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Is Herbal Mouthwash as Effective as Chlorhexidine?: A Review

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ABSTRACT

Pathogenic biofilms contribute to several oral problems, including caries, periodontitis, and other infections. Chlorhexidine has long been considered the gold standard for chemical dental plaque control. However, it is accompanied by adverse effects, such as taste alterations, staining, and cytotoxicity. In response to these challenges, herbal mouthwashes have emerged as a promising alternative treatment, with fewer drawbacks. The primary aim of this review was to assess the effectiveness of herbal mouthwashes in comparison to chlorhexidine. Adhering to the PRISMA guidelines, this review focused on questions concerning the effectiveness of herbal mouthwashes compared to chlorhexidine. A systematic search was executed in prominent databases, including PubMed, SpringerLink, ScienceDirect, and Wiley. Using predefined keywords, five articles were selected for inclusion in the review and subsequent research synthesis. The review findings suggest that herbal mouthwashes exhibit effectiveness comparable to chlorhexidine, accompanied by the added benefit of fewer side effects. However, further research is needed to comprehensively evaluate the long-term safety and efficacy of herbal mouthwash.

KEYWORDS: *Chlorhexidine, effectiveness, herbal, mouthwash, oral health, review*

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BACKGROUND

Many types of bacteria have been discovered in the oral environment, forming multispecies biofilms or extracellular matrices rich in polysaccharides. Biofilm formation triggers a host inflammatory immune response, which, in some circumstances, may be detrimental.^[1,2] Pathogenic biofilms on tooth surfaces may result in the occurrence of caries, periodontitis, peri-implant disease, root canal infections, and other oral infections.^[1] Gingivitis and periodontitis, affecting periodontal tissue, are common illnesses originating from bacteria.^[2] Disrupting and preventing biofilm formation in the oral environment using anti-plaque agents such as chlorhexidine, cetylpyridinium chloride, fluoride, zinc, and stannous chloride is effective.^[3-5]

Currently, various types of mouthwash are commonly used in oral hygiene routines, playing a complementary role considered an addition to toothbrushing as

primary therapy.^[1,2] Mouthwash can diminish biofilm formation in instances of insufficient mechanical debridement caused by ineffective tooth brushing techniques. Antiseptic substances with minimal systemic cytotoxicity and enduring potency align with the optimal criteria for mouthwash, preventing immediate rinsing by salivary flow.^[6]

Chemical mouthwashes, such as chlorhexidine, are effective in preventing plaque development and are considered the gold standard for the chemical control of dental plaque.^[7,8] Both Gram-positive bacteria, such as *Staphylococcus aureus*, and Gram-negative bacteria, such as *Enterococcus faecalis*, *Aggregatibacter actinomycetemcomitans*, and *Porphyromonas gingivalis*, along with yeasts and viruses, are susceptible

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to chlorhexidine.^[2,5] Chlorhexidine increases the permeability of microbial cell membranes, alters protein functions, and precipitates macromolecules in the cytoplasm. It also exhibits bacteriostatic properties by binding nonspecifically to negatively charged membrane phospholipids of bacteria, inhibiting ATPases, and preventing prokaryotic cells from replicating.^[5]

In addition to its beneficial effects, chlorhexidine has associated negative effects, including dysgeusia, dehydration, tooth and tongue pigmentation, and allergic reactions. In human cells *in vitro*, chlorhexidine can cause cytotoxicity, leading to apoptosis and necrotic cell death.^[2,9] To address these adverse effects, herbal mouthwash with antibacterial and anti-inflammatory properties may enhance patient compliance, as it typically has fewer negative effects than chlorhexidine.^[10] Herbal formulations, which contain plant-derived compounds without the risk of teeth staining, exhibit a milder taste, and minimize the potential for dry mouth.^[11,12]

Various medicinal herbs, such as thyme, cloves, green tea, licorice, and peppermint leaves, have been utilized for ages in traditional medicine to address dental issues, such as toothaches, cavities, and gum diseases.^[13] Furthermore, miswak, rosemary, olive oil, myrrh, anise, sesame, ginger, and garlic are used in Middle Eastern countries for treating oral disorders.^[14] Herbal medicines have evolved in dentistry as anti-inflammatory, antibacterial, antiseptic, and therapeutic agents. Traditionally, herbal medicine has been used to address issues like caries, gingivitis, and periodontitis. Additionally, it has applications as an intracanal medication, sialogogue, and tooth whitening agent.^[15] Herbal medicine contains diverse bioactive substances, including phenolic compounds such as flavonoids and phenolic acids, exhibiting antibacterial effects. These substances have the potential to substitute chemical mouthwash.^[2,5] Due to their various biological and medicinal activities and lower cost, herbal mouthwash may contribute to better oral health maintenance.^[2] The active ingredients of herbal mouthwashes are derived from natural sources, such as essential oils, plant extracts, and other botanical compounds. These ingredients are deemed safe and have a history of use in traditional medicine for various purposes. Formulating herbal mouthwashes with lower concentrations of active ingredients contributes to a reduction in adverse effects, such as staining or irritation, enhancing both their effectiveness and safety profile.^[16,17] Compared to chlorhexidine, herbal mouthwashes show no

significant difference in terms of reducing plaque, gingivitis, and gingival bleeding.^[18,19] Additionally, herbal mouthwash yields inconclusive results for maintaining oral hygiene in patients with fixed orthodontics compared with chlorhexidine.^[20]

This review aims to evaluate the existing literature on the efficacy of herbal mouthwash compared to chlorhexidine as a mouthwash.

MATERIALS AND METHODS

This review adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [Figure 1].^[21]

Focused questions

A focused question was developed using the PICO (Population, Intervention, Comparison, and Outcome) framework, serving as the foundation for the inclusion and exclusion criteria for the current review. The focus question was “Are herbal mouthwashes equally effective as chlorhexidine in promoting oral health and managing oral diseases?”

- Population: adult human subjects
- Intervention: use of herbal mouthwash after supragingival debridement or no additional periodontal treatment
- Comparison: use of chlorhexidine mouthwash after supragingival debridement or no additional periodontal treatment
- Outcome: gingiva, lips, oral mucosa, teeth, tongue swab, biofilm, and clinical periodontal parameters, including gingival inflammation, dental plaque, pocket depth, biofilm

Search strategy

Four databases (PubMed, SpringerLink, ScienceDirect, and Wiley) were used to conduct a literature search within 2018–2023. A search string was created using the PICO model. The databases were searched for the following phrases: (“herbal” [MeSH Terms] AND “mouthwash” [MeSH Terms]) OR “mouth rinse” [MeSH Terms] AND “chlorhexidine” [MeSH Terms].

Inclusion/exclusion criteria

The study included full-text articles conducted in English on human subjects, comparing the effectiveness of herbal mouthwash with that of chlorhexidine. The exclusion criteria encompassed studies on animals, *in vitro* experiments, and review papers.

Study selection

All references underwent systematic categorization. Three independent reviewers (SS, JE, and PN)

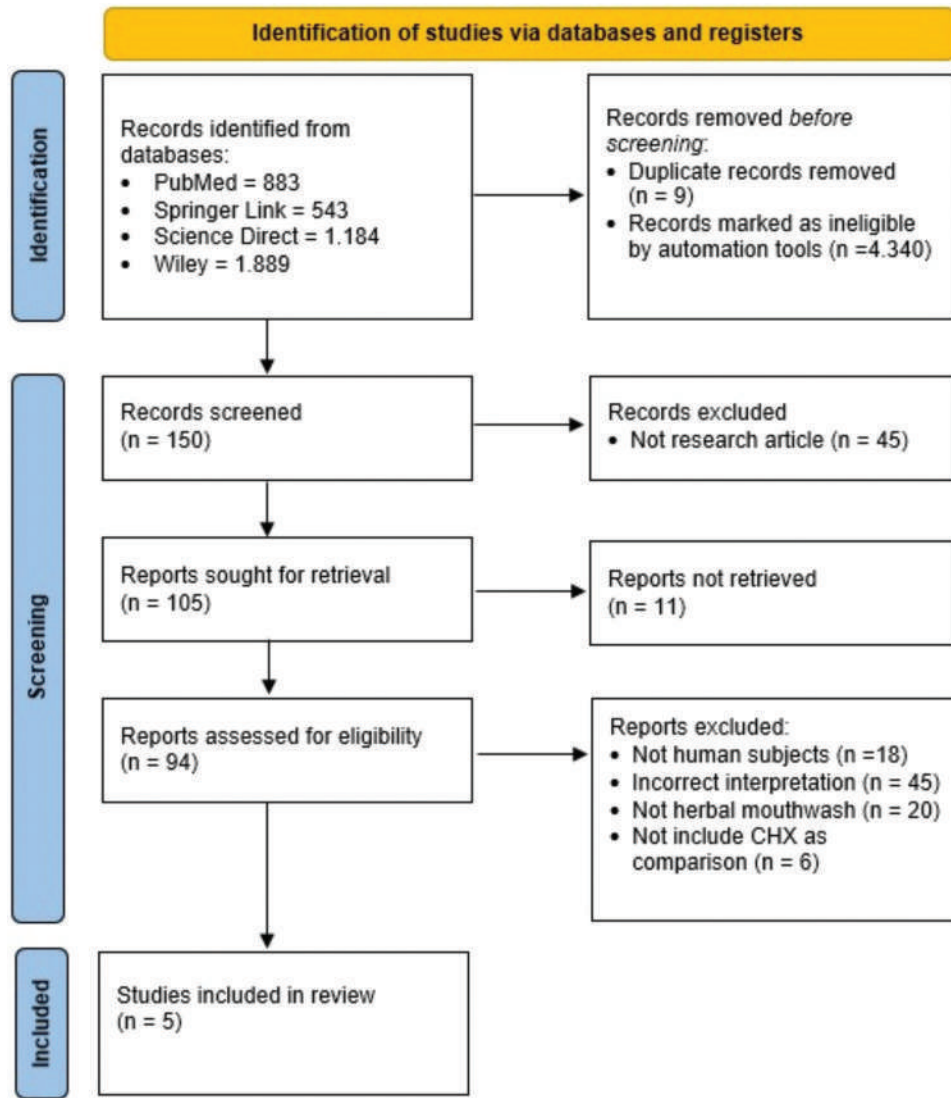


Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for study selection.^[21]

conducted an initial screening based on the titles and abstracts of the articles, followed by a full-text evaluation. Any discrepancies in article eligibility were resolved through inter-reviewer discussion.

RESULTS

In the study's initial phase, searches for articles were conducted using predefined keywords in four databases, complemented by manual searches. After eliminating duplicate titles and using automation tools, 150 articles were initially selected; of these, 45 were excluded due to their non-research nature. Out of the remaining 105 articles, 11 were excluded because they lacked full-text availability. Following the eligibility criteria, 89 articles were excluded for not involving human subjects, incorrect interpretations, lack of focus on herbal mouthwash, or absence of chlorhexidine as

a comparison. Finally, five articles were included in the review and research synthesis [Table 1].

DISCUSSION

Effectively managing oral care products poses challenges.^[22] To prevent plaque formation, a combination of mechanical techniques and chemical substances is necessary. Mechanical plaque prevention methods include brushing and interdental cleaning. Thus, incorporating supplementary antiseptic agents, such as mouthwash, is crucial to enhance oral hygiene and improve periodontal health.^[23] The notable effects of mouthwash on the subgingival biofilm include preventing biofilm accumulation and exhibiting anti-gingivitis properties, followed by its ability to prevent caries.^[24]

Table 1: Articles included in the review and research synthesis

No	Authors	Type of Study	Materials	Sample/parameter	Relevant Findings
1	Casarin et al. ^[1]	Randomized, crossover, double-blind clinical Trial	0.3% <i>Melaleuca alternifolia</i> nanoparticles mouthwash and 0.12% chlorhexidine on biofilm-free (BF) and biofilm-covered (BC) tooth surfaces	Biofilm (QHPI = Quigley & Hein Plaque Index)	0.3% <i>M. alternifolia</i> nanoparticles were as effective as 0.12% chlorhexidine in exhibiting important anti-inflammatory properties in healthy participants
2	Abullais et al. ^[2]	Double-blind randomized controlled trial	Alpine manuka mouthwash and 0.2% chlorhexidine	Dental plaque (plaque index), inflammation such as edema, redness, swelling, and spontaneous bleeding (gingival index), and bleeding upon gentle probing (modified sulcular bleeding index)	Manuka mouthwash was as effective as 0.2% chlorhexidine in managing chronic gingivitis and minimizing the adverse effects (e.g., staining, mucosal burning, and dehydration) associated with the long-term use of chlorhexidine
3	Alzoman et al. ^[28]	Randomized controlled trial	HiOra mouthwash and 0.2% chlorhexidine	Plaque index, bleeding on probing, and probing depth	HiOra mouthwash and 0.2% chlorhexidine had similar effectiveness in treating peri-implant mucositis
4	Jahanshir et al. ^[29]	Comparative randomized triple-blind clinical trial	6.66% clove mouthwash and 0.2% chlorhexidine	Gingiva, lips, oral mucosa, teeth, and tongue swab with Beck Oral Assessment Scale	6.66% clove mouthwash was as effective as 0.2% chlorhexidine in evaluating oral health status in ICU patients on mechanical ventilator
5	Nayak et al. ^[30]	Placebo-controlled double-blind parallel arm, interventional clinical study	0.15% guava mouthwash and 0.2% chlorhexidine	Supragingival plaque (Gracey curette), gingival index, plaque index, microbial count, and antioxidant level	0.15% guava mouthwash was as effective as 0.2% chlorhexidine in lowering plaque scores and maintaining gingival health in patients with chronic generalized moderate-to-severe gingivitis

The recommended effective dosage of chlorhexidine mouthwash is 18–20 mg per use, with concentrations ranging from 0.12% to 0.2%. To optimize its effectiveness, it is advisable to delay chlorhexidine mouthwash use 30 min after toothbrushing. This delay is suggested because certain toothpaste ingredients, such as calcium and anionic surfactants (e.g., sodium lauryl sulfate, sodium dodecyl sulfate, and cocamidopropyl betaine), may diminish their ability to adhere to oral surfaces. The mechanism of action of chlorhexidine involves its positive charge, attracting it to the negatively charged bacterial cell wall. Chlorhexidine forms specific adsorption to phosphate-containing molecules on the bacterial cell surface, facilitating penetration through the bacterial cell wall and damaging its integrity (bacteriostatic effect). This process leads to the release of low-molecular-weight cytoplasmic components, including potassium ions, and the inhibition of certain enzymes. Additionally, chlorhexidine induces cytoplasmic coagulation and precipitation by forming complexes with phosphorylated compounds, such as adenosine triphosphate and nucleic acids (bactericidal effect).^[8] The modification of stimuli affecting salty and bitter taste perception by chlorhexidine leads to a change

in taste perception.^[25] Due to a higher concentration, chlorhexidine may induce a burning sensation and discoloration of the teeth and tongue.^[26,27] Given these adverse effects, herbal mouthwash is considered an alternative to chlorhexidine, especially when dealing with patients who have peri-implant mucositis, chronic periodontitis, or are allergic to chlorhexidine.^[2,28]

