miswak from *Salvadora persica* L. species with a standard length of 15–20 cm and a diameter of 7–10 mm was applied. Two exceptions were Malik et al. (2014) that employed miswak with 20 mm in diameter and Bhambal et al. (2011) who used miswak 15–20 mm in diameter from the Neem tree (*Azadirachta Indica* A.Juss.).

Table 2 outlines the description of oral hygiene practice. The toothbrushing habit generally followed a standard practice of brushing twice per day for 2 min. However, variations were noted whereby, the toothbrush group in Malik et al. (2014) trial was instructed to use the Bass technique while Rifaey et al. (2021) used the Modified Bass technique. In marked contrast, most of the studies did not elaborate on the technique or method of miswak use. In terms of interval, miswak was applied at various frequencies ranging from two times per day to at least five times per day. In a study by Al-Otaibi et al. (2003, 2004), miswak was used before every prayer (at least five times per day). In Baeshen et al. (2017) and Malik et al. (2014), the duration of miswak practice lasted 5 min.

3.3. Meta-analysis result

3.3.1. Exclusive miswak use

3.3.1.1. The effect of miswak on mean plaque reduction. The results from RCTs that compared the mean difference in the plaque score between the use of miswak and toothbrush were pooled to estimate the effectiveness of miswak on plaque reduction. Fig. 2a shows that there was no significant difference in the plaque score reduction between miswak and toothbrush (p= 0.08, SMD: 0.39, and 95% CI: −0.05 to 0.83). Subgroups analysis of the pooled studies were conducted among participants who were gingivitis patients and healthy periodontium shows no significant different of the plaque score reduction of using miswak when compared to the toothbrush (Fig. 2b: p= 0.54, SMD: 0.31, and 95% CI: −0.68 to 1.30, Fig. 2c: p= 0.13, SMD: 0.41, and 95% CI: −0.12 to 0.94). Furthermore, subgroups analysis among studies practiced brush twice daily and brush more than 2 times per day also shows no significant difference (Fig. 2d: p= 0.06, SMD: 0.52, and 95% CI: −0.03 to 1.06, Fig. 2e: p= 0.89, SMD: 0.04, and 95% CI: −0.52 to 0.59).

3.3.1.2. The effect of miswak on mean plaque reduction on the labial surface of anterior teeth. The difference in the mean plaque score between miswak and toothbrush users as well as the efficacy of miswak in reducing the mean plaque score on the labial surface of anterior teeth were compared using the following meta-analysis (see Fig. 3). Photographic stained plaque surfaces were used as the plaque assessment method in the included studies. Fig. 3 shows no significant difference (p= 0.95, SMD: 0.02, and 95% CI: −0.57 to 0.60) in the mean plaque score reduction between miswak and toothbrush groups.

3.3.1.3. The effect of miswak on the reduction of mean gingivitis score. The effectiveness of miswak in reducing the mean gingivitis score was assessed in the following meta-analysis. Fig. 4 shows that there was no significant difference in the standard mean gingivitis score reduction (p= 0.37, SMD: 0.13, and 95% CI: −0.16 to 0.43) between miswak and toothbrush users.

3.3.2. 3.2 adjunctive miswak use

3.3.2.1. The effect of adjunctive miswak on mean plaque reduction. In addition, meta-analysis was also performed to determine the mean difference of plaque scores reduction between those who used toothbrushes alone and those who used a toothbrush with adjunctive miswak. The analysis also aimed to assess the efficacy of adjunctive miswak in

Table 2
The descriptions of oral hygiene practice.

