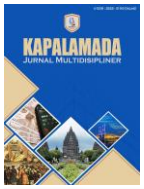
KAPALAMADA: Volume 4 (No 03) 2025 Pp 359-372 e-ISSN: 2828-4194 (Online)



KAPALAMADA: Jurnal Multidisipliner

http://azramedia-indonesia.azramediaindonesia.com/index.php/kapalamada/index
DOI: https://doi.org/10.62668/kapalamada.v4i03.1697
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MISWAK (SALVADORA PERSICA L) AS ORAL CARE ON VENTILATED PATIENTS IN ICU: A SYSTEMATIC REVIEW AND META ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Info Article
Received :
01 Juni 2025
Revised :
02 Agustus 2025
Accepted :
27 Agustus 2025
Publication :
30 September 2025

Keywords:
ICU, Miswak, Mechanical Ventilator, Oral Care, Salvadora Persica L.

Kata Kunci:
ICU, Miswak, Perawatan Mulut, Salvadora Persica L, Ventilasi Mekanik.

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Abstract*: Ventilator-Associated Pneumonia (VAP) is a serious complication in patients receiving mechanical ventilation, as it increases mortality rates and prolongs length of stay in the ICU. Miswak (Salvadora persica L.), known for its antibacterial properties, has been considered as an alternative for oral care. This meta-analysis evaluated the effectiveness of miswak in preventing VAP through three randomized clinical trials that met the inclusion criteria. The findings showed that miswak demonstrated a VAP risk ratio approaching zero compared to chlorhexidine, with fewer adverse effects and better tolerability. The consistency of results across studies indicates potential clinical benefits. The most common regimen was twice daily use during the first three to five days of intubation, which was effective in preventing early bacterial colonization. These findings support miswak as a safe and economical oral care agent, and suggest it as a feasible alternative or adjunct to chemical antiseptics for VAP prevention in the ICU. However, further large-scale, multicenter studies are still needed to strengthen the scientific evidence and support the integration of miswak into evidence-based clinical practice guidelines.*

Abstrak: Ventilator-Associated Pneumonia (VAP) merupakan komplikasi serius pada pasien dengan ventilasi mekanik karena meningkatkan angka mortalitas dan memperpanjang lama perawatan di ICU. Miswak (Salvadora persica L.), yang memiliki sifat antibakteri, dipertimbangkan sebagai alternatif perawatan mulut. Meta-analisis ini mengevaluasi efektivitas miswak dalam pencegahan VAP melalui tiga uji klinis teracak yang memenuhi kriteria inklusi. Hasil analisis menunjukkan bahwa miswak memiliki risk ratio kejadian VAP yang mendekati nol dibandingkan dengan klorheksidin, dengan efek samping lebih rendah serta tingkat tolerabilitas yang lebih baik. Konsistensi hasil antarstudi menunjukkan adanya potensi manfaat klinis. Regimen penggunaan yang paling umum adalah dua kali sehari selama tiga hingga lima hari pertama setelah intubasi, dan terbukti efektif dalam mencegah kolonisasi bakteri dini. Temuan ini mendukung miswak sebagai agen perawatan mulut yang aman, ekonomis, dan layak dipertimbangkan sebagai alternatif maupun pelengkap antiseptik kimia dalam pencegahan VAP di ICU. Meski demikian, penelitian lebih lanjut dengan skala besar dan desain multicenter tetap diperlukan untuk memperkuat bukti ilmiah serta mendorong integrasi miswak ke dalam pedoman praktik klinis berbasis bukti.

INTRODUCTION

Ventilator-Associated Pneumonia (VAP) is a nosocomial lung infection that occurs in patients who undergo mechanical ventilation for more than 48 hours, with a mortality rate reaching 20–30% and an extended length of stay in the intensive care unit (ICU) due to bacterial colonization in the oral cavity migrating to the respiratory tract (Retno Wulan et al., 2024). A large non-randomized study involving 1,666 patients demonstrated that oral care interventions significantly reduced the incidence of VAP from 10.4 to 3.9 episodes per 1,000 ventilator-days (RR = 0.37) (Zhao et al., 2020).