Natural botanical products have shown promise in treating caries, gingivitis, and periodontitis.^[7] Herbal mouthwash, dentifrice, and gels have recently gained popularity. The active components in herbal mouthwash can penetrate the biofilm, reducing calculus formation and bacterial colonization on tooth surfaces.^[1] In this review, we found herbal mouthwash made from *Melaleuca alternifolia*, manuka, HiOra (*Salvadora persica*, *Terminalia bellirica*, *Gossia fragrantissima*, and *Elettaria cardamomum*), *Eugenia caryophyllata* (clove), and *Psidium guajava* L. (guava) leaf to be a promising alternative.^[1,2,28-30]

The following parameters were used to evaluate the effectiveness of herbal mouthwash in this review: plaque index (PI), gingival index (GI), and bleeding on probing (BOP) score.^[1,2,30] The presence of bleeding

during gum probing is a significant factor in attachment loss and disease progression.^[2] Another parameter considered in this review was the presence of biofilm-free and biofilm-covered tooth surfaces, along with the Beck Oral Assessment Scale score.^[1,29] The Beck Oral Assessment Scale instrument includes five indicators for evaluating the condition of the lips, gums, oral mucosa, teeth, tongue, and saliva.^[29]

In a study involving 60 healthy individuals, the use of 0.12% chlorhexidine within 7 days demonstrated a significantly ($P < 0.05$) lower anti-biofilm effect than with that of 0.3% *M. alternifolia*. Although *M. alternifolia* nanoparticles did not inhibit biofilm formation, they exhibited significant anti-inflammatory properties similar to 0.12% chlorhexidine mouthwash ($P > 0.05$). Both the chlorhexidine and *M. alternifolia* groups experienced a reduction in gingival crevicular fluid (GCF) volume, leading to *M. alternifolia* being considered an inflammatory predictor. Given that GCF originates from the microcirculation of gingival tissues, a correlation exists between GCF volume and gingival inflammation. *M. alternifolia* can be characterized by its nanometric particles. This property facilitates the easier penetration of *M. alternifolia* oil into the polymer matrix of the biofilm, thereby enhancing its anti-inflammatory characteristics. *M. alternifolia* also exhibits antiseptic, antibacterial, antifungal, and antiviral effects. Experimental *in vitro* testing has been conducted to assess its efficacy in preventing the formation and adherence of mono-species biofilms of periodontopathogens and cariogenic bacteria.^[1] Additionally, Srikumar *et al.* reported that *M. alternifolia* mouthwash is equally effective as chlorhexidine in reducing halitosis.^[31]

The efficacy of alternative mouthwashes in various periodontal diseases is supported by convincing evidence. In a study involving 45 patients with moderate plaque, manuka derived from New Zealand Nelson Honey, used for 14 days, demonstrated similar effectiveness compared to 0.2% chlorhexidine mouthwash. No differences were observed between chlorhexidine and manuka for PI, GI, and bleeding index at any time point, indicating that manuka mouthwash is promising for managing chronic gingivitis. Manuka mouthwash contains ascorbic acid and antioxidants, including lutein, alpha-linolenic acid, and omega-3 fatty acids, in high concentrations. These antioxidants act as free radical scavengers, preserving the health of periodontal tissues. Ascorbic acid, a strong antioxidant, is essential for preserving connective tissue, osteoid tissues, and dentin integrity. The antibacterial effect works through an osmotic

mechanism involving phenolic and antioxidant actions and the inhibition of enzyme synthesis of hydrogen peroxide.^[32] Importantly, manuka mouthwash offers the additional advantage of minimizing the adverse effects associated with long-term chlorhexidine use, such as staining, mucosal burning, and dehydration.^[2] Another study also found that manuka honey mouthwash has the same effectiveness as 0.2% chlorhexidine mouthwash in reducing gingivitis.^[33]

In the treatment of 48 patients with peri-implant mucositis, HiOra mouthwash derived from Himalaya Drug, Bengaluru, India, proved equally effective compared to 0.2% chlorhexidine mouthwash over 2 weeks of use. No statistically significant differences were observed in peri-implant PI, BOP, and probing depth between the herbal and 0.2% chlorhexidine mouthwash groups after 3, 6, and 12 weeks of follow-up. *S. persica* and *T. bellirica* in HiOra mouthwash are recognized for their ability to prevent plaque formation and to exhibit antimicrobial activity. Benzyl isothiocyanate from *S. persica* is effective against *P. gingivalis* and *A. actinomycetemcomitans*. The undesirable adverse effects of chlorhexidine, such as alterations in taste sensation and burning sensation, might necessitate the use of an oral rinse containing substitutes for chlorhexidine, especially for patients with peri-implant mucositis or chlorhexidine allergy.^[28]

In cases of chronic generalized moderate-to-severe gingivitis, 60 patients were instructed to use *P. guajava* L. leaf mouthwash and 0.2% chlorhexidine mouthwash for 30 days. The results demonstrated that *P. guajava* L. leaf mouthwash had an effectiveness equivalent to 0.2% chlorhexidine mouthwash in reducing plaque scores and preserving gingival health. No statistical difference was observed between the *P. guajava* L. leaf and chlorhexidine mouthwash groups at the first- and third-month intervals, suggesting comparable functional activity in lowering GI scores between the two types of mouthwash. The anti-inflammatory activity of *P. guajava* L. leaf bioactive ingredients, inhibiting prostaglandins, kinin, and histamines, further supports its contribution to gingival health. Additionally, ascorbic acid and phenolic chemicals, such as protocatechuic acid, ferulic acid, quercetin, guavin B, and gallic acid, increase antioxidant levels in saliva. Moreover, it has the capacity to remove hydrogen peroxide, liberate superoxide ions, and prevent hydroxyl radicals.^[30] Therefore, *P. guajava* L. leaf mouthwash could be a substitute for maintaining a healthy gingiva. A similar study on 50 patients with plaque-induced gingivitis also found no significant differences in the PI, GI, and BOP between 0.2% chlorhexidine and

herbal mouthwash consisting of *Myrtus communis*, *Quercus brantii*, *Punica granatum*, *Portulaca olerace*, and *Boswellia serrata*. Even the herbal mouthwash improved the periodontal condition after 2 weeks.^[18] These findings highlight the importance of considering herbal mouthwash as an option to improve periodontal health outcomes.

Mouthwash plays a crucial role for ICU patients using mechanical ventilators in reducing the colonization of oropharyngeal bacteria, which can lead to ventilator-associated pneumonia. Maintaining adequate oral hygiene has been proven to lower the incidence of ventilator-associated pneumonia in ICU patients. In a study involving 168 eligible ICU patients over 5 consecutive days, herbal mouthwash containing 6.66% *E. caryophyllata* demonstrated effectiveness comparable to that of 0.2% chlorhexidine mouthwash when applied using swabs to the mucous membrane of the mouth, tongue, and gums. The active ingredients of clove mouthwash, such as acetyleugenol, beta-caryophyllene, and vanillin, exhibit effectiveness against Gram-negative bacteria.^[29] Another study by Siriyanyongwong *et al.* also indicated that herbal mouthwash can mitigate the side effects associated with chlorhexidine mouthwash in ICU patients.^[34] Therefore, herbal mouthwash stands out as a simple and cost-effective alternative to oral care in these patients.^[35]

Nonetheless, the potential adverse effects of herbal mouthwash remain unclear, necessitating further research. It is crucial to conduct additional studies to gain a comprehensive understanding of any associated risks. Additionally, the development of guidelines, supported by evidence, is essential to ensure the safe and effective use of herbal mouthwash.

CONCLUSION

Herbal mouthwash is as effective as chlorhexidine in managing gingivitis and peri-implant mucositis and exhibits significant anti-inflammatory properties. Considering this, herbal mouthwash could be regarded as a viable option for enhancing oral health across various patient conditions.

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Conflicts of interest

There are no conflicts of interest.

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Is Herbal Mouthwash as Effective as Chlorhexidine?: A Review

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Review Article

Is Herbal Mouthwash as Effective as Chlorhexidine?: A Review

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ABSTRACT

Pathogenic biofilms contribute to several oral problems, including caries, periodontitis, and other infections. Chlorhexidine has long been considered the gold standard for chemical dental plaque control. However, it is accompanied by adverse effects, such as taste alterations, staining, and cytotoxicity. In response to these challenges, herbal mouthwashes have emerged as a promising alternative treatment, with fewer drawbacks. The primary aim of this review was to assess the effectiveness of herbal mouthwashes in comparison to chlorhexidine. Adhering to the PRISMA guidelines, this review focused on questions concerning the effectiveness of herbal mouthwashes compared to chlorhexidine. A systematic search was executed in prominent databases, including PubMed, SpringerLink, ScienceDirect, and Wiley. Using predefined keywords, five articles were selected for inclusion in the review and subsequent research synthesis. The review findings suggest that herbal mouthwashes exhibit effectiveness comparable to chlorhexidine, accompanied by the added benefit of fewer side effects. However, further research is needed to comprehensively evaluate the long-term safety and efficacy of herbal mouthwash.

KEYWORDS: *Chlorhexidine, effectiveness, herbal, mouthwash, oral health, review*

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BACKGROUND

Many types of bacteria have been discovered in the oral environment, forming multispecies biofilms or extracellular matrices rich in polysaccharides. Biofilm formation triggers a host inflammatory immune response, which, in some circumstances, may be detrimental.^[1,2] Pathogenic biofilms on tooth surfaces may result in the occurrence of caries, periodontitis, peri-implant disease, root canal infections, and other oral infections.^[1] Gingivitis and periodontitis, affecting periodontal tissue, are common illnesses originating from bacteria.^[2] Disrupting and preventing biofilm formation in the oral environment using anti-plaque agents such as chlorhexidine, cetylpyridinium chloride, fluoride, zinc, and stannous chloride is effective.^[3-5]

Currently, various types of mouthwash are commonly used in oral hygiene routines, playing a complementary role considered an addition to toothbrushing as

primary therapy.^[1,2] Mouthwash can diminish biofilm formation in instances of insufficient mechanical debridement caused by ineffective tooth brushing techniques. Antiseptic substances with minimal systemic cytotoxicity and enduring potency align with the optimal criteria for mouthwash, preventing immediate rinsing by salivary flow.^[6]

Chemical mouthwashes, such as chlorhexidine, are effective in preventing plaque development and are considered the gold standard for the chemical control of dental plaque.^[7,8] Both Gram-positive bacteria, such as *Staphylococcus aureus*, and Gram-negative bacteria, such as *Enterococcus faecalis*, *Aggregatibacter actinomycetemcomitans*, and *Porphyromonas gingivalis*, along with yeasts and viruses, are susceptible

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to chlorhexidine.^[2,5] Chlorhexidine increases the permeability of microbial cell membranes, alters protein functions, and precipitates macromolecules in the cytoplasm. It also exhibits bacteriostatic properties by binding nonspecifically to negatively charged membrane phospholipids of bacteria, inhibiting ATPases, and preventing prokaryotic cells from replicating.^[5]

In addition to its beneficial effects, chlorhexidine has associated negative effects, including dysgeusia, dehydration, tooth and tongue pigmentation, and allergic reactions. In human cells *in vitro*, chlorhexidine can cause cytotoxicity, leading to apoptosis and necrotic cell death.^[2,9] To address these adverse effects, herbal mouthwash with antibacterial and anti-inflammatory properties may enhance patient compliance, as it typically has fewer negative effects than chlorhexidine.^[10] Herbal formulations, which contain plant-derived compounds without the risk of teeth staining, exhibit a milder taste, and minimize the potential for dry mouth.^[11,12]

Various medicinal herbs, such as thyme, cloves, green tea, licorice, and peppermint leaves, have been utilized for ages in traditional medicine to address dental issues, such as toothaches, cavities, and gum diseases.^[13] Furthermore, miswak, rosemary, olive oil, myrrh, anise, sesame, ginger, and garlic are used in Middle Eastern countries for treating oral disorders.^[14] Herbal medicines have evolved in dentistry as anti-inflammatory, antibacterial, antiseptic, and therapeutic agents. Traditionally, herbal medicine has been used to address issues like caries, gingivitis, and periodontitis. Additionally, it has applications as an intracanal medication, sialogogue, and tooth whitening agent.^[15] Herbal medicine contains diverse bioactive substances, including phenolic compounds such as flavonoids and phenolic acids, exhibiting antibacterial effects. These substances have the potential to substitute chemical mouthwash.^[2,5] Due to their various biological and medicinal activities and lower cost, herbal mouthwash may contribute to better oral health maintenance.^[2] The active ingredients of herbal mouthwashes are derived from natural sources, such as essential oils, plant extracts, and other botanical compounds. These ingredients are deemed safe and have a history of use in traditional medicine for various purposes. Formulating herbal mouthwashes with lower concentrations of active ingredients contributes to a reduction in adverse effects, such as staining or irritation, enhancing both their effectiveness and safety profile.^[16,17] Compared to chlorhexidine, herbal mouthwashes show no

significant difference in terms of reducing plaque, gingivitis, and gingival bleeding.^[18,19] Additionally, herbal mouthwash yields inconclusive results for maintaining oral hygiene in patients with fixed orthodontics compared with chlorhexidine.^[20]

This review aims to evaluate the existing literature on the efficacy of herbal mouthwash compared to chlorhexidine as a mouthwash.

8

MATERIALS AND METHODS

This review adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [Figure 1].^[21]

Focused questions

A focused question was developed using the PICO (Population, Intervention, Comparison, and Outcome) framework, serving as the foundation for the inclusion and exclusion criteria for the current review. The focus question was “Are herbal mouthwashes equally effective as chlorhexidine in promoting oral health and managing oral diseases?”

- Population: adult human subjects
- Intervention: use of herbal mouthwash after supragingival debridement or no additional periodontal treatment
- Comparison: use of chlorhexidine mouthwash after supragingival debridement or no additional periodontal treatment
- Outcome: gingiva, lips, oral mucosa, teeth, tongue swab, biofilm, and clinical periodontal parameters, including gingival inflammation, dental plaque, pocket depth, biofilm

Search strategy

Four databases (PubMed, SpringerLink, ScienceDirect, and Wiley) were used to conduct a literature search within 2018–2023. A search string was created using the PICO model. The databases were searched for the following phrases: (“herbal” [MeSH Terms] AND “mouthwash” [MeSH Terms]) OR “mouth rinse” [MeSH Terms] AND “chlorhexidine” [MeSH Terms].

Inclusion/exclusion criteria

The study included full-text articles conducted in English on human subjects, comparing the effectiveness of herbal mouthwash with that of chlorhexidine. The exclusion criteria encompassed studies on animals, *in vitro* experiments, and review papers.