No.	Reference	Year	Toothbrush				Miswak				
							Method		Practice		
			Brushing technique	Frequency	Time	Duration	Grasp technique	Brushing technique	Frequency	Time	Duration
1	Al-Otaibi et al.	2003	Not reported	2 times/day	Morning and evening before going to bed	Not reported	Not reported	Not reported	5 times/day	Before each prayer	Not reported
2	Al-Otaibi et al.	2004	Not reported	2 times/day	Morning and evening before going to bed	Not reported	Not reported	Not reported	5 times/day	Before each prayer	Not reported
3	Baeshen et al.	2017	Adopted technique by Sjogren et al. 1995	2 times/day	Morning and night	2 min	Not reported	Based on Almas & Al-Lafi 1997	2 times/day	Morning and night.	5 min
4	Rifaey et al.	2020	Modified Bass technique	2 times/day	Not reported	Not reported	Not reported	Not reported	2 times/day	Not reported	Not reported
5	Patel et al.	2012	Not reported	3 times/day	Morning, mid-day, and evening	Not reported	Not reported	Not reported	3 times/day	Morning, mid-day, and evening	Not reported
6	Malik et al.	2014	Bass method	2 times/day	After breakfast and before going to bed	2 min	Not reported	Not reported	2 times/day	After breakfast and before going to bed	2–5 min.
7	Batwa et al.	2006	Not reported	At 30, 60 and 120 s	Not reported	Not reported	Not reported	Not reported	1, 2 and 3 times per day	Not reported	Not reported
8	Bhambal et al.	2011	Not reported	2 times/day	Morning and evening	Not reported	Not reported	Not reported	2 times/day	Morning and evening.	Not reported
9	Dizaye et al.	2020	Not reported	2 times/day	Not reported	At least 2 min	Not reported	Not reported	2 times/day	Not reported	At least 2 min
10	Riasat et al.	2021	Not reported	2 times/day	After breakfast and dinner	Not reported	Not reported	Not reported	2 times/day	After breakfast and dinner	Not reported