Miswak, derived from the twigs or roots of Salvadora persica, has long been used as a natural oral hygiene tool across various regions, with support from the WHO since 1986. An international consensus in 2000 also recommended further evaluation of its efficacy (Nordin et al., 2020). Its bioactive components such as benzyl isothiocyanate, alkaloids, natural fluoride, and tannins exhibit antibacterial properties against both gram-positive and gram-negative bacteria that cause dental plaque and respiratory infections (Haque & Alsareii, 2021). Evidence-based reviews from 2010 to 2020 have shown that S. persica in various forms (e.g., aqueous extracts, toothpaste, mouthwash) effectively reduces plaque, gingivitis, and dental caries, and promotes gingival tissue healing without cytotoxicity to oral cells (Nordin et al., 2020). In vitro studies have demonstrated high antimicrobial activity of miswak against Streptococcus mutans, S. faecalis, Pseudomonas aeruginosa, and Candida albicans, with broad inhibition zones and low MIC values (<1 mg/ml) (Haque & Alsareii, 2021). The relevance of miswak in preventing VAP has been evaluated in clinical studies. One randomized controlled trial involving 70 intubated patients compared oral care using miswak with chlorhexidine, showing a VAP incidence of 0% in the miswak group versus 17.1% in the control group ($p = 0.01$), indicating a significant preventive effect (Mohammad et al., 2024). One such study reported that no patients in the miswak group developed VAP, while 17.1% of patients in the CHX group were diagnosed with VAP ($p = 0.01$) (Irani et al., 2020). The miswak procedure involved brushing gently over all tooth surfaces twice daily for five days.

These findings are supported by a systematic review and network meta-analysis that included 29 RCTs on herbal oral care in ICUs up to September 2023. The analysis showed that miswak had an odds ratio of 0.27 (95% CI: 0.07–0.91) for reducing VAP incidence, proving more effective than CHX (Li et al., 2024). The review also noted that certain Chinese herbal products showed similar efficacy, highlighting the need for

further research on long-term safety and implementation. Despite its promising potential, the meta-analysis by Li in 2024 also reported limitations such as protocol heterogeneity, variation in application frequency, and inconsistencies in methodological quality; only a few studies applied clear blinding and randomization techniques (Li et al., 2024). Furthermore, critical aspects like long-term oral safety, mucosal tolerability, and gingival health effects remain insufficiently addressed, emphasizing the need for large-scale future studies. Miswak has been identified as a promising herbal oral care product that can serve as an alternative to conventional antiseptics. Overall, miswak offers a natural, affordable, and effective solution for reducing oral bacterial colonization and the incidence of VAP in ventilated patients. Thus, it emerges as a viable herbal oral care agent to prevent VAP, especially as an alternative or complement to CHX. Evidence from clinical RCTs and network meta-analyses supports the potential integration of miswak into ICU practice. Further high-quality studies are needed to strengthen recommendations for incorporating miswak into evidence-based VAP prevention guidelines.

METHOD

Study Design and Reporting

This study adopts a literature review design based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature search was conducted electronically to identify relevant sources aligned with the research questions (Haddaway et al., 2022; Page et al., 2021). Databases included Google Scholar, PubMed, ScienceDirect, CINAH and ProQuest. The data search was conducted on 07. 30, 2025

Research Questions

This study aims to systematically address the following research questions:

RQ1 : Is oral care using miswak effective in reducing the incidence of Ventilator-Associated Pneumonia (VAP)?

RQ2 : What is the optimal frequency of oral care using miswak to effectively reduce the occurrence of VAP?

Search Strategy

The data search conducted generic keywords developed based on the PICO framework and Medical Subject Headings (MeSH) terminology. The keywords used were: Population: "Patient on Ventilator" Intervention: "Oral Care" AND "Salvadora

Persica" OR "Miswak" The search was limited to articles published between January 2020 and June 2025. To avoid misinterpretation and facilitate accurate translation, only articles published in English were included.

Data Screening Process

The inclusion and exclusion criteria for the literature selection were as follows: Inclusion Criteria: Studies discussing oral care interventions using miswak in mechanically ventilated patients, available in full text, and published between 2020 and 2025. Exclusion Criteria: Studies involving populations other than mechanically ventilated patients, inaccessible articles, and articles not written in English. All retrieved references were exported to Zotero for duplicate detection and preliminary screening of titles and abstracts, as illustrated in Figure 1. This step was also essential to ensure no duplicate studies were included. The selection process was conducted independently by researchers in blind mode to maintain objectivity. All references that passed the initial screening were then assessed in full-text format to determine eligibility.