Study selection

All references underwent systematic categorization. Three independent reviewers (SS, JE, and PN)

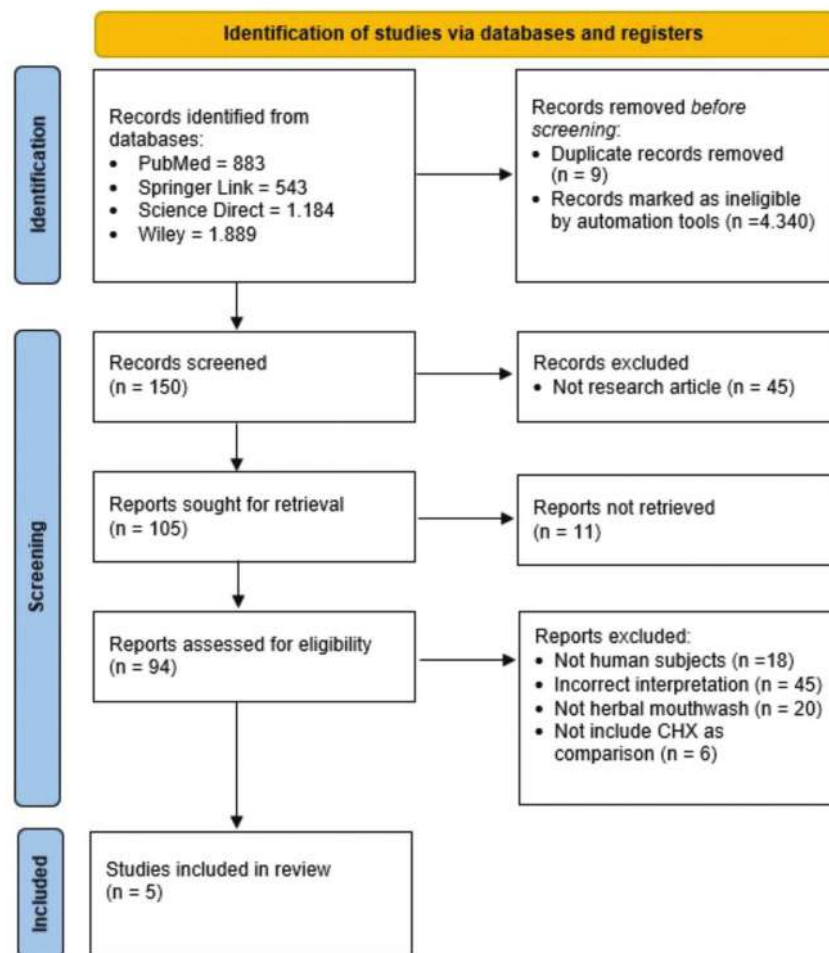


Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for study selection.^[21]

conducted an initial screening based on the titles and abstracts of the articles, followed by a full-text evaluation. Any discrepancies in article eligibility were resolved through inter-reviewer discussion.

RESULTS

In the study's initial phase, searches for articles were conducted using predefined keywords in four databases, complemented by manual searches. After eliminating duplicate titles and using automation tools, 150 articles were initially selected; of these, 45 were excluded due to their non-research nature. Out of the remaining 105 articles, 11 were excluded because they lacked full-text availability. Following the eligibility criteria, 89 articles were excluded for not involving human subjects, incorrect interpretations, lack of focus on herbal mouthwash, or absence of chlorhexidine as

a comparison. Finally, five articles were included in the review and research synthesis [Table 1].

DISCUSSION

Effectively managing oral care products poses challenges.^[22] To prevent plaque formation, a combination of mechanical techniques and chemical substances is necessary. Mechanical plaque prevention methods include brushing and interdental cleaning. Thus, incorporating supplementary antiseptic agents, such as mouthwash, is crucial to enhance oral hygiene and improve periodontal health.^[23] The notable effects of mouthwash on the subgingival biofilm include preventing biofilm accumulation and exhibiting anti-gingivitis properties, followed by its ability to prevent caries.^[24]

Table 1: Articles included in the review and research synthesis

No	Authors	Type of Study	Materials	Sample/parameter	Relevant Findings
1	Casarin et al. ^[1]	Randomized, crossover, double-blind clinical Trial	0.3% <i>Melaleuca alternifolia</i> nanoparticles mouthwash and 0.12% chlorhexidine on biofilm-free (BF) and biofilm-covered (BC) tooth surfaces	Biofilm (QHPI = Quigley & Hein Plaque Index)	0.3% <i>M. alternifolia</i> nanoparticles were as effective as 0.12% chlorhexidine in exhibiting important anti-inflammatory properties in healthy participants
2	Abullais et al. ^[2]	Double-blind randomized controlled trial	Alpine manuka mouthwash and 0.2% chlorhexidine	Dental plaque (plaque index), inflammation such as edema, redness, swelling, and spontaneous bleeding (gingival index), and bleeding upon gentle probing (modified sulcular bleeding index)	Manuka mouthwash was as effective as 0.2% chlorhexidine in managing chronic gingivitis and minimizing the adverse effects (e.g., staining, mucosal burning, and dehydration) associated with the long-term use of chlorhexidine
3	Alzoman et al. ^[28]	Randomized controlled trial	HiOra mouthwash and 0.2% chlorhexidine	Plaque index, bleeding on probing, and probing depth	HiOra mouthwash and 0.2% chlorhexidine had similar effectiveness in treating peri-implant mucositis
4	Jahanshir et al. ^[29]	Comparative randomized triple-blind clinical trial	6.66% clove mouthwash and 0.2% chlorhexidine	Gingiva, lips, oral mucosa, teeth, and tongue swab with Beck Oral Assessment Scale	6.66% clove mouthwash was as effective as 0.2% chlorhexidine in evaluating oral health status in ICU patients on mechanical ventilator
5	Nayak et al. ^[30]	Placebo-controlled double-blind parallel arm, interventional clinical study	0.15% guava mouthwash and 0.2% chlorhexidine	Supragingival plaque (Gracey curette), gingival index, plaque index, microbial count, and antioxidant level	0.15% guava mouthwash was as effective as 0.2% chlorhexidine in lowering plaque scores and maintaining gingival health in patients with chronic generalized moderate-to-severe gingivitis

The recommended effective dosage of chlorhexidine mouthwash is 18–20mg per use, with concentrations ranging from 0.12% to 0.2%. To optimize its effectiveness, it is advisable to delay chlorhexidine mouthwash use 30min after toothbrushing. This delay is suggested because certain toothpaste ingredients, such as calcium and anionic surfactants (e.g., sodium lauryl sulfate, sodium dodecyl sulfate, and cocamidopropyl betaine), may diminish their ability to adhere to oral surfaces. The mechanism of action of chlorhexidine involves its positive charge, attracting it to the negatively charged bacterial cell wall. Chlorhexidine forms specific adsorption to phosphate-containing molecules on the bacterial cell surface, facilitating penetration through the bacterial cell wall and damaging its integrity (bacteriostatic effect). This process leads to the release of low-molecular-weight cytoplasmic components, including potassium ions, and the inhibition of certain enzymes. Additionally, chlorhexidine induces cytoplasmic coagulation and precipitation by forming complexes with phosphorylated compounds, such as adenosine triphosphate and nucleic acids (bactericidal effect).^[8] The modification of stimuli affecting salty and bitter taste perception by chlorhexidine leads to a change

in taste perception.^[25] Due to a higher concentration, chlorhexidine may induce a burning sensation and discoloration of the teeth and tongue.^[26,27] Given these adverse effects, herbal mouthwash is considered an alternative to chlorhexidine, especially when dealing with patients who have peri-implant mucositis, chronic periodontitis, or are allergic to chlorhexidine.^[2,28]

Natural botanical products have shown promise in treating caries, gingivitis, and periodontitis.^[7] Herbal mouthwash, dentifrice, and gels have recently gained popularity. The active components in herbal mouthwash can penetrate the biofilm, reducing calculus formation and bacterial colonization on tooth surfaces.^[1] In this review, we found herbal mouthwash made from *Melaleuca alternifolia*, manuka, HiOra (*Salvadora persica*, *Terminalia bellirica*, *Gossia fragrantissima*, and *Elettaria cardamomum*), *Eugenia caryophyllata* (clove), and *Psidium guajava* L. (guava) leaf to be a promising alternative.^[1,2,28-30]

The following parameters were used to evaluate the effectiveness of herbal mouthwash in this review: plaque index (PI), gingival index (GI), and bleeding on probing (BOP) score.^[1,2,30] The presence of bleeding

during gum probing is a significant factor in attachment loss and disease progression.^[2] Another parameter considered in this review was the presence of biofilm-free and biofilm-covered tooth surfaces, along with the Beck Oral Assessment Scale score.^[1,29] The Beck Oral Assessment Scale instrument includes five indicators for evaluating the condition of the lips, gums, oral mucosa, teeth, tongue, and saliva.^[29]

In a study involving 60 healthy individuals, the use of 0.12% chlorhexidine within 7 days demonstrated a significantly ($P < 0.05$) lower anti-biofilm effect than with that of 0.3% *M. alternifolia*. Although *M. alternifolia* nanoparticles did not inhibit biofilm formation, they exhibited significant anti-inflammatory properties similar to 0.12% chlorhexidine mouthwash ($P > 0.05$). Both the chlorhexidine and *M. alternifolia* groups experienced a reduction in gingival crevicular fluid (GCF) volume, leading to *M. alternifolia* being considered an inflammatory predictor. Given that GCF originates from the microcirculation of gingival tissues, a correlation exists between GCF volume and gingival inflammation. *M. alternifolia* can be characterized by its nanometric particles. This property facilitates the easier penetration of *M. alternifolia* oil into the polymer matrix of the biofilm, thereby enhancing its anti-inflammatory characteristics. *M. alternifolia* also exhibits antiseptic, antibacterial, antifungal, and antiviral effects. Experimental *in vitro* testing has been conducted to assess its efficacy in preventing the formation and adherence of mono-species biofilms of periodontopathogens and cariogenic bacteria.^[1] Additionally, Srikumar *et al.* reported that *M. alternifolia* mouthwash is equally effective as chlorhexidine in reducing halitosis.^[31]

The efficacy of alternative mouthwashes in various periodontal diseases is supported by convincing evidence. In a study involving 45 patients with moderate plaque, manuka derived from New Zealand Nelson Honey, used for 14 days, demonstrated similar effectiveness compared to 0.2% chlorhexidine mouthwash. No differences were observed between chlorhexidine and manuka for PI, GI, and bleeding index at any time point, indicating that manuka mouthwash is promising for managing chronic gingivitis. Manuka mouthwash contains ascorbic acid and antioxidants, including lutein, alpha-linolenic acid, and omega-3 fatty acids, in high concentrations. These antioxidants act as free radical scavengers, preserving the health of periodontal tissues. Ascorbic acid, a strong antioxidant, is essential for preserving connective tissue, osteoid tissues, and dentin integrity. The antibacterial effect works through an osmotic

mechanism involving phenolic and antioxidant actions and the inhibition of enzyme synthesis of hydrogen peroxide.^[32] Importantly, manuka mouthwash offers the additional advantage of minimizing the adverse effects associated with long-term chlorhexidine use, such as staining, mucosal burning, and dehydration.^[2] Another study also found that manuka honey mouthwash has the same effectiveness as 0.2% chlorhexidine mouthwash in reducing gingivitis.^[33]

In the treatment of 48 patients with peri-implant mucositis, HiOra mouthwash derived from Himalaya Drug, Bengaluru, India, proved equally effective compared to 0.2% chlorhexidine mouthwash over 2 weeks of use. No statistically significant differences were observed in peri-implant PI, BOP, and probing depth between the herbal and 0.2% chlorhexidine mouthwash groups after 3, 6, and 12 weeks of follow-up. *S. persica* and *T. bellirica* in HiOra mouthwash are recognized for their ability to prevent plaque formation and to exhibit antimicrobial activity. Benzyl isothiocyanate from *S. persica* is effective against *P. gingivalis* and *A. actinomycetemcomitans*. The undesirable adverse effects of chlorhexidine, such as alterations in taste sensation and burning sensation, might necessitate the use of an oral rinse containing substitutes for chlorhexidine, especially for patients with peri-implant mucositis or chlorhexidine allergy.^[28]

In cases of chronic generalized moderate-to-severe gingivitis, 60 patients were instructed to use *P. guajava* L. leaf mouthwash and 0.2% chlorhexidine mouthwash for 30 days. The results demonstrated that *P. guajava* L. leaf mouthwash had an effectiveness equivalent to 0.2% chlorhexidine mouthwash in reducing plaque scores and preserving gingival health. No statistical difference was observed between the *P. guajava* L. leaf and chlorhexidine mouthwash groups at the first- and third-month intervals, suggesting comparable functional activity in lowering GI scores between the two types of mouthwash. The anti-inflammatory activity of *P. guajava* L. leaf bioactive ingredients, inhibiting prostaglandins, kinin, and histamines, further supports its contribution to gingival health. Additionally, ascorbic acid and phenolic chemicals, such as protocatechuic acid, ferulic acid, quercetin, guavin B, and gallic acid, increase antioxidant levels in saliva. Moreover, it has the capacity to remove hydrogen peroxide, liberate superoxide ions, and prevent hydroxyl radicals.^[30] Therefore, *P. guajava* L. leaf mouthwash could be a substitute for maintaining a healthy gingiva. A similar study on 50 patients with plaque-induced gingivitis also found no significant differences in the PI, GI, and BOP between 0.2% chlorhexidine and

herbal mouthwash consisting of *Myrtus communis*, *Quercus brantii*, *Punica granatum*, *Portulaca olerace*, and *Boswellia serrata*. Even the herbal mouthwash improved the periodontal condition after 2 weeks.^[18] These findings highlight the importance of considering herbal mouthwash as an option to improve periodontal health outcomes.

Mouthwash plays a crucial role for ICU patients using mechanical ventilators in reducing the colonization of oropharyngeal bacteria, which can lead to ventilator-associated pneumonia. Maintaining adequate oral hygiene has been proven to lower the incidence of ventilator-associated pneumonia in ICU patients. In a study involving 168 eligible ICU patients over 5 consecutive days, herbal mouthwash containing 6.66% *E. caryophyllata* demonstrated effectiveness comparable to that of 0.2% chlorhexidine mouthwash when applied using swabs to the mucous membrane of the mouth, tongue, and gums. The active ingredients of clove mouthwash, such as acetylenol, beta-caryophyllene, and vanillin, exhibit effectiveness against Gram-negative bacteria.^[29] Another study by Siriyanyongwong *et al.* also indicated that herbal mouthwash can mitigate the side effects associated with chlorhexidine mouthwash in ICU patients.^[34] Therefore, herbal mouthwash stands out as a simple and cost-effective alternative to oral care in these patients.^[35]

Nonetheless, the potential adverse effects of herbal mouthwash remain unclear, necessitating further research. It is crucial to conduct additional studies to gain a comprehensive understanding of any associated risks. Additionally, the development of guidelines, supported by evidence, is essential to ensure the safe and effective use of herbal mouthwash.

CONCLUSION

Herbal mouthwash is as effective as chlorhexidine in managing gingivitis and peri-implant mucositis and exhibits significant anti-inflammatory properties. Considering this, herbal mouthwash could be regarded as a viable option for enhancing oral health across various patient conditions.

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Conflicts of interest

There are no conflicts of interest.