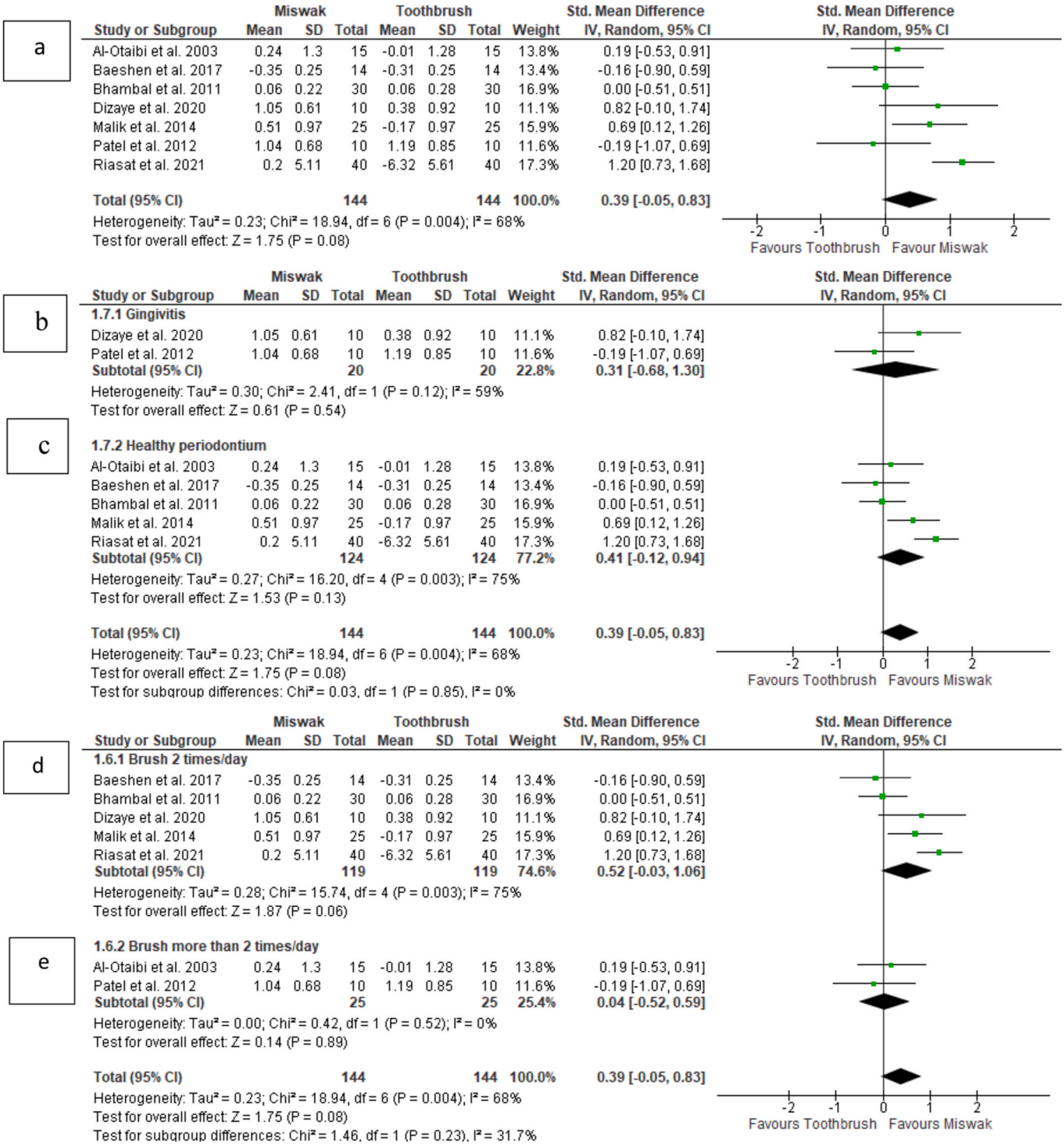

Fig. 2. Fig. 2a:Forest plot for meta-analysis of mean plaque score between miswak and toothbrush Fig. 2b & 2c: Forest plot for meta-analysis of mean plaque score between miswak and toothbrush for subgroup gingivitis patients and healthy periodontium Fig. 2d & 2e: Forest plot for meta-analysis of mean plaque score between miswak and toothbrush for subgroup brush twice daily and more than 2 times/day.

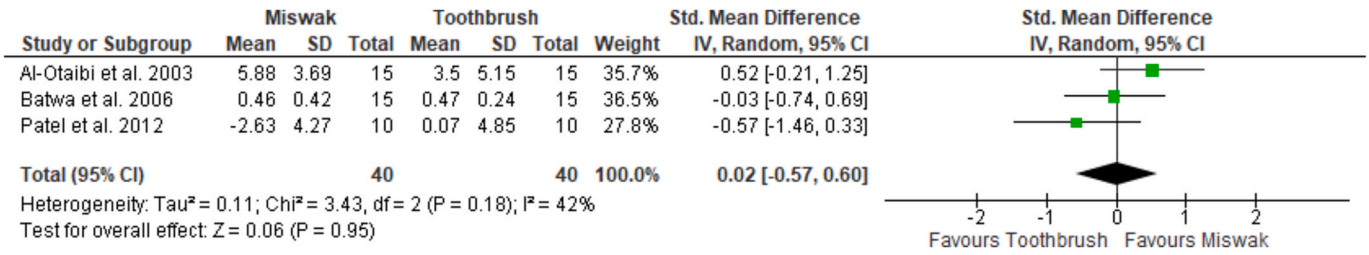

Fig. 3. Forest plot for meta-analysis of mean plaque scores on the labial surface of the maxillary anterior teeth between the miswak and toothbrush users.

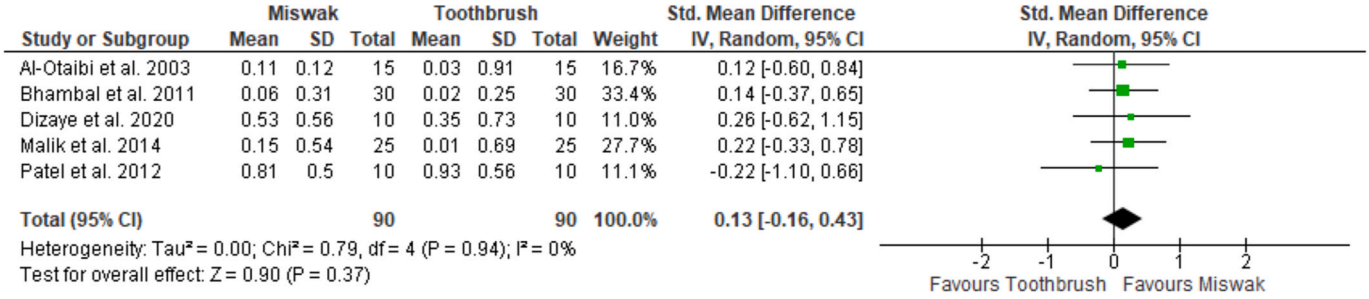

Fig. 4. Forest plot for meta-analysis of mean gingivitis scores between the miswak and toothbrush users.