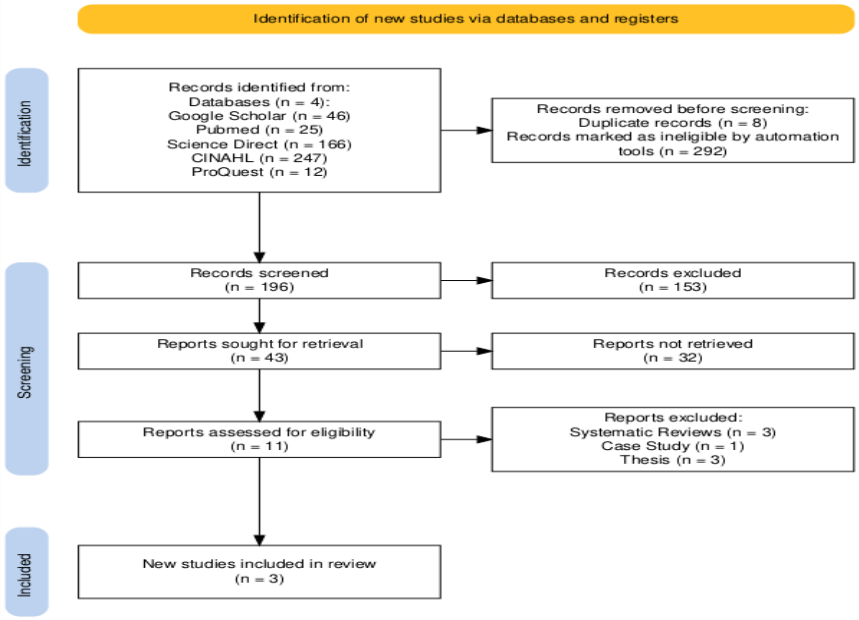

Figure 1. PRISMA Flow Diagram

Data Collection

Data were independently extracted by the authors through a blinded review process. An Excel worksheet was utilized to systematically compile concise one-page summaries. The worksheet documented critical information, including a summary of each article, research design, study setting, population characteristics and sample size, study findings, and an assessment of methodological quality based on the ROBINS-I tool for detecting bias.

Synthesis of Meta Analysis

The analysis was performed using OpenMEE, an open-source and cross-platform software designed for ecological and evolutionary meta-analyses. A quantitative summary of the combined findings was planned in advance. The final interpretation of the aggregated results was adjusted based on the observed level of heterogeneity. Heterogeneity was evaluated using the Cochrane Q-test with a significance level set at alpha = 0.05. Additionally, the extent of heterogeneity was quantified and interpreted using the I^2 statistic, following guidelines from the Cochrane Handbook for Systematic Reviews of Interventions. The I^2 value reflects the proportion of total variability among studies attributable to heterogeneity rather than random chance (Higgins & Green, 2020). Depending on the heterogeneity degree, the pooled findings were presented, discussed, and generalized accordingly. Studies excluded from the meta-analysis were still incorporated into the systematic review to prevent possible misinterpretations. Final effect sizes were calculated and reported with corresponding confidence intervals (CI) with cohen as a reference (Cohen, 2009). This approach is appropriate for estimating effect sizes across studies with diverse outcome measurement frameworks.

Assessment of Article Eligibility

Articles that met the inclusion criteria were then assessed for quality using the ROBINS-I Critical Appraisal Tool for assessment the bias. As shown in Table 1, all included articles were rated as being of high quality. Following the quality appraisal, researchers independently conducted data extraction using a standardized data extraction form and examined each article's methodological approach to ensure consistency with the research questions and objectives.

Table 1. Assessment of Article Eligibility using ROBINS-I

Bias Domain	Irani et al. (2020)	Karimi et al. (2024)	Kiabi et al. (2023)
Bias due to confounding	Low risk	Low risk	Low risk
Bias in selection of participants	Low risk	Low risk	Low risk
Bias in classification of interventions	Low risk	Low risk	Low risk
Bias due to deviations from intended interventions	Low risk	Low risk	Low risk
Bias due to missing data	Low risk	Low risk	Low risk
Bias in measurement of outcomes	Moderate risk	Moderate risk	Low risk
Bias in selection of the reported result	Low risk	Low risk	Low risk
Other bias (e.g., analysis approach)	Moderate risk	Moderate risk	Moderate risk