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PAGE 1

PAGE 2

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sdj Author New Submission Acknowledgement letter: sdj_53_23

Scientific Dental Journal

Dear Dr. Dr. Shaila Soesanto,

Scientific Dental Journal has received your manuscript entitled "Is Herbal Mouthwash as Effective as Chlorhexidine ? Systematic Review " for consideration for publication. The reference number for this manuscript is "sdj_53_23". Kindly quote this in future correspondences related to this manuscript.

The manuscript is being reviewed for possible publication with the understanding that it is being submitted to ONE journal at a time and has NOT been published, simultaneously submitted, or already accepted for publication elsewhere either as a whole or in a part.

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Yours sincerely,
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Sheila Soesanto <shelasoesanto@trisakti.ac.id> to Scientific

Set, Nov 26, 2023, 2:15 PM

Dear Editorial Team,

Thank you for providing the valuable comments on our manuscript. We have already upload the revised manuscript. We look forward to the possibility of having our revised manuscript considered for publication.

drg. Sheila Soesanto, MKG
Pharmacology Department
Faculty of Dentistry



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17 of 21

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Scientific Dental Journal <editor@sdjdentj.com> to me

Thu, Nov 30, 2023, 9:20AM

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Scientific Dental Journal <editor@scidentj.com> to me Sat, Dec 2, 2023, 12:00 PM

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Scientific Dental Journal <editor@scidentj.com> to me Thu, Jan 11, 2:45 PM

Dear Soesanto,

An edited and formatted version of your manuscript sdj_53_23 entitled "Is Herbal Mouthwash as Effective as Chlorhexidine ? - a Review" which is scheduled for publication in a forthcoming issue of Scientific Dental Journal, has been uploaded on our site <https://review.jow.maknow.com/sdj>.

You are requested to check the same and upload corrected file within 5 days. If there are no changes click "No change" on the site.

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Thanking you,
Journal Editor

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Sheila Soesanto - sheilasoesanto@trisakti.ac.id
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Sun, Jan 14, 10:48 AM

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I have made some corrections through the website.
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drg. Sheila Soesanto, MKG
Pharmacology Department
Faculty of Dentistry



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Sun, Jan 14, 10:50 AM

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We shall get back to you soon for any further corrections.

Please note that the journal reserves the right to make changes in the language, grammar, presentation, etc. to suit the journal's requirements.

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Thu, Jan 18, 7:42 AM

Dear Dr. Sheila Soesanto,

We would like to inform you of the manuscript-handling and proofreader (native speaker) fee for your article "Is Herbal Mouthwash as Effective as Chlorhexidine? A Review" that will be published in Volume 7 Issue 3 2023.

Please kindly make a bank transfer payment worth USD 100 (Rp. 1.500.000,-) to:

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Account No: 801 022 0197
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We would like to hear from you soon.
Thank you.

Sincerely yours,
Dr. Muhammad Ihsan Rizal
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Thu, Jan 18, 8:42 PM

Dear Editor,

Attached is the proof of payment for article : " Is Herbal Mouthwash as Effective as Chlorhexidine?: A Review"
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Shaikh, Abdullah
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Sun, Jan 21, 2:34 PM

Dear Author,

We have incorporated all the corrections and attached an updated pdf for your review.
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Best Regards,

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Sheila Soesanto <sheila.soesanto@trisakti.ac.id>
to Abdullloh

Dear Editor,
I have already check the manuscript.
It is ready for online publication.

Thank you so much for your attention

dr. Sheila Soesanto, MKG
Pharmacology Department
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1 of 21
Mon, Jan 22, 11:29AM

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1 **Is Herbal Mouthwash as Effective as Chlorhexidine? : a Review**

2
3 **ABSTRACT**

4 Pathogenic biofilms can lead to various oral problems, including caries, periodontitis, and other
5 infections. Chlorhexidine (CHX) has been traditionally considered the gold standard in chemical dental
6 plaque control. However, CHX has some adverse effects, such as taste alterations, staining, and
7 cytotoxicity. To overcome this issue, herbal mouthwashes offer a promising alternative treatment with
8 fewer adverse effects. The objective of this review is to assess the effectiveness of herbal mouthwashes
9 compared to CHX. This review followed the PRISMA guidelines and focused on questions related to
10 the effectiveness of herbal mouthwashes compared to chlorhexidine. Search was conducted in PubMed,
11 SpringerLink, ScienceDirect, and Wiley. **Using the predefined keywords, five articles** were included in
12 the review and research synthesis. The findings showed that **herbal mouthwashes were as effective as**
13 **CHX**. Herbal mouthwash also exhibited fewer side effects than CHX. However, further research is
14 needed to comprehensively evaluate the long-term safety and efficacy of herbal mouthwash.

15 **Keywords:**

16 chlorhexidine, effectiveness, herbal, mouthwash, oral health, review

Commented [A1]: The title is changed from systematic review to a review

Commented [A2]: The abstract does not comply with background, objectives, methods, results and conclusion

Commented [A3R2]: Thank you for your feedback, but we followed the guidelines provided by SDJ. We also noticed that the abstract on published manuscript was written in an unstructured manner.

Commented [A4]: The abstract was well written, but some concerns need to be addressed.

Please reconstruct the result as the authors has mentioned as "herbal mouthwashes, such as Manuka, HiOra, and guava leaf extracts, were as effective as CHX in managing gingivitis, peri-implant mucositis, and maintaining oral health" (line 13-15) which can be misunderstood as the results came from 3 separate studies. Conclusion should be more concise in answering the study question.

Commented [A5R4]: Thank you for your suggestion. Changes has been made in line 12-13

18 **BACKGROUND**

19 Many kinds of bacteria were discovered in the oral environment that formed a multispecies biofilm or
 20 extracellular matrix rich in polysaccharides. Biofilm formation triggered a host inflammatory immune
 21 response, which in some circumstances may be harmful.^{1,2} Pathogenic biofilm on tooth surfaces could
 22 lead to the development of caries, periodontitis, peri-implant disease, root canal infections, and other
 23 oral infections.¹ Gingivitis and periodontitis, which affect the periodontal tissue, are common illnesses
 24 that originate from bacteria.² The disruption and prevention of biofilm formation in the oral environment
 25 has been demonstrated to be effective with the use of anti-plaque agents such as chlorhexidine (CHX),
 26 cetylpyridinium chloride, fluoride, zinc, and stannous chloride.³⁻⁵

27
 28 Nowadays, many kinds of mouthwash are commonly used in the oral hygiene routine and play a
 29 complementary role that is considered as an addition to toothbrushing as primary therapy.^{1,2} Mouthwash
 30 might reduce biofilm formation if there is inadequate mechanical debridement caused by poor tooth
 31 brushing techniques. Antiseptic substances with a very low systemic cytotoxicity and long-lasting
 32 potency meet the ideal criteria for mouthwash. It prevents the mouthwash from being immediately
 33 rinsed by the salivary flow.⁶

34
 35 Chemical mouthwash such as chlorhexidine (CHX) have been reported to be effective in preventing
 36 plaque development. Chlorhexidine is considered as the gold standard in the chemical control of dental
 37 plaque.^{7,8} Both Gram-positive bacteria such as *Staphylococcus aureus* and Gram-negative bacteria such
 38 as *Enterococcus faecalis*, *Aggregatibacter actinomycetemcomitans*, and *Porphyromonas gingivalis*
 39 microorganisms, also yeasts and viruses are susceptible to CHX.^{2,5} Chlorhexidine increases the
 40 permeability of microbial cell membranes, changes protein functions, and precipitates macromolecules
 41 in the cytoplasm. Due to the inhibition of ATPases, which prevents prokaryotic cells from replicating,
 42 it also has bacteriostatic properties by binding non-specifically to negatively charged membrane
 43 phospholipids of bacteria.⁵

44
 45 Beside the beneficial effects, there are some negative effects of CHX such as dysgeusia, dehydration,
 46 tooth and tongue pigmentation, and allergic reaction. In human cells in vitro, CHX could cause
 47 cytotoxicity which can lead to apoptosis and necrotic cell death.^{2,9} To overcome these adverse effects,
 48 herbal mouthwash with antibacterial and anti-inflammatory properties may improve compliance among
 49 patients since they have less negative effects compared to CHX.¹⁰ Herbal formulation contained plant-
 50 derived compounds without the risk of teeth staining, had milder taste, and minimized the potential for
 51 dry mouth.^{11,12}

52
 53 Various medicinal herbs have been utilized for ages in traditional medicine to overcome dental issues.
 54 Herbs and spices like thyme, cloves, green tea, licorice, and peppermint leaves can effectively treat
 55 and prevent dental problems like toothache, caries, and gum disease.¹⁴ Miswak, rosemary, olive oil,
 56 myrrh, anise, sesame, ginger, and garlic are also been used in Middle Eastern countries for treating oral
 57 disorder.¹⁴ Herbal medicine has been developed in dentistry as anti-inflammatory,
 58 antibacterial, antiseptic, and therapeutic agents. Herbal medicine traditionally used to treat caries,
 59 gingivitis, and periodontitis. It is also used as an intracanal medication, sialagogue, and tooth
 60 whitening.¹⁵ Several studies have shown that herbal medicine contains various bioactive substances,
 61 such as phenolic compounds, including flavonoids and phenolic acids, which possess antibacterial
 62 effects. These substances have the potential to replace chemical mouthwash.^{2,5} Due to their various
 63 biological and medicinal activities and cheaper cost, herbal mouthwash may compromise better oral
 64 health maintenance.² The active ingredients of herbal mouthwashes come from natural sources such as
 65 essential oils, plant extracts, and other botanical compounds. These ingredients are considered safe and
 66 have been used in traditional medicine for various purposes. Herbal mouthwashes formulated with
 67 lower concentrations of active ingredients will reduce of adverse effects like staining or irritation. These

Commented [A6]: The authors should mention about substantivity (line 36) of herbal mouthwash compares with CHX mouthwash, not only the antimicrobial and antiinflammation properties.

The authors highlighted the use of herbal mouthwash as “they have less negative effects compared to CHX” (line 54) and “higher safety margins” (line 63) compare to chlorhexidine, please add more references and provide more information to support this claim.

Commented [A7R6]: We appreciate your valuable review. At line 31-33 we only explain about the ideal criteria for mouthwash.

The substantivity of herbal mouthwash compared to CHX has been added in line 68-71

More information about less negative effects of herbal mouthwash compared to CHX has been added in line 49-51

Some explanations related to herbal mouthwash safety margin has been added in line 64-68

Commented [A8]: there are two repetitions of words such as

Commented [A9R8]: thank you for your correction. Changes done in line 25

Commented [A10]: It is recommended to present several expert opinions that support this and also the prevalence of the use of this herbal mouthwash

Commented [A11R10]: Thank you for your suggestion.

Several expert opinion has been added in line 54-57. But unfortunately, we are unable to find the prevalence of herbal mouthwash use.

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68 facts contribute to their effectiveness and enhance their safety profile.^{16,17} Compared to CHX, herbal
69 mouthwashes show no difference in reducing plaque, gingivitis, and gingival bleeding.^{18,19} Besides,
70 herbal mouthwash show inconclusive result for maintaining oral hygiene in patients with fixed
71 orthodontic compared to CHX.²⁰

72
73 The aim of this review is to assess the available paper on the efficacy of herbal mouthwash compared
74 to chlorhexidine as a mouthwash.

75 **MATERIALS AND METHODES**

76
77 This review was conducted according to the Preferred Reporting Items for Systematic Reviews and
78 Meta-Analyses (PRISMA) guideline (Figure 1).²¹

79
80 **Focused questions**

81 Focused question was developed using PICO (Population, Intervention, Comparison, and Outcome)
82 which served as the basis for the inclusion and exclusion criteria for the current review. The focus
83 question is: "Are herbal mouthwashes equally effective as chlorhexidine in promoting oral health and
84 managing oral diseases?"

- 85 • Population : adult human subjects
- 86 • Intervention : use of herbal mouthwash following supragingival debridement or no
87 additional periodontal treatment
- 88 • Comparison : use of chlorhexidine mouthwash following supragingival debridement or no
89 additional periodontal treatment
- 90 • Outcome : gingiva, lips, oral mucosa, teeth, tongue swab, biofilm, and clinical
91 periodontal parameters, including gingival inflammation, dental plaque, pocket depth, biofilm

92
93 **Search Strategy**

94 Four databases (PubMed, SpringerLink, ScienceDirect, and Wiley) were used to conduct literature
95 search within 2018-2023. A search string was created using the PICO model. The databases were
96 searched for the phrase ("herbal" [MeSH Terms] AND "mouthwash" [MeSH Terms]) OR "mouthrinse"
97 [MeSH Terms] AND "chlorhexidine" [MeSH Terms].

98
99 **Inclusion/exclusion criteria**

100 The inclusion criteria for this study were full-text articles conducted in English on human subjects and
101 herbal mouthwash effectiveness was compared to chlorhexidine. The exclusion criteria were studies on
102 animals, in vitro experiments, and review papers.

103
104 **Study Selection**

105 All references were systematically categorized. Three independent reviewers (PN, JE, and SS)
106 conducted an initial screening based on the titles and abstracts of the articles. Subsequently, an
107 evaluation of the full texts was performed. Any differences in the evaluation of article eligibility were
108 resolved through inter-reviewer discussion.

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109 **RESULT**

110
111 In the initial phase of the study, searches for articles was conducted using pre-defined keywords in four
112 databases and performed manual searches. After removing the duplication title and using automation
113 tools, 150 articles were selected. Of these, 45 articles were excluded due to their non-research articles.
114 Out of 105 articles, 11 articles were excluded because they did not have the full text available. Following
115 the application of the eligibility criteria, 89 articles were excluded because they did not involve human
116 subjects, had incorrect interpretations, did not focus on herbal mouthwash, or did not include CHX as
117 a comparison. Finally, five articles were included in the review and research synthesis. (Table 1)

Commented [A12]: I am not sure that the authors wanted to address 4,499 articles or 4,499 articles (line 12 and 107, and figure 1)
Figure 1 appears twice in this manuscript (page 12 and 13)

Commented [A13R12]: Changes has been made in line 11, 111-112, and figure 1.