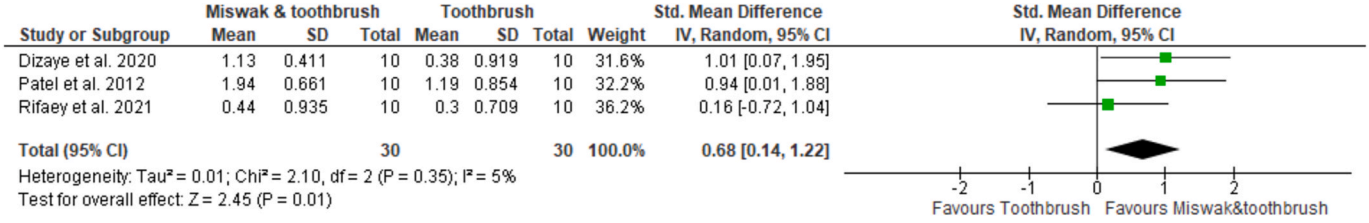

Fig. 5. Forest plot for meta-analysis of mean plaque scores between miswak with toothbrush and toothbrush only.

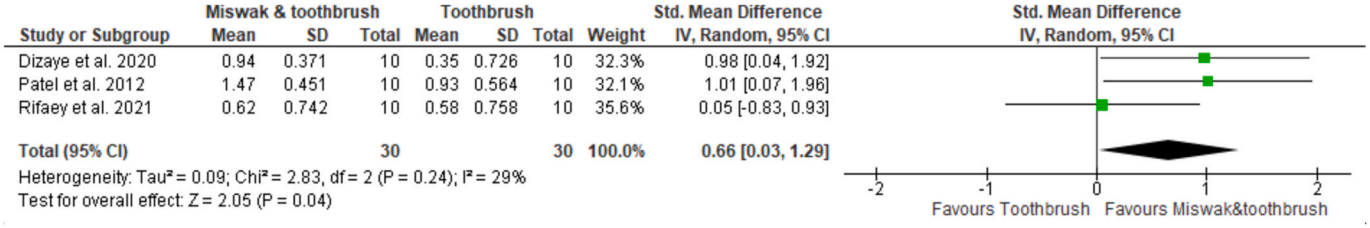

Fig. 6. Forest plot for meta-analysis of mean gingivitis scores between the usage of adjunctive miswak and only toothbrush.

reducing the mean plaque score in gingivitis patients. Fig. 5 shows that adjunctive application of miswak led to a significantly higher mean plaque score reduction compared to toothbrush usage alone (p= 0.01, SMD: 0.68, and 95% CI: 0.14 to 1.22).

3.3.2.2. The effect of adjunctive miswak on mean gingivitis score reduction. The following meta-analysis compared the difference in the mean gingivitis scores between adjunctive miswak and toothbrush users. It also assessed the effectiveness of adjunctive miswak in reducing the mean gingivitis score among patients with gingivitis. Fig. 6 shows a significant difference in the mean of gingivitis score reduction between the use of adjunctive miswak as compared to using only toothbrush. The result favoured the usage of adjunctive miswak (p= 0.04, SMD: 0.66, and 95% CI: 0.03 to 1.29).

3.4. Qualitative synthesis on the effects of miswak on bacterial plaque

Two comparative studies were analysing the bacterial characteristics of oral plaque. Al-Otaibi et al. (2003, 2004) gathered clinical parameters that were appropriate to assess periodontal health, including the collection of subgingival plaque samples for bacterial quantification. The results were presented in two separate reports. Of the 12 subgingival bacteria species in the miswak or toothbrush users, only one species, i.e. *Aggregatibacter actinomycetemcomitans* showed a reduced level after using miswak (Al-Otaibi et al., 2004). On the contrary, Rifaey et al. (2021) found an increased level of *A. actinomycetemcomitans* species in the supragingival plaque of gingivitis patients after using either a toothbrush alone or with adjunctive miswak.