Figure 2. ROBINS-I Traffic Plot

RESULTS AND DISCUSSION

Results

Meta Analysis

Table 2 illustrates that oral care with miswak significantly reduced the incidence of ventilator-associated pneumonia (VAP) compared to chlorhexidine, with an incidence rate of 0% in the miswak group versus 17.1% in the chlorhexidine group ($p = 0.01$). In a separate study, although differences in the incidence of early-onset and late-onset VAP between the miswak plus aloe vera group and the chlorhexidine group were not statistically significant, a trend toward reduced chronic VAP was observed in the miswak plus aloe vera group. Conversely, the chlorhexidine group demonstrated a significant increase in VAP incidence from early-onset to late-onset cases ($p < 0.02$). Furthermore, the use of the herbal mouthwash Persica was found to be equally effective as chlorhexidine in preventing VAP, with no significant difference in pneumonia incidence between the two groups (16% vs. 12%, $p = 1.0$). Notably, Persica was associated with a substantially lower rate of adverse effects compared to chlorhexidine (8% vs. 44%, $p = 0.008$).

Table 2**.** Synthesis of Literature Review

No	Author(s), year and Country	Title	Study design	Intervention	Outcomes
1	Irani et al., (2020) Iran	The Effect of Oral Care with Miswak Versus Chlorh exidine on the Inciden ce of Ventilat or-Associated Pneumonia: A Clinical Trial Study	- Single-blind Randomized Clinical Trial (RCT)	- Intervention: Oral care with miswak - Control: Oral care with 0.2 % chlorhexidine mouthwash	- Incidence of VA P: 0% in the miswak gr oup vs. 17.1% (6 patients) in the chlorhexid ine group - Significant result (p = 0.0 1) indic ating miswak wa s mo effecti ve in preventing VAP
2	Karimi, Kia et al., (2024)	Comparing the Effectiveness of	Single-blind Randomized Clinical Trial	- Intervention: Mouthwash with 10%	- Early-onset VAP: 28.6% (miswak + alo e

	Iran	Miswak+Aloe Vera Mouthwash with Chlorhexidine Mouthwash on the Prevention of Ventilator-Induced Pneumonia: A Randomized Clinical Trial		Miswak + 94% Aloe Vera (Barij Essans, Kashan), administered twice daily for 5 days - Control: Chlorhexidine gluconate (CHG) 0.2% mouthwash (Shahr Daru), twice daily for 5 days - Administered to ICU patients with mechanical intubation for at least 72 hours	vera) vs. 11.4% (CHG) (not sig nifican t) - Late-onset VAP: 22.9% (miswak + aloe vera) vs. 40% (CHG) (not significant - Although not statistically sig nificant, a trend toward reduced chro nic VAP was observed in the miswak + aloe vera group - CHG group sho wed a significa nt increase in VAP from early to late-onset (p < 0.02)
3	Kiabi et al., (2023) **Iran**	The Difference in Mouthwash Side Effects of Persica and Chlorhexidine for Preventing Ventilator-induced Pneumonia among Patients Admitted to the Intensive Care Unit	Double-blind Randomized Clinical Trial	- Intervention group: Oral care with Pers ica (10 cc, twi ce daily, for 6 minutes) + Oral-B Soft toothbrush - Control grou p: Oral care with 0.2% Chl orhexidine (10 cc, twice dai ly, for 6 minu tes) + Oral-B Soft tooth brush - Duration: Up to the 3rd day of intubation - All patients were in semi-Fowler's posi tion, PEEP applied, cuff pressure moni tored daily	- No significant difference in pneumonia inci dence (Persica: 16%, CHX: 12%; p = 1.0) - No significant differences in ICU stay, intub ation duration, ventilation, CP IS, SOFA, or mortality - Significantly fewer side effe cts in the Pers ica group (8% vs. 44%; p = 0.008) - Conclusion: Per sica is as effect tive as CHX in preventing VAP with fewer side effects

The results of this meta-analysis, in Figure 3 yielded a risk of ratio estimate of 0.007, with a 95% confidence interval ranging from -0.139 to 0.152, and a p-value of