DISCUSSION

Maintaining effective plaque management with oral care products can be challenging.²² To prevent plaque formation, a combination of mechanical techniques and chemical substances is needed. Brushing and interdental cleaning are examples of mechanical plaque prevention methods.²³ Hence, it is crucial to add supplementary antiseptic agents such as mouthwash to enhance oral hygiene and improve periodontal health.²² The most beneficial effects of mouthwash on the subgingival biofilm are the prevention of biofilm accumulation and its anti-gingivitis properties, followed by its ability to prevent caries.²⁴

The effective dosage of CHX mouthwash is 18 to 20 mg per use, with concentrations ranging between 0.12% and 0.2%. To enhance the effectiveness of CHX mouthwash, it is recommended to delay its use by 30 minutes after toothbrushing, as certain toothpaste ingredients, such as calcium and anionic surfactants (e.g., sodium lauryl sulfate, sodium dodecyl sulfate, and cocamidopropyl betaine), may reduce its ability to adhere to oral surfaces. The mechanism of action of chlorhexidine involves its positive charge which attract to the negatively charged bacterial cell wall. It forms specific adsorption to phosphate-containing molecules on the bacterial cell surface, facilitating penetration through bacteria cell wall, and damage its integrity (bacteriostatic effect). This process results in the release of low-molecular-weight cytoplasmic components, including potassium ions, and the inhibition of certain enzymes. Furthermore, chlorhexidine induces cytoplasmic coagulation and precipitation by forming complexes with phosphorylated compounds, such as adenosine triphosphate (ATP) and nucleic acids (bactericidal effect).⁸ The alteration of stimuli in salty and bitter taste perception by CHX results in a change in taste perception.²⁵ Due to higher concentration, CHX may cause burning sensation and teeth and tongue discoloration.^{26,27} With these adverse effects, herbal mouthwash is considered as an alternative to CHX, particularly when dealing with patients who have peri-implant mucositis, chronic periodontitis, or allergic to CHX.^{2,28}

Natural botanical products appear to be promising for the treatment of caries, gingivitis, and periodontitis.⁷ Herbal mouthwash, dentifrice, and gels have gained popularity in recent years. The active components in herbal mouthwash can penetrate the biofilm and reduce calculus formation, hence reducing bacterial colonization on tooth surfaces.²² In these review, we found that herbal mouthwash from *Melaleuca alternifolia*, Manuka, HiOra (*Salvadora persica*, *Terminalia bellirica*, *Gossia fragrantissima*, and *Elettaria cardamomum*), *Eugenia caryophyllata* (clove) and *Psidium guajava L.* (guava) leaf can be promising herbal mouthwash.^{1,2,28-30}

Parameters used to evaluate the effectiveness of herbal mouthwash in this review are Plaque Index (PI), Gingival Index (GI), and Bleeding on Probing (BOP) score.^{1,2,30} The presence of bleeding when probing the gums is a significant factor of attachment loss and disease progression.²² Another parameter that is used in this review is biofilm-free and biofilm-covered on tooth surfaces and BOAS (Beck Oral Assessment Scale) score.^{1,29} The BOAS instrument comprises five indicators, assessing the condition of the lips, gums, oral mucosa, teeth, tongue, and saliva.²⁹

In 60 healthy individuals, the use of 0.12% CHX within 7 days had significantly ($p < 0.05$) lower anti-biofilm effect regarding to 0.3% *Melaleuca alternifolia* (MEL). Although MEL nanoparticle did not inhibit biofilm formation, it showed significant anti-inflammatory properties similar to 0.12% CHX mouthwash ($p > 0.05$). A reduction in gingival crevicular fluid (GCF) volume occurred in both CHX and MEL group, making MEL being considered as inflammatory predictor. Considering that GCF originates from the microcirculation of gingival tissues, there is a correlation between GCF volume and gingival inflammation. *Melaleuca alternifolia* could be defined to the nanometric particles, which makes it easier for MEL oil to penetrate the polymer matrix of the biofilm and improve its anti-inflammatory characteristics. *Melaleuca alternifolia* also demonstrates antiseptic, antibacterial,

Commented [A14]: No need to repeat the content the authors have already mentioned in introduction again and again.

I am not sure what is the meaning when the authors addressed that "For CHX mouthwash to be effective, it's recommended to wait at least 30 minutes after tooth brushing" Does it mean we have to wait at least 30 minutes to rinse the mouth with CHX after tooth brushing? Or it means we should not drink or eat for 30 minutes after rinsing the mouth with CHX? If so, it can mislead the audience to conclude that CHX has lower effectiveness and need longer time to react with oral microbe compare with herbal mouthwash and also the fact that CHX mouthwash has high substantivity in oral cavity compare with other mouthwash.

Please provide more information about mechanism of action of CHX, so the audience will understand more clearly about CHX side effect and adverse effects.

I think the information from Table 1 is too little. In discussion part, the authors should mentioned more about the sample size, how long did the subjects use the mouthwash? and also the statistic that previous studies use to strengthen the idea that herbal mouthwash has similar effectiveness when compared with CHX mouthwash.

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The information explaining the use of CHX after toothbrushing is stated in lines 128-131. If CHX is used after toothbrushing, it is recommended to delay for 30 minutes.

The mechanism of action of CHX is added in line 131-140

More information related to sample size, The duration of mouthwash use, and statistic are added in line 159-165, 172-177, 188-205, 209-212, and 220

Commented [A16]: Is BOAS an abbreviation? If so, it can be extended

Commented [A17R16]: Yes, BOAS is an abbreviation. Correction has been made in line 155-156

168 antifungal, and antiviral effects. It has been experimentally tested in vitro to prevent the formation and
169 adherence of mono-species biofilms of periodontopathogens and cariogenic bacteria.¹ Srikumar *et al*
170 also stated that MEL mouthwash is equally effective as CHX in reducing halitosis.³¹

171
172 The efficacy of alternative mouthwash in various periodontal diseases have presented a convincing
173 evidence. In a study of 45 patients with moderate plaque, Manuka derived from New Zealand Nelson
174 Honey used for 14 days showing the same effectiveness compared to 0.2% CHX mouthwash. There
175 were no difference between CHX and Manuka for PI, GI, and Bleeding Index at any time point. This
176 suggests that Manuka mouthwash has emerged as a promising mouthwash in managing chronic
177 gingivitis. It has been known that Manuka mouthwash contains ascorbic acid and antioxidants,
178 including lutein, alpha-linolenic acid, and omega-3 fatty acids in high concentration. The antioxidants
179 act as free radical scavengers and aid in preserving health of periodontal tissues. Ascorbic acid is also
180 known as a strong antioxidant that is necessary for preserving connective tissue, osteoid tissues, and
181 dentin integrity. The antibacterial effect works through an osmotic mechanism involving phenolic and
182 antioxidant actions and upon the inhibin enzyme's synthesis of hydrogen peroxide.³² Notably, Manuka
183 mouthwash offers the additional advantage of minimizing adverse effects associated with long-term
184 CHX use, such as staining, mucosal burning, and dehydration.² Other study also found that
185 Manuka honey mouthwash has the same effectiveness as 0.2 % CHX mouthwash in reducing
186 gingivitis.³³

187
188 For the treatment of 48 patient with peri-implant mucositis, HiOra mouthwash derived from Himalaya
189 Drug, Bengaluru, India has proven equally effective compared to 0.2% CHX mouthwash in 2 weeks of
190 use. There was no statistically significant difference in peri-implant PI, BOP, and Probing Depth
191 between herbal and 0.2% CHX mouthwash group after 3, 6, and 12 weeks follow up. *S. persica* and *T.*
192 *bellirica* in HiOra mouthwash are recognized for their ability to prevent plaque formation and exhibit
193 antimicrobial activity. Benzyl isothiocyanate from *S. persica* is effective against *Porphyromonas*
194 *gingivalis* and *Aggregatibacter actinomycetemcomitans*. The undesirable adverse effects of CHX such
195 as alterations in taste sensation and burning sensation, might require the use of an oral rinse containing
196 substitutes for CHX, especially for patients with peri-implant mucositis or CHX allergy.²⁸

197
198 In cases of chronic generalized moderate to severe gingivitis, 60 patients had to use 0.15% *Psidium*
199 *guajava* L. (guava) leaf mouthwash and 0.2% CHX mouthwash for 30 days. The result demonstrated
200 that *P. guajava* L. leaf mouthwash had effectiveness equivalent to 0.2% CHX mouthwash in reducing
201 plaque scores and preserving gingival health. There was no statistical difference between *Psidium*
202 *guajava* L. leaf and chlorhexidine mouthwash groups at first and third-month intervals. This suggests
203 comparable functional activity in lowering gingival index scores between two mouthwashes. The anti-
204 inflammatory activity of *P. guajava* L. leaf bioactive ingredients, inhibit prostaglandins, kinin, and
205 histamines, further supports its contribution to gingival health. Furthermore, ascorbic acid and phenolic
206 chemicals such as protocatechuic acid, ferulic acid, quercetin, guavin B, and gallic acid increase
207 antioxidant levels in saliva. Additionally, it has the capacity to remove hydrogen peroxide, liberate
208 superoxide ions, and prevent hydroxyl radicals.³⁰ Therefore, *P. guajava* L. leaf mouthwash could be an
209 alternative for maintaining healthy gingiva. Similar study on 50 patients with plaque-induced gingivitis
210 also found that there are no significant differences found in the PI, GI, and BOP between 0.2% CHX
211 and herbal mouthwash consist of *Myrtus communis*, *Quercus brantii*, *Punica granatum*, *Portulaca*
212 *olerace*, and *Boswellia serrata*. Even herbal mouthwash could improve the periodontal condition after
213 two weeks.¹⁸ These findings showed the importance of considering herbal mouthwash as an option to
214 improve periodontal health outcomes.

215
216 Mouthwash is also essential for ICU patients using mechanical ventilators to reduce the colonization of
217 oropharyngeal bacteria, which cause Ventilator-Associated Pneumonia (VAP). Adequate oral hygiene
218 has been found to lower the incidence of VAP in ICU patients. Herbal mouthwash containing 6.66% *E.*

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219 *caryophyllata* was just as effective as 0.2% CHX mouthwash when applied using swabs to the mucous
220 membrane of mouth, tongue, and gums to 168 eligible ICU patients for 5 days in a row. The active
221 ingredients of clove mouthwash such as acetylenol, beta-caryophyllene, and vanillin, can be
222 effective against Gram-negative bacteria.²⁹ Another study by Siriyanyongwong et al also found that
223 herbal mouthwash can reduce side effects from CHX mouthwash in ICU patients.³⁴ Therefore, herbal
224 mouthwash can be considered as simple and low-cost mouthwash.

225
226 The adverse effects of herbal mouthwash are still unknown, so further research needs to be conducted.
227 It is crucial to develop guidelines, supported by evidence, for the use of herbal mouthwash.

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228 **CONCLUSION**

229 Herbal mouthwash had the same effectiveness as CHX in managing gingivitis, peri-implant mucositis,
230 and exhibiting important anti-inflammatory properties. Herbal mouthwash could be considered as an
231 option to improve oral health in different kinds of patient conditions.

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340 TABLES

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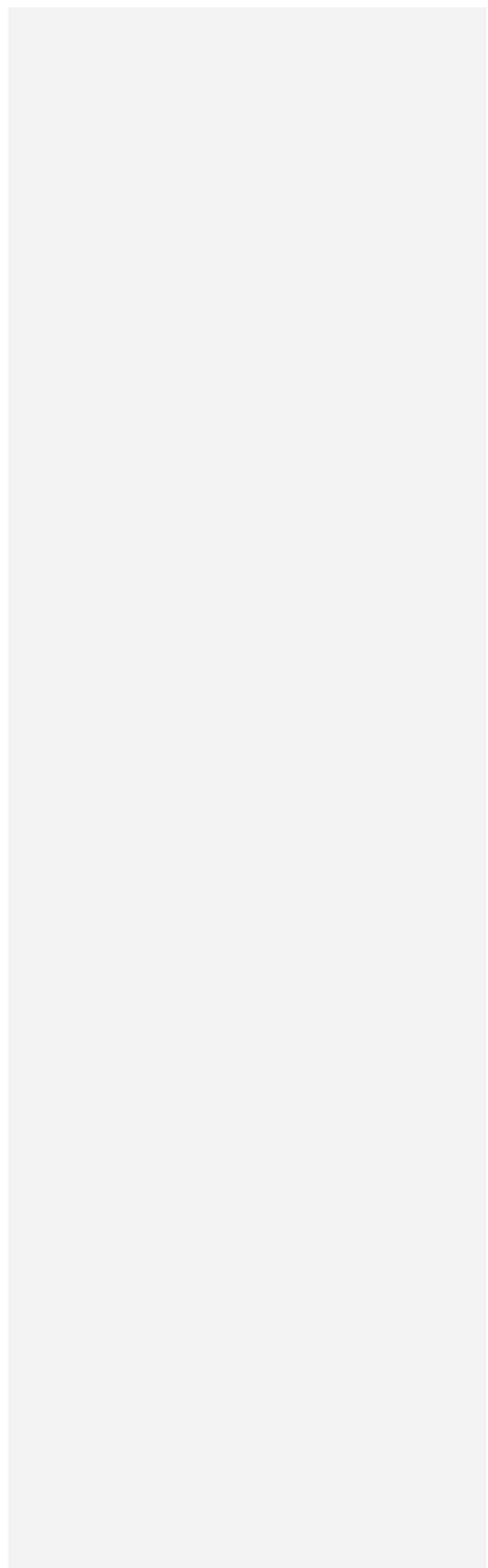
Table 1. Paper Result

No	Author	Type of Study	Materials	Sample/parameter	Relevant Findings
1	Casarin, M <i>et al</i> ¹	Randomized, crossover, double-blind clinical trial	0.3% <i>Melaleuca alternifolia</i> nanoparticles mouthwash and 0.12% CHX on biofilm-free (BF) and biofilm-covered (BC) tooth surfaces	Biofilm (QHPI =Quigley & Hein Plaque Index)	0.3% <i>Melaleuca alternifolia</i> nanoparticles was as effective as 0.12% CHX in exhibiting important anti-inflammatory properties on healthy participants
2	Abullais, SS <i>et al</i> ²	Double-blind randomized controlled trial	Alpine Manuka mouthwash and 0.2% CHX	Dental plaque (Plaque index), inflammation such as edema, redness, swelling, and spontaneous bleeding (Gingival index), bleeding upon gentle probing (Modified Sulcular Bleeding index)	Manuka mouthwash was as effective as 0.2% CHX in managing chronic gingivitis and minimizing the adverse effects (e.g. staining, mucosal burning, and dehydration) associated with long-term use of CHX
3	Alzoman, H <i>et al</i> ²⁸	A randomized controlled trial	HiOra mouthwash and 0.2% CHX	Plaque index, bleeding on probing, probing depth	HiOra mouthwash and 0.2% CHX had the same effectiveness in treating peri-implant mucositis
4	Jahanshir M <i>et al</i> ²⁹	A Comparative randomized triple-blind clinical trial	6.66% Clove mouthwash and 0.2% CHX	Gingiva, lips, oral mucosa, teeth, and tongue swab with Beck Oral Assessment Scale (BOAS)	6.66% Clove mouthwash was as effective as 0.2% CHX in evaluating oral health status in ICU patient undergoing mechanical ventilator
5	Nayak N <i>et al</i> ³⁰	Placebo-controlled double blind parallel arm, interventional clinical study	0.15% Guava mouthwash and 0.2% CHX	Supragingival plaque (Gracey curette), Gingival Index, Plaque Index, microbial count, and antioxidant level	0.15% Guava mouthwash was as effective as 0.2% CHX in lowering plaque scores and maintaining gingival health on chronic generalized moderate to severe gingivitis patient

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1 **Is Herbal Mouthwash as Effective as Chlorhexidine?: A Review**

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11
12
13 **Abstract**

14 Pathogenic biofilms contribute to several oral problems, including caries, periodontitis, and
15 other infections. Chlorhexidine has long been considered the gold standard for chemical dental
16 plaque control. However, it is accompanied by adverse effects, such as taste alterations,
17 staining, and cytotoxicity. In response to these challenges, herbal mouthwashes have emerged
18 as a promising alternative treatment, with fewer drawbacks. The primary aim of this review
19 was to assess the effectiveness of herbal mouthwashes in comparison to chlorhexidine.
20 Adhering to the PRISMA guidelines, this review focused on questions concerning the
21 effectiveness of herbal mouthwashes compared to chlorhexidine. A systematic search was
22 executed in prominent databases, including PubMed, SpringerLink, ScienceDirect, and Wiley.
23 Using predefined keywords, five articles were selected for inclusion in the review and
24 subsequent research synthesis. The review findings suggest that herbal mouthwashes exhibit
25 effectiveness comparable to chlorhexidine, accompanied by the added benefit of fewer side
26 effects. However, further research is needed to comprehensively evaluate the long-term safety
27 and efficacy of herbal mouthwash.

