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Review Article

Herbal mouthwashes for oral mucositis in cancer therapy: A systematic review

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Abstract

Background: Oral mucositis (OM) is a distressing and often debilitating side effect of cancer treatment, significantly impacting the quality of life of patients undergoing chemotherapy and radiotherapy. This review aims to evaluate existing data on the impact of herbal mouthwashes in managing OM in cancer patients.

Methods: An extensive literature review was conducted in top electronic databases, such as PubMed, Science Direct, and Google Scholar, for articles published between 2013 and 2023. The search employed keywords such as "herbal mouthwash," "oral mucositis," and "cancer." The review was conducted following the PRISMA guidelines.

Results: This review included 11 studies. The herbal ingredients used in the mouthwashes varied across studies, including chamomile, peppermint, aloe vera, turmeric, and curcumin. The outcomes assessed included the time of onset, duration, incidence, and severity of OM. Findings indicated promising efficacy in reducing the severity of OM, relieving pain, and promoting wound healing.

Conclusion: Although herbal interventions show promise in managing OM, the variability in study designs, herbal formulations, and reporting practices highlights the need for further research and standardization in this area.

Keywords: Oral mucositis, Mouthwashes, Herbal mouthwash, Anti-inflammatory agents, Analgesics, Anti-infective agents

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Introduction

Oral mucositis (OM) is a common toxicity of cancer treatments, including chemotherapy and/or radiotherapy (RT).[1] Approximately 40% of patients undergoing standard chemotherapy and 30% to 60% of those receiving radiotherapy, particularly for head and neck cancers, are likely to develop OM during their treatment regimen.[2] This often results in the discontinuation of RT or a reduction in the dosage of chemotherapy, which has detrimental effects on the therapeutic efficacy of the course of treatment; thus, OM is an RT or chemotherapy dose-limiting complication in cancer patients.[3] OM occurs when the lining of the mouth, known as the mucosa, becomes inflamed. It often presents as atrophy, swelling, erythema, and ulceration.[4] This is frequently associated with pain, odynophagia (pain when swallowing), xerostomia, and altered taste perception.[2] patients may find it extremely difficult to eat and drink, leading to malnutrition and dehydration, lowering their quality of life. These effects not only disrupt cancer treatment schedules due to dose reductions or treatment delays but also lead to economic burdens associated with extended hospitalization and the need for complex pain management strategies.[5,6] There are other scales, such as the Common Terminology Criteria for Adverse Events (CTCAE) and the Oral Mucositis Assessment Scale (OMAS). However, the WHO scale is the most common grading scale for OM.[7,8] The following grading scale of lesion severity is labelled between grade 0, in which no symptom can be identified, and grade 4, in which the worst possible symptoms are observed. Despite several theories on the mechanisms whereby mucositis arises, the exact pathophysiology of mucositis remains mostly unknown.[9] There is a hypothesis by Sonis[10] that describes the five phases of the intricate biological process of mucositis: initiation, up-regulation of signaling pathways, amplification of inflammation, ulceration, and healing.[11] In the initiation phase, chemotherapy and radiation induce DNA damage, producing reactive oxygen species (ROS). This sets off a chain reaction of inflammatory events that leads to the production of further pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), all of which

aggravate tissue damage.[10,12] OM progression depends on various treatment-related factors, such as the dose intensity of the anticancer therapy regimen, the nature of treatment administered, and patient-related factors, such as oral health prior to disease state.[4,13,14] Patients with poor oral hygiene and nutritional health are also more likely to develop OM.[15] This morbid condition is a significant oncological concern, with a prevalence ranging from 10% to 100%, depending on the cytotoxic regimen and patient-associated variables.[4] It is predicted that OM may develop in 40% of patients after standard chemotherapy.[16] Meanwhile, individuals undergoing RT, particularly those with head and neck cancer, may experience a 30% to 60% risk of mucositis.[16] In a study, oral and/or gastrointestinal (GI) mucositis occurred in 303 out of 599 patients (51%) undergoing chemotherapy for solid tumor or lymphoma.[2]

Furthermore, OM also has a significant economic impact. A study shows that the average hospitalization costs for patients receiving chemotherapy each cycle would be $3893 without mucositis, $6277 with OM, $9132 with GI mucositis, and $9161 with both GI and OM.[5] Another study showed that the incremental cost of OM ranged from $5000 to $30 000 for patients receiving RT, whereas patients receiving chemotherapy incurred costs of $3700 per cycle.[1] Other measures for treating OM include zinc, benzydamine mouthwash, low-level laser therapy, cryotherapy, and keratinocyte growth factor-1 (KGF-1).[17] This involves regular teeth brushing with a soft-bristle brush using a non-medicated and alcohol-free mouthwash and non-detergent toothpaste.[15,16] It is also advisable have regular oral check-ups and pre-treatment dental examinations. In some cases, procedure such as tooth extractions may be necessary before treatment.[16] Furthermore, patients with OM are advised to restrict their diet to foods that do not irritate the mucosa, maintain adequate hydration, and avoid smoking.[13]