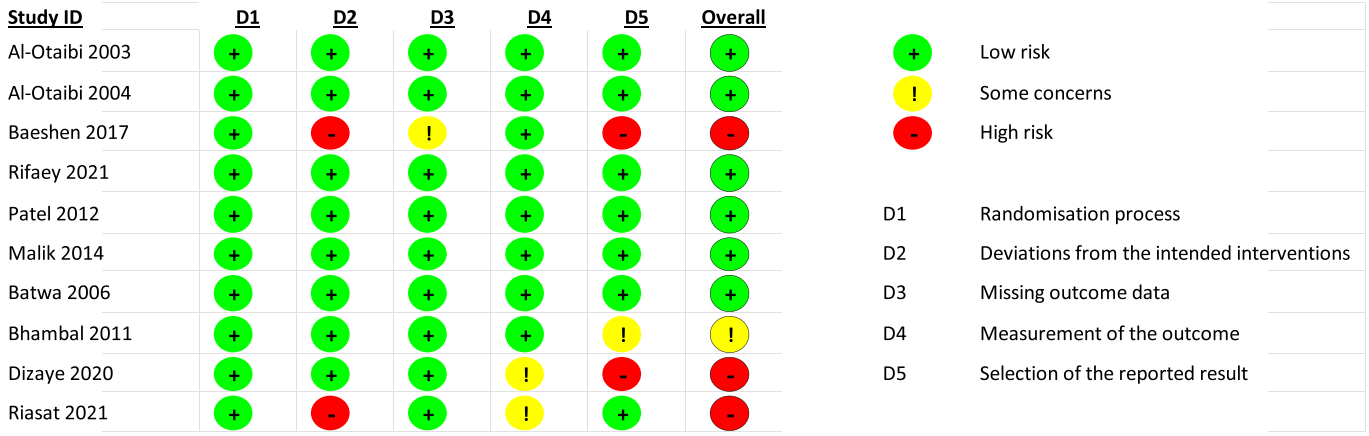

Fig. 7. A summary table of the risk of bias.

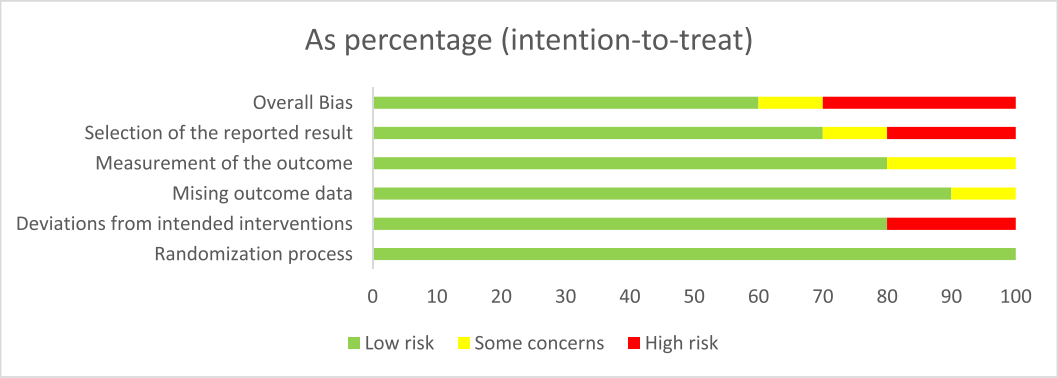

Fig. 8. The graphical presentation of the risk of bias in the percentage of all the included studies.

3.5. Assessment of risk of bias for included studies

Although the quality of studies varied, none were excluded because of poor quality. Figs. 7 and 8 show the summary of the author's judgement about the risk of bias by domain for every study. The detailed appraisal of the risk of bias together with the author's comment is presented as a supplementary materials-RoB2. The risk of bias for this group of studies described as following:

a) Randomisation process

The included studies have shown low risk of randomisation procedures. At least randomisation generation sequence clearly described by six reports (Al-Otaibi et al., 2003, 2004; Rifaey et al., 2021; Batwa et al., 2006; Bhambal et al., 2011; Malik et al., 2014) and the remaining four studies (Baeshen et al., 2017; Dizaye and Othman, 2020; Patel et al., 2012; Riasat et al., 2021) were not fully reported. Furthermore, there was baseline imbalances across intervention groups (Riasat et al., 2021).

b) Deviations from intended interventions

Probably the blinding of participants on assigned intervention was compromised because the tools used were distinctive, but any deviations from intended intervention were unlikely to impact on the outcome. There was one study (Dizaye and Othman, 2020) not clearly described the blinding of outcome assessor and another study has no information of masking the assessor (Riasat et al., 2021). The remaining included studies had a low risk of bias in this parameter, as all the clearly stated on method of blinding. Furthermore, no participants were analysed in the wrong intervention groups. However, there were studies used inappropriate analysis to estimate the outcome effect (Baeshen et al., 2017; Riasat et al., 2021).

c) Missing outcome data

There was a study by Baeshen et al. (2017) encountered one participant developed of side effect that maybe related to miswak. This participant was withdrawn from the trial and his data was excluded from analysis.