28
29 **Keywords:** chlorhexidine, effectiveness, herbal, mouthwash, oral health, review

30
31 **Key Messages:**

32 This review evaluates herbal mouthwashes as alternatives to chlorhexidine, the gold standard
33 for plaque control. Findings suggest comparable effectiveness with fewer side effects,
34 emphasizing the need for further research to assess long-term safety and efficacy.

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35 **Background**

36 Many types of bacteria have been discovered in the oral environment, forming multispecies
37 biofilms or extracellular matrices rich in polysaccharides. Biofilm formation triggers a host
38 inflammatory immune response, which, in some circumstances, may be detrimental.^[1,2]
39 Pathogenic biofilms on tooth surfaces may result in the occurrence of caries, periodontitis, peri-
40 implant disease, root canal infections, and other oral infections.^[1] Gingivitis and periodontitis,
41 affecting periodontal tissue, are common illnesses originating from bacteria.^[2] Disrupting and
42 preventing biofilm formation in the oral environment using anti-plaque agents such as
43 chlorhexidine, cetylpyridinium chloride, fluoride, zinc, and stannous chloride is effective.^[3-5]

44
45 Currently, various types of mouthwash are commonly used in oral hygiene routines, playing a
46 complementary role considered an addition to toothbrushing as primary therapy.^[1,2] Mouthwash
47 can diminish biofilm formation in instances of insufficient mechanical debridement caused by
48 ineffective tooth brushing techniques. Antiseptic substances with minimal systemic
49 cytotoxicity and enduring potency align with the optimal criteria for mouthwash, preventing
50 immediate rinsing by salivary flow.^[6]

51
52 Chemical mouthwashes, such as chlorhexidine, are effective in preventing plaque development
53 and are considered the gold standard for the chemical control of dental plaque.^[7,8] Both Gram-
54 positive bacteria, such as *Staphylococcus aureus*, and Gram-negative bacteria, such as
55 *Enterococcus faecalis*, *Aggregatibacter actinomycetemcomitans*, and *Porphyromonas*
56 *gingivalis*, along with yeasts and viruses, are susceptible to chlorhexidine.^[2,5] Chlorhexidine
57 increases the permeability of microbial cell membranes, alters protein functions, and
58 precipitates macromolecules in the cytoplasm. It also exhibits bacteriostatic properties by

Commented [A7]: The journal guidelines state to identify references in text, tables, and legends by Arabic numerals in superscript with square bracket after the punctuation marks. Thus, I have made changes throughout accordingly.

Commented [A8]: Tip: "Gram" should be capitalized and never hyphenated when used as Gram stain. Gram negative and gram positive should be lowercase; hyphenate these terms only when used as an adjective, e.g., gram-positive bacteria.

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59 binding non-specifically to negatively charged membrane phospholipids of bacteria, inhibiting
60 ATPases, and preventing prokaryotic cells from replicating.^[5]

61
62 In addition to its beneficial effects, chlorhexidine has associated negative effects, including
63 dysgeusia, dehydration, tooth and tongue pigmentation, and allergic reactions. In human cells
64 in vitro, chlorhexidine can cause cytotoxicity, leading to apoptosis and necrotic cell death.^[2,9]

65 To address these adverse effects, herbal mouthwash with antibacterial and anti-inflammatory
66 properties may enhance patient compliance, as it typically has fewer negative effects than
67 chlorhexidine.^[10] Herbal formulations, which contain plant-derived compounds without the risk
68 of teeth staining, exhibit a milder taste, and minimize the potential for dry mouth.^[11,12]

69
70 Various medicinal herbs, such as thyme, cloves, green tea, licorice, and peppermint leaves, have
71 been utilized for ages in traditional medicine to address dental issues, such as toothaches,
72 cavities, and gum diseases.^[13] Furthermore, miswak, rosemary, olive oil, myrrh, anise, sesame,
73 ginger, and garlic are used in Middle Eastern countries for treating oral disorders.^[14] Herbal
74 medicines have evolved in dentistry as anti-inflammatory, antibacterial, antiseptic, and
75 therapeutic agents. Traditionally, herbal medicine has been used to address issues like caries,
76 gingivitis, and periodontitis. Additionally, it has applications as an intracanal medication,
77 sialogogue, and tooth whitening agent.^[15] Herbal medicine contains diverse bioactive
78 substances, including phenolic compounds such as flavonoids and phenolic acids, exhibiting
79 antibacterial effects. These substances have the potential to substitute chemical mouthwash.^[2,5]

80 Due to their various biological and medicinal activities and lower cost, herbal mouthwash may
81 contribute to better oral health maintenance.^[2] The active ingredients of herbal mouthwashes
82 are derived from natural sources, such as essential oils, plant extracts, and other botanical

83 compounds. These ingredients are deemed safe and have a history of use in traditional medicine
84 for various purposes. Formulating herbal mouthwashes with lower concentrations of active
85 ingredients contributes to a reduction in adverse effects, such as staining or irritation, enhancing
86 both their effectiveness and safety profile.^[16,17] Compared to chlorhexidine, herbal
87 mouthwashes show no significant difference in terms of reducing plaque, gingivitis, and
88 gingival bleeding.^[18,19] Additionally, herbal mouthwash yields inconclusive results for
89 maintaining oral hygiene in patients with fixed orthodontics compared with chlorhexidine.^[20]
90 This review aims to evaluate the existing literature on the efficacy of herbal mouthwash
91 compared to chlorhexidine as a mouthwash.

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“Compared to/compared with” are frequently used in academic documents. “Compared to” is used to stress on the similarities between objects, whereas “compared with” is used to stress on the differences.

92 **Materials and methods**

93 This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-
94 Analyses (PRISMA) guidelines (Figure 1).^[21]

95

96 **Focused questions**

97 A focused question was developed using the PICO (Population, Intervention, Comparison, and
98 Outcome) framework, serving as the foundation for the inclusion and exclusion criteria for the
99 current review. The focus question was “Are herbal mouthwashes equally effective as
100 chlorhexidine in promoting oral health and managing oral diseases?”

- 101 • Population : adult human subjects
- 102 • Intervention : use of herbal mouthwash after supragingival debridement or no
103 additional periodontal treatment
- 104 • Comparison : use of chlorhexidine mouthwash after supragingival debridement or no
105 additional periodontal treatment
- 106 • Outcome : gingiva, lips, oral mucosa, teeth, tongue swab, biofilm, and clinical
107 periodontal parameters, including gingival inflammation, dental plaque, pocket depth,
108 biofilm

109

110 **Search strategy**

111 Four databases (PubMed, SpringerLink, ScienceDirect, and Wiley) were used to conduct a
112 literature search within 2018–2023. A search string was created using the PICO model. The
113 databases were searched for the following phrases: (“herbal” [MeSH Terms] AND
114 “mouthwash” [MeSH Terms]) OR “mouth rinse” [MeSH Terms] AND “chlorhexidine”
115 [MeSH Terms].

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- Submit good quality color images.
- Each image should be less than 2 MB in size.
- Images can be submitted as jpeg files.
- Do not zip the files.
- Legends for the figures/images should be included at the end of the article file.

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116 **Inclusion/exclusion criteria**

117 The study included full-text articles conducted in English on human subjects, comparing the
118 effectiveness of herbal mouthwash with that of chlorhexidine. The exclusion criteria
119 encompassed studies on animals, in vitro experiments, and review papers.

120

121 **Study selection**

122 All references underwent systematic categorization. Three independent reviewers (SS, JE, and
123 SS) conducted an initial screening based on the titles and abstracts of the articles, followed by
124 a full-text evaluation. Any discrepancies in article eligibility were resolved through inter-
125 reviewer discussion.

126 **Results**

127 In the study's initial phase, searches for articles were conducted using predefined keywords in
128 four databases, complemented by manual searches. After eliminating duplicate titles and using
129 automation tools, 150 articles were initially selected; of these, 45 were excluded due to their
130 non-research nature. Out of the remaining 105 articles, 11 were excluded because they lacked
131 full-text availability. Following the eligibility criteria, 89 articles were excluded for not
132 involving human subjects, incorrect interpretations, lack of focus on herbal mouthwash, or
133 absence of chlorhexidine as a comparison. Finally, five articles were included in the review and
134 research synthesis (Table 1).

135 **Discussion**

136 Effectively managing oral care products poses challenges.^[22] To prevent plaque formation, a
137 combination of mechanical techniques and chemical substances is necessary. Mechanical
138 plaque prevention methods include brushing and interdental cleaning. Thus, incorporating
139 supplementary antiseptic agents, such as mouthwash, is crucial to enhance oral hygiene and
140 improve periodontal health.^[23] The notable effects of mouthwash on the subgingival biofilm
141 include preventing biofilm accumulation and exhibiting anti-gingivitis properties, followed by
142 its ability to prevent caries.^[24]

143

144 The recommended effective dosage of chlorhexidine mouthwash is 18–20 mg per use, with
145 concentrations ranging from 0.12% to 0.2%. To optimize its effectiveness, it is advisable to
146 delay chlorhexidine mouthwash use 30 min after toothbrushing. This delay is suggested because
147 certain toothpaste ingredients, such as calcium and anionic surfactants (e.g., sodium lauryl
148 sulfate, sodium dodecyl sulfate, and cocamidopropyl betaine), may diminish their ability to
149 adhere to oral surfaces. The mechanism of action of chlorhexidine involves its positive charge,
150 attracting it to the negatively charged bacterial cell wall. Chlorhexidine forms specific
151 adsorption to phosphate-containing molecules on the bacterial cell surface, facilitating
152 penetration through the bacterial cell wall and damaging its integrity (bacteriostatic effect). This
153 process leads to the release of low-molecular-weight cytoplasmic components, including
154 potassium ions, and the inhibition of certain enzymes. Additionally, chlorhexidine induces
155 cytoplasmic coagulation and precipitation by forming complexes with phosphorylated
156 compounds, such as adenosine triphosphate and nucleic acids (bactericidal effect).^[8] The
157 modification of stimuli affecting salty and bitter taste perception by chlorhexidine leads to a
158 change in taste perception.^[25] Due to a higher concentration, chlorhexidine may induce a

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159 burning sensation and discoloration of the teeth and tongue.^[26,27] Given these adverse effects,
160 herbal mouthwash is considered an alternative to chlorhexidine, especially when dealing with
161 patients who have peri-implant mucositis, chronic periodontitis, or are allergic to
162 chlorhexidine.^[2,28]

163
164 Natural botanical products have shown promise in treating caries, gingivitis, and
165 periodontitis.^[7] Herbal mouthwash, dentifrice, and gels have recently gained popularity. The
166 active components in herbal mouthwash can penetrate the biofilm, reducing calculus formation
167 and bacterial colonization on tooth surfaces.^[1] In this review, we found herbal mouthwash made
168 from *Melaleuca alternifolia*, manuka, HiOra (*Salvadora persica*, *Terminalia bellirica*, *Gossia*
169 *fragrantissima*, and *Elettaria cardamomum*), *Eugenia caryophyllata* (clove), and *Psidium*
170 *guajava* L. (guava) leaf to be a promising alternative.^[1,2,28-30]

171
172 The following parameters were used to evaluate the effectiveness of herbal mouthwash in this
173 review: plaque index (PI), gingival index (GI), and bleeding on probing (BOP) score.^[1,2,30] The
174 presence of bleeding during gum probing is a significant factor in attachment loss and disease
175 progression.^[2] Another parameter considered in this review was the presence of biofilm-free
176 and biofilm-covered tooth surfaces, along with the Beck Oral Assessment Scale score.^[1,29] The
177 Beck Oral Assessment Scale instrument includes five indicators for evaluating the condition of
178 the lips, gums, oral mucosa, teeth, tongue, and saliva.^[29]

179
180 In a study involving 60 healthy individuals, the use of 0.12% chlorhexidine within 7 days
181 demonstrated a significantly ($p < 0.05$) lower anti-biofilm effect than with that of 0.3% *M.*
182 *alternifolia*. Although *M. alternifolia* nanoparticles did not inhibit biofilm formation, they

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183 exhibited significant anti-inflammatory properties similar to 0.12% chlorhexidine mouthwash
184 ($p > 0.05$). Both the chlorhexidine and *M. alternifolia* groups experienced a reduction in
185 gingival crevicular fluid (GCF) volume, leading to *M. alternifolia* being considered an
186 inflammatory predictor. Given that GCF originates from the microcirculation of gingival
187 tissues, a correlation exists between GCF volume and gingival inflammation. *M. alternifolia*
188 can be characterized by its nanometric particles. This property facilitates the easier penetration
189 of *M. alternifolia* oil into the polymer matrix of the biofilm, thereby enhancing its anti-
190 inflammatory characteristics. *M. alternifolia* also exhibits antiseptic, antibacterial, antifungal,
191 and antiviral effects. Experimental in vitro testing has been conducted to assess its efficacy in
192 preventing the formation and adherence of mono-species biofilms of periodontopathogens and
193 cariogenic bacteria.^[1] Additionally, Srikumar *et al.* reported that *M. alternifolia* mouthwash is
194 equally effective as chlorhexidine in reducing halitosis.^[31]

195
196 The efficacy of alternative mouthwashes in various periodontal diseases is supported by
197 convincing evidence. In a study involving 45 patients with moderate plaque, manuka derived
198 from New Zealand Nelson Honey, used for 14 days, demonstrated similar effectiveness
199 compared to 0.2% chlorhexidine mouthwash. No differences were observed between
200 chlorhexidine and manuka for PI, GI, and bleeding index at any time point, indicating that
201 manuka mouthwash is promising for managing chronic gingivitis. Manuka mouthwash contains
202 ascorbic acid and antioxidants, including lutein, alpha-linolenic acid, and omega-3 fatty acids,
203 in high concentrations. These antioxidants act as free radical scavengers, preserving the health
204 of periodontal tissues. Ascorbic acid, a strong antioxidant, is essential for preserving connective
205 tissue, osteoid tissues, and dentin integrity. The antibacterial effect works through an osmotic
206 mechanism involving phenolic and antioxidant actions and the inhibition of enzyme synthesis