0.930. According to Cohen's criteria (1988), this value falls well below the threshold of approaching zero, indicating that statistically, the effect of implementing oral care using Miswak on the risk of developing VAP is minimal and nearly negligible. The confidence interval includes zero, and the high p-value confirms the absence of statistical significance. The standard error associated with the estimate is 0.074, further reinforcing the reliability of this non-significant result. Additionally, the heterogeneity analysis shows complete consistency across the included studies, with a tau² of 0, Q (df = 2) = 0.002, p = 0.999, and I^2 = 0%, indicating no observed heterogeneity. The accompanying forest plot illustrates this consistency, as the effect estimates from all three studies—Kiabi et al. (2023), Karimi et al. (2024), and Irani et al. (2020)—are closely clustered around zero with overlapping confidence intervals and no significant individual outcomes. Although the included studies are methodologically consistent, the aggregated evidence suggests that the intervention has minimal.

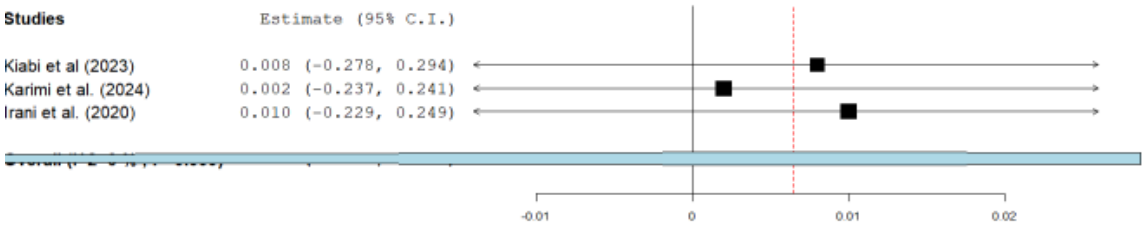

Figure 3. Forest Plot of Individual Studies

Subgroup Analysis and Heterogeneity

Figure 4 illustrates the comparative effectiveness of Miswak and chlorhexidine in preventing ventilator-associated pneumonia (VAP). For the Miswak subgroup, the pooled effect estimate showed a risk ratio (RR) of 0.054 with a 95% confidence interval ranging from -0.157 to 0.266, and an I^2 value of 0% (p = 0.862), indicating no heterogeneity among the analyzed studies. This consistency suggests that studies evaluating Miswak produced similar results, although the effect was not statistically significant. In contrast, the chlorhexidine subgroup demonstrated a higher pooled RR estimate of 0.294, with a 95% confidence interval ranging from -0.189 to 0.777, accompanied by substantial heterogeneity (I^2 = 80.53%, p = 0.006), indicating significant variability in outcomes among studies.

Overall, the combined risk ratio (RR) from both subgroups was 0.175 (95% CI: -0.071 to 0.421) with moderate heterogeneity (I^2 = 62.72%, p = 0.020). It should be noted that the confidence interval including negative values suggests that the metric used is

likely not a pure risk ratio but another effect size measure, such as the standardized mean difference (SMD). According to Cohen's criteria (1988), this value is considered small, indicating that statistically, the effect of implementing oral care using Miswak on the risk of developing VAP is minimal and nearly negligible. In summary, although chlorhexidine showed a slightly higher risk of VAP compared to Miswak, the results exhibited moderate variation across studies, as indicated by the heterogeneity value (I^2 = 62.72%). Meanwhile, Miswak demonstrated a consistent but minimal risk. Based on Cohen's criteria, the intervention risk ratio in both groups can be considered small and clinically limited, with a statistically significant advantage observed.

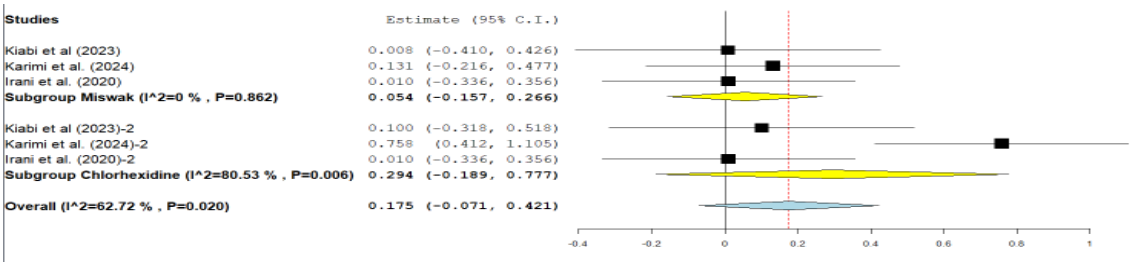

Figure 4. Plot of Subgroup Analysis based Miswak vs Chlorhexidine as Oral Care in Ventilated Patient