d) Measurement of the outcome

The measurement methods were varying, but yet appropriate. The outcome assessors in most included studies were blinded and they were independent researchers. Thus, the measurements were unlikely to be influenced by knowledge of the intervention received. However, studies by Dizaye and Othman (2020) and Riasat et al. (2021) has no report regarding blinding of the examiner or outcome assessor.

f) Selection of reported result

Although, most of the included studies reported the outcome as planned, one study (Baeshen et al., 2017) has described on combined result for miswak and toothbrush. There was one study did not present the result of association between intervention and outcome, as planned (Dizaye and Othman, 2020).

g) Overall bias

There were some concerns in overall bias and mainly due to the selection of reported results.

3.6. Quality of evidence

The evidence was downgraded in at least two steps, the first step for risk of bias and again inconsistency. It applies low-certainty evidence that could indicate limited confidence in the effect estimate of miswak on the reduction of mean plaque compared to toothbrush alone, thus resulting in possible difference from the true effect. Meanwhile, the effect estimate of miswak on mean plaque reduction on labial surface of anterior teeth was indicated as high confidence, because of low risk of bias and has no significant evidence of heterogeneity. When selective reporting of outcome was addressed in at least one of the studies, the certainty of the evidence was downgraded by one level for risk of bias. It compromised the confidence level, leading to moderate confidence in the effect estimates of miswak on the reduction of mean gingivitis score. Therefore, the true effect may be close to estimated effect.

Moderate certainty also applied to the evidence of the effect of adjunctive miswak on the reduction of mean gingivitis score (SMD: 0.66, and 95% CI: 0.03 to 1.29) and to the evidence of the effect of adjunctive miswak on the reduction of mean plaque score (SMD: 0.68, and 95% CI: 0.14 to 1.22). The evidence was downgraded by one level for risk of bias, even though there was no significant evidence of heterogeneity and none of studies were commercial-sponsored. The details of the author's judgement on the GRADE assessment are shown as a supplementary material.

3.7. Sensitivity analysis

Statistical heterogeneity was present in the pooled estimated effect. The subgroups analysis on the miswak effect on mean difference of plaque score reduction according to the type of participants and frequency of toothbrushing was found to be similar to the prior subgroups (refers to Fig. 2b, 2c, 2d, and 2e), thus indicating that the result of the meta-analysis showed stability and reliability. The result also showed that miswak was comparably in reducing plaque score in patients with gingivitis and healthy periodontium when applied either two times per day or more. However, subgroup analysis of other outcomes was not considered to be necessary as they were either no heterogeneity or meaningless. Due to an insufficient number of included studies, the funnel plot for each outcome were not used.

4. Discussion

Compared to previous systematic reviews and meta-analyses, our study included more studies, and the latest articles including those that were published in 2020 and 2021. More specific outcomes are reported based on various study characteristics and in particular the finding highlight the positive effects of adjunctive miswak. Thus, this study provides the latest update on the evidence based contributed by previous systematic reviews and meta-analyses. Importantly, our findings are in accordance, and further adds to the evidence seen with a recent systematic review of the impact of miswak on plaque and bleeding scores of healthy individuals with wide range age, as compared to conventional toothbrushes by Adam et al. (2021). They discovered the SMD of plaque score was comparable between miswak and toothbrush. Moreover, the effect of miswak as an anti-gingivitis agent was even better than the toothbrush. This is consistent with our findings whereby the SMD of plaque scores among adults was comparable between miswak and toothbrush, with high certainty of evidence on the labial surface of anterior teeth. However, this meta-analysis discovered that the SMD of gingivitis score reduction was comparable between the groups. These outcomes were moderately confident that the true effect is likely to be close to the estimated effect. A similar quality of evidence was also discovered in the pooled of studies by previous review (Adam et al., 2021).

Additionally, this review revealed novel findings indicated moderate certainty that the true effect of adjunctive miswak on the reduction of mean plaque score (p= 0.01, SMD: 0.68 and 95% CI: 0.14 to 1.22) and mean gingivitis score (p= 0.04, SMD: 0.66 and 95% CI: 0.03 to 1.29) maybe close to the estimated effect. There was no significant evidence of heterogeneity across the pooled studies of mean difference of plaque score (I^2= 5%, p= 0.35) and gingivitis score (I^2= 29%, p= 0.24). Nevertheless, all the included studies declared no financial or other conflicts, thus it might not have contributed to increased bias.