207 of hydrogen peroxide.^[32] Importantly, manuka mouthwash offers the additional advantage of
208 minimizing the adverse effects associated with long-term chlorhexidine use, such as staining,
209 mucosal burning, and dehydration.^[2] Another study also found that manuka honey mouthwash
210 has the same effectiveness as 0.2% chlorhexidine mouthwash in reducing gingivitis.^[33]

211
212 In the treatment of 48 patients with peri-implant mucositis, HiOra mouthwash derived from
213 Himalaya Drug, Bengaluru, India, proved equally effective compared to 0.2% chlorhexidine
214 mouthwash over 2 weeks of use. No statistically significant differences were observed in peri-
215 implant PI, BOP, and probing depth between the herbal and 0.2% chlorhexidine mouthwash
216 groups after 3, 6, and 12 weeks of follow-up. *S. persica* and *T. bellirica* in HiOra mouthwash
217 are recognized for their ability to prevent plaque formation and to exhibit antimicrobial activity.
218 Benzyl isothiocyanate from *S. persica* is effective against *P. gingivalis* and *A.*
219 *actinomycetemcomitans*. The undesirable adverse effects of chlorhexidine, such as alterations
220 in taste sensation and burning sensation, might necessitate the use of an oral rinse containing
221 substitutes for chlorhexidine, especially for patients with peri-implant mucositis or
222 chlorhexidine allergy.^[28]

223
224 In cases of chronic generalized moderate to severe gingivitis, 60 patients were instructed to use
225 *P. guajava* L. leaf mouthwash and 0.2% chlorhexidine mouthwash for 30 days. The results
226 demonstrated that *P. guajava* L. leaf mouthwash had an effectiveness equivalent to 0.2%
227 chlorhexidine mouthwash in reducing plaque scores and preserving gingival health. No
228 statistical difference was observed between the *P. guajava* L. leaf and chlorhexidine
229 mouthwash groups at the first-and third-month intervals, suggesting comparable functional
230 activity in lowering gingival index scores between the two types of mouthwash. The anti-

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231 inflammatory activity of *P. guajava* L. leaf bioactive ingredients, inhibiting prostaglandins,
232 kinin, and histamines, further supports its contribution to gingival health. Additionally, ascorbic
233 acid and phenolic chemicals, such as protocatechuic acid, ferulic acid, quercetin, guavin B, and
234 gallic acid, increase antioxidant levels in saliva. Moreover, it has the capacity to remove
235 hydrogen peroxide, liberate superoxide ions, and prevent hydroxyl radicals.^[30] Therefore, *P.*
236 *guajava* L. leaf mouthwash could be a substitute for maintaining a healthy gingiva. A similar
237 study on 50 patients with plaque-induced gingivitis also found no significant differences in the
238 PI, GI, and BOP between 0.2% chlorhexidine and herbal mouthwash consisting of *Myrtus*
239 *communis*, *Quercus brantii*, *Punica granatum*, *Portulaca olerace*, and *Boswellia serrata*. Even
240 the herbal mouthwash improved the periodontal condition after 2 weeks.^[18] These findings
241 highlight the importance of considering herbal mouthwash as an option to improve periodontal
242 health outcomes.

244 Mouthwash plays a crucial role for ICU patients using mechanical ventilators in reducing the
245 colonization of oropharyngeal bacteria, which can lead to ventilator-associated pneumonia.
246 Maintaining adequate oral hygiene has been proven to lower the incidence of ventilator-
247 associated pneumonia in ICU patients. In a study involving 168 eligible ICU patients over 5
248 consecutive days, herbal mouthwash containing 6.66% *E. caryophyllata* demonstrated
249 effectiveness comparable to that of 0.2% chlorhexidine mouthwash when applied using swabs
250 to the mucous membrane of the mouth, tongue, and gums. The active ingredients of clove
251 mouthwash, such as acetyleugenol, beta-caryophyllene, and vanillin, exhibit effectiveness
252 against Gram-negative bacteria.^[29] Another study by Siriyanyongwong et al. also indicated that
253 herbal mouthwash can mitigate the side effects associated with chlorhexidine mouthwash in

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254 ICU patients.^[34] Therefore, herbal mouthwash stands out as a simple and cost-effective
255 alternative to oral care in these patients.^[35]

256

257 Nonetheless, the potential adverse effects of herbal mouthwash remain unclear, necessitating
258 further research. It is crucial to conduct additional studies to gain a comprehensive
259 understanding of any associated risks. Additionally, the development of guidelines, supported
260 by evidence, is essential to ensure the safe and effective use of herbal mouthwash.

261 **Conclusion**

262 Herbal mouthwash is as effective as chlorhexidine in managing gingivitis and peri-implant
263 mucositis and exhibits significant anti-inflammatory properties. Considering this, herbal
264 mouthwash could be regarded as a viable option for enhancing oral health across various patient
265 conditions.

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377

378 **Table 1.** Articles included in the review and research synthesis

No	Author	Type of Study	Materials	Sample/parameter	Relevant Findings
1	Casarin, M <i>et al</i> ^[1]	Randomized, crossover, double-blind clinical trial	0.3% <i>Melaleuca alternifolia</i> nanoparticles mouthwash and 0.12% chlorhexidine on biofilm-free (BF) and biofilm-covered (BC) tooth surfaces	Biofilm (QHPI = Quigley & Hein Plaque Index)	0.3% <i>M. alternifolia</i> nanoparticles were as effective as 0.12% chlorhexidine in exhibiting important anti-inflammatory properties in healthy participants
2	Abullais, SS <i>et al</i> ^[2]	Double-blind randomized controlled trial	Alpine manuka mouthwash and 0.2% chlorhexidine	Dental plaque (plaque index), inflammation such as edema, redness, swelling, and spontaneous bleeding (gingival index), and bleeding upon gentle probing (modified sulcular bleeding index)	Manuka mouthwash was as effective as 0.2% chlorhexidine in managing chronic gingivitis and minimizing the adverse effects (e.g. staining, mucosal burning, and dehydration) associated with the

long-term use of
chlorhexidine

3	Alzoman, H <i>et al</i> ^[28]	Randomized controlled trial	HiOra mouthwash and 0.2% chlorhexidine	Plaque index, bleeding on probing, and probing depth	HiOra mouthwash and 0.2% chlorhexidine had similar effectiveness in treating peri-implant mucositis
4	Jahanshir M <i>et al</i> ^[29]	Comparative randomized triple-blind clinical trial	6.66% clove mouthwash and 0.2% chlorhexidine	Gingiva, lips, oral mucosa, teeth, and tongue swab with Beck Oral Assessment Scale	6.66% clove mouthwash was as effective as 0.2% chlorhexidine in evaluating oral health status in ICU patients on mechanical ventilator
5	Nayak N <i>et al</i> ^[30]	Placebo-controlled double blind	0.15% guava mouthwash and 0.2%	Supragingival plaque (Gracey curette), gingival	0.15% guava mouthwash was as effective as 0.2%

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parallel arm, chlorhexidine index, plaque index, chlorhexidine in
interventional microbial count, and lowering plaque scores
clinical study antioxidant level and maintaining
gingival health in
patients with chronic
generalized moderate-
to-severe gingivitis

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Review Article

Is Herbal Mouthwash as Effective as Chlorhexidine?: A Review

Sheila Soesanto, Jessica Endriyana, Triska Natassya

Departement of Oral
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ABSTRACT

Pathogenic biofilms contribute to several oral problems, including caries, periodontitis, and other infections. Chlorhexidine has long been considered the gold standard for chemical dental plaque control. However, it is accompanied by adverse effects, such as taste alterations, staining, and cytotoxicity. In response to these challenges, herbal mouthwashes have emerged as a promising alternative treatment, with fewer drawbacks. The primary aim of this review was to assess the effectiveness of herbal mouthwashes in comparison to chlorhexidine. Adhering to the PRISMA guidelines, this review focused on questions concerning the effectiveness of herbal mouthwashes compared to chlorhexidine. A systematic search was executed in prominent databases, including PubMed, SpringerLink, ScienceDirect, and Wiley. Using predefined keywords, five articles were selected for inclusion in the review and subsequent research synthesis. The review findings suggest that herbal mouthwashes exhibit effectiveness comparable to chlorhexidine, accompanied by the added benefit of fewer side effects. However, further research is needed to comprehensively evaluate the long-term safety and efficacy of herbal mouthwash.

KEYWORDS: Chlorhexidine, effectiveness, herbal, mouthwash, oral health, review

KEY MESSAGES: This review evaluates herbal mouthwashes as alternatives to chlorhexidine, the gold standard for plaque control. Findings suggest comparable effectiveness with fewer side effects, emphasizing the need for further research to assess long-term safety and efficacy.

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BACKGROUND

Many types of bacteria have been discovered in the oral environment, forming multispecies biofilms or extracellular matrices rich in polysaccharides. Biofilm formation triggers a host inflammatory immune response, which, in some circumstances, may be detrimental.^[1,2] Pathogenic biofilms on tooth surfaces may result in the occurrence of caries, periodontitis, peri-implant disease, root canal infections, and other oral infections.^[1] Gingivitis and periodontitis, affecting periodontal tissue, are common illnesses originating from bacteria.^[2] Disrupting and preventing biofilm formation in the oral environment using anti-plaque

agents such as chlorhexidine, cetylpyridinium chloride, fluoride, zinc, and stannous chloride is effective.^[3-5]

Currently, various types of mouthwash are commonly used in oral hygiene routines, playing a complementary role considered an addition to toothbrushing as primary therapy.^[1,2] Mouthwash can diminish biofilm formation in instances of insufficient mechanical debridement caused by ineffective tooth brushing techniques. Antiseptic substances with minimal systemic cytotoxicity and enduring potency align

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with the optimal criteria for mouthwash, preventing immediate rinsing by salivary flow.^[6]

Chemical mouthwashes, such as chlorhexidine, are effective in preventing plaque development and are considered the gold standard for the chemical control of dental plaque.^[7,8] Both Gram-positive bacteria, such as *Staphylococcus aureus*, and Gram-negative bacteria, such as *Enterococcus faecalis*, *Aggregatibacter actinomycetemcomitans*, and *Porphyromonas gingivalis*, along with yeasts and viruses, are susceptible to chlorhexidine.^[2,5] Chlorhexidine increases the permeability of microbial cell membranes, alters protein functions, and precipitates macromolecules in the cytoplasm. It also exhibits bacteriostatic properties by binding nonspecifically to negatively charged membrane phospholipids of bacteria, inhibiting ATPases, and preventing prokaryotic cells from replicating.^[5]

In addition to its beneficial effects, chlorhexidine has associated negative effects, including dysgeusia, dehydration, tooth and tongue pigmentation, and allergic reactions. In human cells *in vitro*, chlorhexidine can cause cytotoxicity, leading to apoptosis and necrotic cell death.^[2,9] To address these adverse effects, herbal mouthwash with antibacterial and anti-inflammatory properties may enhance patient compliance, as it typically has fewer negative effects than chlorhexidine.^[10] Herbal formulations, which contain plant-derived compounds without the risk of teeth staining, exhibit a milder taste, and minimize the potential for dry mouth.^[11,12]

Various medicinal herbs, such as thyme, cloves, green tea, licorice, and peppermint leaves, have been utilized for ages in traditional medicine to address dental issues, such as toothaches, cavities, and gum diseases.^[13] Furthermore, miswak, rosemary, olive oil, myrrh, anise, sesame, ginger, and garlic are used in Middle Eastern countries for treating oral disorders.^[14] Herbal medicines have evolved in dentistry as anti-inflammatory, antibacterial, antiseptic, and therapeutic agents. Traditionally, herbal medicine has been used to address issues like caries, gingivitis, and periodontitis. Additionally, it has applications as an intracanal medication, sialogogue, and tooth whitening agent.^[15] Herbal medicine contains diverse bioactive substances, including phenolic compounds such as flavonoids and phenolic acids, exhibiting antibacterial effects. These substances have the potential to substitute chemical mouthwash.^[2,5] Due to their various biological and medicinal activities and lower cost, herbal mouthwash may contribute to better oral health maintenance.^[2] The active

ingredients of herbal mouthwashes are derived from natural sources, such as essential oils, plant extracts, and other botanical compounds. These ingredients are deemed safe and have a history of use in traditional medicine for various purposes. Formulating herbal mouthwashes with lower concentrations of active ingredients contributes to a reduction in adverse effects, such as staining or irritation, enhancing both their effectiveness and safety profile.^[16,17] Compared to chlorhexidine, herbal mouthwashes show no significant difference in terms of reducing plaque, gingivitis, and gingival bleeding.^[18,19] Additionally, herbal mouthwash yields inconclusive results for maintaining oral hygiene in patients with fixed orthodontics compared with chlorhexidine.^[20]

This review aims to evaluate the existing literature on the efficacy of herbal mouthwash compared to chlorhexidine as a mouthwash.

MATERIALS AND METHODS

This review adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [Figure 1].^[21]

Focused questions

A focused question was developed using the PICO (Population, Intervention, Comparison, and Outcome) framework, serving as the foundation for the inclusion and exclusion criteria for the current review. The focus question was “Are herbal mouthwashes equally effective as chlorhexidine in promoting oral health and managing oral diseases?”

- Population: adult human subjects
- Intervention: use of herbal mouthwash after supragingival debridement or no additional periodontal treatment
- Comparison: use of chlorhexidine mouthwash after supragingival debridement or no additional periodontal treatment
- Outcome: gingiva, lips, oral mucosa, teeth, tongue swab, biofilm, and clinical periodontal parameters, including gingival inflammation, dental plaque, pocket depth, biofilm

Search strategy

Four databases (PubMed, SpringerLink, ScienceDirect, and Wiley) were used to conduct a literature search within 2018–2023. A search string was created using the PICO model. The databases were searched for the following phrases: (“herbal” [MeSH Terms] AND “mouthwash” [MeSH Terms]) OR “mouth rinse” [MeSH Terms] AND “chlorhexidine” [MeSH Terms].