Publication Bias

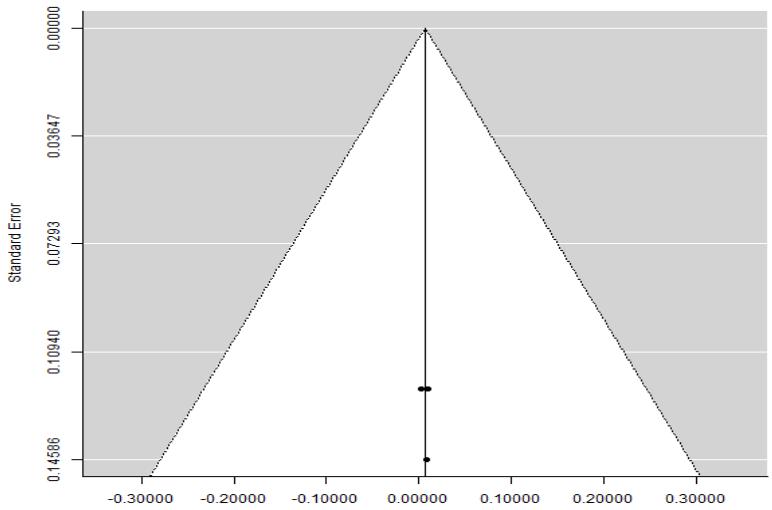

Figure 5. Funnel Plot of Publication Bias

The meta-analysis results indicate a non-significant overall effect, as evidenced by the observed p-value of 0.4648, which exceeds the conventional threshold of 0.05. The Fail-safe N calculated using Rosenthal's approach is zero, suggesting that no additional unpublished or missing studies with null results are required to nullify the existing findings. This indicates that the current meta-analytic conclusion is robust against potential publication bias. Figure 5 supporting, the funnel plot demonstrates a

symmetrical distribution of studies around the mean effect size, with no evident asymmetry or clustering on either side of the plot. The absence of funnel plot asymmetry further suggests minimal risk of publication bias influencing the results. Taken together, these findings reinforce the reliability of the meta-analysis, although the non-significant effect size implies that the intervention or exposure under investigation may not have a meaningful impact based on the available data.

Discussion

Ventilator-Associated Pneumonia (VAP) is one of the most serious complications among patients undergoing mechanical ventilation in intensive care units (ICUs). Oral care has long been recommended as a preventive strategy to reduce the risk of this infection. In this context, the use of miswak (Salvadora persica) as an alternative oral care agent has attracted attention due to its bioactive compounds with antibacterial properties (Haque & Alsareii, 2021). This systematic review and Meta analysis of randomized controlled trials (RCTs) that evaluated the effectiveness of miswak in preventing VAP among ventilated patients.

In addressing the first research question (RQ1), the findings from all three studies indicate that miswak has potential in reducing the incidence of VAP, albeit with varying degrees of effectiveness. The study by Irani et al., (2020) demonstrated the most significant result, with 0% VAP incidence in the miswak group compared to 17.1% in the chlorhexidine (CHX) group, accompanied by a statistically significant p-value ($p = 0.01$). This provides strong evidence that miswak, when used appropriately, can serve as an effective preventive agent against VAP.

The second study by (Karimi, Kia et al., 2024) introduced a variation by combining miswak with aloe vera. Although the findings were not statistically significant, there was a downward trend in late-onset VAP in the miswak + aloe vera group compared to CHX (22.9% vs. 40%). This suggests that miswak may offer long-term protection against lower respiratory tract infections, although larger sample sizes are needed for confirmation.

The third study by Kiabi et al., (2023) focused on the side effects and safety of using Persica mouthwash (a derivative of miswak). In this double-blind study, VAP incidence in the Persica group was 16%, which was not significantly different from the CHX group (12%; $p = 1.0$). However, a notable finding was the significantly lower rate of side effects in the Persica group (8% vs. 44%; $p = 0.008$), suggesting that miswak may be better tolerated than chemical antiseptics like CHX.