Assuming a difference in the real treatment effects across the studies due to sampling variability, a random-effect model was applied in our study. However, a moderate inconsistency was still detected in the meta-analysis between miswak and toothbrush for the outcome of the effect of miswak on mean plaque reduction. The heterogeneity can be explained by the subgroup analysis on the frequency of toothbrushing (two times and more than two times per day) and type of participant (healthy periodontium and gingivitis patients). Furthermore, subgroup analysis according to the difference in the methodology and participants that was conducted prior to the rating of the strength of evidence also helped to explain the heterogeneity of point estimates, Jassoma et al. (2019) adopted a similar approach. Moreover, our study determined the effectiveness of exclusive miswak or adjunctive application on reduction of plaque and gingivitis, by analysing changes in the mean (mean difference and SD of mean difference) and thus increased the precision and consistency. This approach was contrast to the previous reviews by Adam et al. (2021) and Jassoma et al. (2019) that adopted the comparison between mean of pre- and post-treatment within intervention and control group, and mean for post-intervention between groups.

Lastly, our results also highlighted the positive effects of miswak on mean plaque and mean gingivitis score reduction in patients with gingivitis or healthy periodontium. The reduction was also comparable to using the toothbrush alone. Furthermore, the effects were significant when miswak was used in conjunction with the toothbrush. These findings support the recommendation by the World Health Organisation (WHO) to apply miswak as an oral hygiene tool, especially by the population with access to the source (World Health Organization, 1987). The adjunctive miswak practice is also consistent and relevant with the current practice by the involved communities worldwide (Abidi et al., 2018; Al-Ghamdi et al., 2015; Al-Hammadi et al., 2018; Baharin et al., 2016; Dogar, 2019; Gana and Garba, 2020). However, majority of the studies in this review did not report on technique of brushing with miswak and applied variable frequency of miswak use with limited reports on the duration of toothbrushing. This is consistent with previous review which discovered various practice of miswak across children and adult populations (Adam et al., 2021). There were some previous studies that reported on disadvantageous of miswak use due to improper practice (Saleh et al., 2017; Karia and Kelleher, 2014). Therefore, these concerns support our recommendation to further explore on advantages and proper method of miswak practice to ensure optima clinical safety and outcomes. Once available, a high quality of evidence base for miswak will be valuable resource to guide a clinical advice on population, community and individual practice setting.

5. Limitations

The heterogeneity between studies could be explained by difference in methodology, miswak species and study populations. Heterogeneity was overcome by analysed using random effects instead of fixed effects analysis. In addition, subgroup analysis was performed whenever possible, for factors that are believed to be the cause. However, an inadequate number of included studies has restricted this effort. Moreover, the risk of bias has had the greatest impact on lowering the level of certainty across the evidence for certain outcomes. Despite the number

of studies being modest, none were commercially financed, hence there was no evidence of publication bias. Additionally, investigator-sponsored studies usually prioritize publication thus the presence of unpublished or grey literature would be unlikely for this systematic review. Finally, a funnel plot could not be produced due to a lack of included studies.

6. Conclusion

In this meta-analysis, the results indicated that exclusive miswak use was comparable to toothbrush in reduced plaque score and gingivitis. The effect of miswak was more significant when used as an adjunctive to the toothbrush. Despite certain findings, showing a lower certainty level and inadequate reporting of study parameter, the benefits of miswak demonstrated by this meta-analysis are significant. To build a high-quality evidence base for clinical practice guidelines, more research should be done with rigorous assessment of proper method of miswak practice to ensure optimum effectiveness and safety.

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7. CRediT authorship contribution statement

Haslinda Ramli: Designed and conducted the review, data acquisition and interpretation, performed all statistical analyses, drafted the original manuscript, and edited the final version manuscript. Khairun Nain Nor Aripin: participated in the review design, critical revision on meta-analysis results and edited the manuscript. Shahida Mohd Said: participated in the review design, conducted the review, validated the selection of studies, data acquisition and interpretation, and critically revised and edited the manuscript. Rohazila Mohamad Hanafiah: critical revision on manuscript and focused on biological plant activity. Tuti Ningseh Mohd Dom: participated in the review design, conducted the review, and validated the selection of studies, data acquisition and interpretation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2022.115598.

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