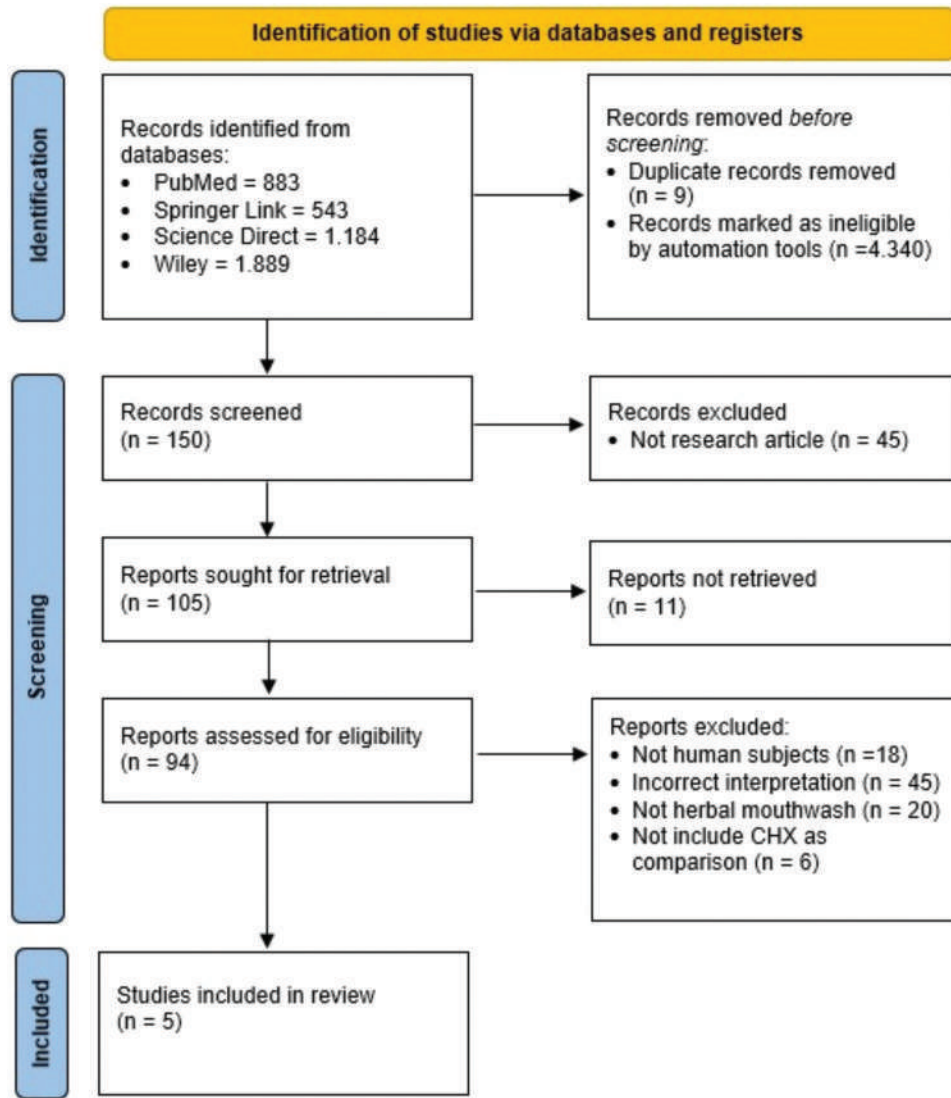


Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for study selection.^[21]

Inclusion/exclusion criteria

The study included full-text articles conducted in English on human subjects, comparing the effectiveness of herbal mouthwash with that of chlorhexidine. The exclusion criteria encompassed studies on animals, *in vitro* experiments, and review papers.

Study selection

All references underwent systematic categorization. Three independent reviewers (SS, JE, and SS) conducted an initial screening based on the titles and abstracts of the articles, followed by a full-text evaluation. Any discrepancies in article eligibility were resolved through inter-reviewer discussion.

RESULTS

In the study's initial phase, searches for articles were conducted using predefined keywords in four

databases, complemented by manual searches. After eliminating duplicate titles and using automation tools, 150 articles were initially selected; of these, 45 were excluded due to their non-research nature. Out of the remaining 105 articles, 11 were excluded because they lacked full-text availability. Following the eligibility criteria, 89 articles were excluded for not involving human subjects, incorrect interpretations, lack of focus on herbal mouthwash, or absence of chlorhexidine as a comparison. Finally, five articles were included in the review and research synthesis [Table 1].

DISCUSSION

Effectively managing oral care products poses challenges.^[22] To prevent plaque formation, a combination of mechanical techniques and chemical substances is necessary. Mechanical plaque prevention

Table 1: Articles included in the review and research synthesis

No	Authors	Type of Study	Materials	Sample/parameter	Relevant Findings
1	Casarin et al. ^[1]	Randomized, crossover, double-blind clinical Trial	0.3% <i>Melaleuca alternifolia</i> nanoparticles mouthwash and 0.12% chlorhexidine on biofilm-free (BF) and biofilm-covered (BC) tooth surfaces	Biofilm (QHPI = Quigley & Hein Plaque Index)	0.3% <i>M. alternifolia</i> nanoparticles were as effective as 0.12% chlorhexidine in exhibiting important anti-inflammatory properties in healthy participants
2	Abullais et al. ^[2]	Double-blind randomized controlled trial	Alpine manuka mouthwash and 0.2% chlorhexidine	Dental plaque (plaque index), inflammation such as edema, redness, swelling, and spontaneous bleeding (gingival index), and bleeding upon gentle probing (modified sulcular bleeding index)	Manuka mouthwash was as effective as 0.2% chlorhexidine in managing chronic gingivitis and minimizing the adverse effects (e.g., staining, mucosal burning, and dehydration) associated with the long-term use of chlorhexidine
3	Alzoman et al. ^[28]	Randomized controlled trial	HiOra mouthwash and 0.2% chlorhexidine	Plaque index, bleeding on probing, and probing depth	HiOra mouthwash and 0.2% chlorhexidine had similar effectiveness in treating peri-implant mucositis
4	Jahanshir et al. ^[29]	Comparative randomized triple-blind clinical trial	6.66% clove mouthwash and 0.2% chlorhexidine	Gingiva, lips, oral mucosa, teeth, and tongue swab with Beck Oral Assessment Scale	6.66% clove mouthwash was as effective as 0.2% chlorhexidine in evaluating oral health status in ICU patients on mechanical ventilator
5	Nayak et al. ^[30]	Placebo-controlled double-blind parallel arm, interventional clinical study	0.15% guava mouthwash and 0.2% chlorhexidine	Supragingival plaque (Gracey curette), gingival index, plaque index, microbial count, and antioxidant level	0.15% guava mouthwash was as effective as 0.2% chlorhexidine in lowering plaque scores and maintaining gingival health in patients with chronic generalized moderate-to-severe gingivitis

methods include brushing and interdental cleaning. Thus, incorporating supplementary antiseptic agents, such as mouthwash, is crucial to enhance oral hygiene and improve periodontal health.^[23] The notable effects of mouthwash on the subgingival biofilm include preventing biofilm accumulation and exhibiting anti-gingivitis properties, followed by its ability to prevent caries.^[24]

The recommended effective dosage of chlorhexidine mouthwash is 18–20 mg per use, with concentrations ranging from 0.12% to 0.2%. To optimize its effectiveness, it is advisable to delay chlorhexidine mouthwash use 30 min after toothbrushing. This delay is suggested because certain toothpaste ingredients, such as calcium and anionic surfactants (e.g., sodium lauryl sulfate, sodium dodecyl sulfate, and cocamidopropyl betaine), may diminish their ability to adhere to oral surfaces. The mechanism of action of chlorhexidine involves its positive charge, attracting it to the negatively charged bacterial cell wall. Chlorhexidine forms specific adsorption to phosphate-containing molecules on the bacterial cell surface, facilitating penetration through the bacterial cell wall and damaging its integrity

(bacteriostatic effect). This process leads to the release of low-molecular-weight cytoplasmic components, including potassium ions, and the inhibition of certain enzymes. Additionally, chlorhexidine induces cytoplasmic coagulation and precipitation by forming complexes with phosphorylated compounds, such as adenosine triphosphate and nucleic acids (bactericidal effect).^[8] The modification of stimuli affecting salty and bitter taste perception by chlorhexidine leads to a change in taste perception.^[25] Due to a higher concentration, chlorhexidine may induce a burning sensation and discoloration of the teeth and tongue.^[26,27] Given these adverse effects, herbal mouthwash is considered an alternative to chlorhexidine, especially when dealing with patients who have peri-implant mucositis, chronic periodontitis, or are allergic to chlorhexidine.^[2,28]

Natural botanical products have shown promise in treating caries, gingivitis, and periodontitis.^[7] Herbal mouthwash, dentifrice, and gels have recently gained popularity. The active components in herbal mouthwash can penetrate the biofilm, reducing calculus formation and bacterial colonization on tooth surfaces.^[1] In this review, we found herbal mouthwash made from

Melaleuca alternifolia, manuka, HiOra (*Salvadora persica*, *Terminalia bellirica*, *Gossia fragrantissima*, and *Elettaria cardamomum*), *Eugenia caryophyllata* (clove), and *Psidium guajava* L. (guava) leaf to be a promising alternative.^[1,2,28-30]

The following parameters were used to evaluate the effectiveness of herbal mouthwash in this review: plaque index (PI), gingival index (GI), and bleeding on probing (BOP) score.^[1,2,30] The presence of bleeding during gum probing is a significant factor in attachment loss and disease progression.^[2] Another parameter considered in this review was the presence of biofilm-free and biofilm-covered tooth surfaces, along with the Beck Oral Assessment Scale score.^[1,29] The Beck Oral Assessment Scale instrument includes five indicators for evaluating the condition of the lips, gums, oral mucosa, teeth, tongue, and saliva.^[29]

In a study involving 60 healthy individuals, the use of 0.12% chlorhexidine within 7 days demonstrated a significantly ($P < 0.05$) lower anti-biofilm effect than with that of 0.3% *M. alternifolia*. Although *M. alternifolia* nanoparticles did not inhibit biofilm formation, they exhibited significant anti-inflammatory properties similar to 0.12% chlorhexidine mouthwash ($P > 0.05$). Both the chlorhexidine and *M. alternifolia* groups experienced a reduction in gingival crevicular fluid (GCF) volume, leading to *M. alternifolia* being considered an inflammatory predictor. Given that GCF originates from the microcirculation of gingival tissues, a correlation exists between GCF volume and gingival inflammation. *M. alternifolia* can be characterized by its nanometric particles. This property facilitates the easier penetration of *M. alternifolia* oil into the polymer matrix of the biofilm, thereby enhancing its anti-inflammatory characteristics. *M. alternifolia* also exhibits antiseptic, antibacterial, antifungal, and antiviral effects. Experimental *in vitro* testing has been conducted to assess its efficacy in preventing the formation and adherence of mono-species biofilms of periodontopathogens and cariogenic bacteria.^[1] Additionally, Srikumar *et al.*^[31] reported that *M. alternifolia* mouthwash is equally effective as chlorhexidine in reducing halitosis.

The efficacy of alternative mouthwashes in various periodontal diseases is supported by convincing evidence. In a study involving 45 patients with moderate plaque, manuka derived from New Zealand Nelson Honey, used for 14 days, demonstrated similar effectiveness compared to 0.2% chlorhexidine mouthwash. No differences were observed between chlorhexidine and manuka for PI, GI, and bleeding index at any time point, indicating that manuka

mouthwash is promising for managing chronic gingivitis. Manuka mouthwash contains ascorbic acid and antioxidants, including lutein, alpha-linolenic acid, and omega-3 fatty acids, in high concentrations. These antioxidants act as free radical scavengers, preserving the health of periodontal tissues. Ascorbic acid, a strong antioxidant, is essential for preserving connective tissue, osteoid tissues, and dentin integrity. The antibacterial effect works through an osmotic mechanism involving phenolic and antioxidant actions and the inhibition of enzyme synthesis of hydrogen peroxide.^[32] Importantly, manuka mouthwash offers the additional advantage of minimizing the adverse effects associated with long-term chlorhexidine use, such as staining, mucosal burning, and dehydration.^[2] Another study also found that manuka honey mouthwash has the same effectiveness as 0.2% chlorhexidine mouthwash in reducing gingivitis.^[33]

In the treatment of 48 patients with peri-implant mucositis, HiOra mouthwash derived from Himalaya Drug, Bengaluru, India, proved equally effective compared to 0.2% chlorhexidine mouthwash over 2 weeks of use. No statistically significant differences were observed in peri-implant PI, BOP, and probing depth between the herbal and 0.2% chlorhexidine mouthwash groups after 3, 6, and 12 weeks of follow-up. *S. persica* and *T. bellirica* in HiOra mouthwash are recognized for their ability to prevent plaque formation and to exhibit antimicrobial activity. Benzyl isothiocyanate from *S. persica* is effective against *P. gingivalis* and *A. actinomycetemcomitans*. The undesirable adverse effects of chlorhexidine, such as alterations in taste sensation and burning sensation, might necessitate the use of an oral rinse containing substitutes for chlorhexidine, especially for patients with peri-implant mucositis or chlorhexidine allergy.^[28]

In cases of chronic generalized moderate-to-severe gingivitis, 60 patients were instructed to use *P. guajava* L. leaf mouthwash and 0.2% chlorhexidine mouthwash for 30 days. The results demonstrated that *P. guajava* L. leaf mouthwash had an effectiveness equivalent to 0.2% chlorhexidine mouthwash in reducing plaque scores and preserving gingival health. No statistical difference was observed between the *P. guajava* L. leaf and chlorhexidine mouthwash groups at the first- and third-month intervals, suggesting comparable functional activity in lowering GI scores between the two types of mouthwash. The anti-inflammatory activity of *P. guajava* L. leaf bioactive ingredients, inhibiting prostaglandins, kinin, and histamines, further supports its contribution to gingival health. Additionally, ascorbic acid and phenolic chemicals,

such as protocatechuic acid, ferulic acid, quercetin, guavin B, and gallic acid, increase antioxidant levels in saliva. Moreover, it has the capacity to remove hydrogen peroxide, liberate superoxide ions, and prevent hydroxyl radicals.^[30] Therefore, *P. guajava* L. leaf mouthwash could be a substitute for maintaining a healthy gingiva. A similar study on 50 patients with plaque-induced gingivitis also found no significant differences in the PI, GI, and BOP between 0.2% chlorhexidine and herbal mouthwash consisting of *Myrtus communis*, *Quercus brantii*, *Punica granatum*, *Portulaca olerace*, and *Boswellia serrata*. Even the herbal mouthwash improved the periodontal condition after 2 weeks.^[18] These findings highlight the importance of considering herbal mouthwash as an option to improve periodontal health outcomes.

Mouthwash plays a crucial role for ICU patients using mechanical ventilators in reducing the colonization of oropharyngeal bacteria, which can lead to ventilator-associated pneumonia. Maintaining adequate oral hygiene has been proven to lower the incidence of ventilator-associated pneumonia in ICU patients. In a study involving 168 eligible ICU patients over 5 consecutive days, herbal mouthwash containing 6.66% *E. caryophyllata* demonstrated effectiveness comparable to that of 0.2% chlorhexidine mouthwash when applied using swabs to the mucous membrane of the mouth, tongue, and gums. The active ingredients of clove mouthwash, such as acetyleugenol, beta-caryophyllene, and vanillin, exhibit effectiveness against Gram-negative bacteria.^[29] Another study by Siriyanyongwong *et al.*^[34] also indicated that herbal mouthwash can mitigate the side effects associated with chlorhexidine mouthwash in ICU patients. Therefore, herbal mouthwash stands out as a simple and cost-effective alternative to oral care in these patients.^[35]

Nonetheless, the potential adverse effects of herbal mouthwash remain unclear, necessitating further research. It is crucial to conduct additional studies to gain a comprehensive understanding of any associated risks. Additionally, the development of guidelines, supported by evidence, is essential to ensure the safe and effective use of herbal mouthwash.

CONCLUSION

Herbal mouthwash is as effective as chlorhexidine in managing gingivitis and peri-implant mucositis and exhibits significant anti-inflammatory properties. Considering this, herbal mouthwash could be regarded as a viable option for enhancing oral health across various patient conditions.

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Conflicts of interest

There are no conflicts of interest.

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