Considering the overall results, it can be concluded that miswak is effective in reducing the incidence of VAP, especially when compared to CHX under controlled conditions. The findings by (Irani et al., 2020) provide the strongest evidence and are supported by the other two studies, which, while not statistically significant, demonstrate good safety and tolerability (Li et al., 2024). In response to the second research question (RQ2), regarding the frequency of oral care using miswak, all three studies provided consistent guidance. Each applied a frequency of twice daily (2×/day) during the first 3–5 days of mechanical ventilation. Irani et al. reported optimal outcomes with this regimen over five days. Similarly, Karimi, Kia et al., (2024) used the same protocol, and Kiabi et al. (2023) administered the intervention until the third day of intubation.

This suggests that a minimum frequency of twice daily for 3–5 days is a consistent and effective intervention to reduce the risk of VAP, particularly during the early phase of intubation, when bacterial colonization risk is highest (Karimi, Kia et al., 2024; Nordin et al., 2020). No studies directly compared higher or lower frequencies, so an ideal quantitative frequency cannot yet be concluded, but twice daily remains the commonly applied standard. Beyond its effectiveness in preventing VAP, miswak offers additional advantages such as low cost, high availability, and minimal side effects, making it a promising alternative for resource-limited hospitals or in developing countries. In intensive care settings where infection risk is high and chemical antiseptics often lead to resistance or mucosal irritation miswak presents a more natural, herbal-based approach (Nordin et al., 2020).

However, some methodological limitations were observed in the reviewed studies, such as the absence of double-blinding in two of the three trials, and the lack of explicit intention-to-treat analyses, highlighting the need for further research with more rigorous methodological quality. The robust RCT design seen in Kiabi et al., (2023) should serve as a model for future studies. Overall, this review provides strong preliminary evidence that miswak can be incorporated into oral care protocols for ventilated patients to prevent VAP, with an optimal frequency of twice daily during the early phase of mechanical ventilation. Nonetheless, large-scale, multicenter trials are required to strengthen the scientific basis and support its integration into evidence-based ICU guidelines.

Strength and Limitations

This Meta-analysis has the strength of synthesizing evidence from randomized controlled trials, which are considered the gold standard in evaluating clinical

interventions. The included studies consistently applied standardized oral care protocols, and the findings highlight both effectiveness and safety aspects of miswak compared to chlorhexidine. However, several limitations must be acknowledged. The number of available RCTs remains limited, with relatively small sample sizes, reducing the statistical power to detect meaningful differences. Methodological heterogeneity was observed in terms of intervention formulations, outcome measurements, and follow-up duration. Additionally, two of the three included trials lacked double-blinding, which increases the risk of performance and detection bias. These limitations indicate the need for more rigorous and larger-scale studies.

Clinical Implications

The findings suggest that Miswak (Salvadora persica L.) could be integrated as a safe, cost-effective, and culturally acceptable option for oral care in mechanically ventilated patients, particularly in settings with limited resources. Specifically, these results indicate that the use of Miswak for oral care in ICU patients carries virtually no risk of developing ventilator-associated pneumonia (VAP), with the risk approaching zero. By demonstrating comparable or superior preventive potential against ventilator-associated pneumonia and fewer adverse effects than chlorhexidine, miswak offers an attractive alternative or adjunct to standard chemical antiseptics. Its incorporation into ICU oral care protocols may contribute to reducing infection rates, lowering healthcare costs, and improving patient safety outcomes. Nonetheless, clear guidelines and further evidence from high-quality trials are required before widespread adoption.

CONCLUSION

This systematic review indicates that miswak (Salvadora persica L.) is a promising alternative oral care agent for mechanically ventilated patients, with RCT evidence—most notably Irani et al. (2020)—showing a reduction in ventilator-associated pneumonia (VAP) incidence (0% vs. 17.1% with chlorhexidine). Although the meta-analysis found a small, non-significant effect, study results were consistent, especially regarding safety, as miswak caused fewer adverse effects than chlorhexidine. For RQ1, miswak appears effective in lowering VAP risk and serves as a natural substitute for chemical antiseptics. For RQ2, twice-daily oral care with miswak over 3–5 days early in ventilation was the most common regimen, sufficient to prevent bacterial colonization. Overall, miswak is a

safe, accessible, and potentially effective ICU intervention, but larger, double-blind, multicenter trials are needed to confirm its efficacy and standardize protocols.

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