Conventional therapeutic strategies for OM are aimed at managing symptoms rather than addressing the condition's underlying causes. Topical anesthetics, including lidocaine, are frequently employed to numb the oral mucosa and provide temporary pain relief. Systemic analgesics, such as opioids, are used in more severe cases but carry risks of side effects, including constipation, sedation, and dependence[4]. Moreover, antimicrobial mouthwashes, such as those containing chlorhexidine (CHX), are widely prescribed to reduce the risk of infections in mucositis lesions. However, CHX has been associated with adverse effects such as mucosal dryness, taste disturbances, and even exacerbation of mucosal irritation in some patients.[18,19] Similarly, alcohol-containing mouthwashes, commonly used for their antiseptic properties, can cause significant irritation to the already compromised mucosa, potentially worsening the condition. While these interventions provide some degree of symptomatic relief, they do not address the inflammatory processes driving OM, leaving a gap in effective long-term management.[7] Over-the-counter analgesics, such as ibuprofen or paracetamol, and topical mouth rinses containing morphine or anaesthetics like lidocaine may be given to relieve OM-induced pain.[20,21] For patients with severe OM, systemic analgesics, typically including opioids, along with topical medications, may be needed for effective pain management[21]. Furthermore, studies have shown that topical antibiotic lozenges containing amphotericin-B, polymyxin-B, and tobramycin reduce radiotherapy-induced OM.[22] Anti-inflammatory agents like benzydamine help reduce OM and radiation-induced pain, and mucosal protectants like sodium alginate protect the mucosal lining from further damage and may be applied to oral ulcers.[22]

The growing interest in herbal interventions for managing OM stems from their broad range of bioactive properties, including anti-inflammatory, antimicrobial, and antioxidant activities. Herbal medicines appeal to cancer patients due to their safety profile, availability, and cost-effectiveness.[23] Unlike conventional therapies, herbal mouthwashes offer the potential to target multiple aspects of OM pathophysiology simultaneously, including reducing inflammation, preventing secondary infections, and promoting wound healing.[24] Curcumin, which is derived from turmeric (*Curcuma longa*), has been researched in the past for its ability to act as an anti-inflammatory and an oxidant. Curcumin has been demonstrated to suppress the nuclear factor kappa B (NF-κB), which is the principal activator for the production of pro-inflammatory cytokines and, therefore, effectively suppresses inflammation at the mucositis lesion site.[24]

Among the herbal agents studied, chamomile (*Matricaria recutita*) and aloe vera (*Aloe barbadensis*) have shown significant promise. Chamomile is well known for its anti-inflammatory, antimicrobial, and wound-healing properties.[25] Studies have demonstrated that chamomile mouthwashes can reduce the severity and duration of OM, largely by modulating the inflammatory response and promoting the re-epithelialization of damaged mucosal tissue.[25] *Aloe vera*, another widely researched herbal agent, has also been shown to possess anti-inflammatory and healing properties, making it effective in reducing the severity of OM in cancer patients.[26] Other herbal agents such as clove (*Syzygium aromaticum*), sage (*Salvia officinalis*), and thyme (*Thymus vulgaris*) have demonstrated potent antimicrobial, analgesic, and anti-inflammatory effects. Clove, rich in eugenol, is particularly effective in reducing pain and inflammation in OM patients, and sage and thyme have been shown to reduce the microbial load in the oral cavity, further mitigating the risk of secondary infections in OM lesions.[27] These findings highlight the potential for herbal mouthwashes to offer a multifaceted approach to OM management by addressing the condition's inflammatory aspects and

preventing complications such as infections.[25] In recent years, herbal mouthwashes have garnered significant attention as a complementary or alternative therapy for managing OM in cancer patients. This interest is driven by the potential therapeutic benefits of herbal ingredients, which offer anti-inflammatory, antimicrobial, and wound-healing properties, often with fewer side effects than conventional treatments. However, a key challenge in assessing their efficacy lies in the wide variability of herbal formulations used across different studies. Each formulation may utilize unique combinations of herbal components, contributing to a range of outcomes in the management of OM. This clinical review aims to critically evaluate the diverse array of herbal mouthwashes used in treating OM, highlighting the specific herbal ingredients that show the most promise. By synthesizing findings from available clinical studies, this review will provide a comprehensive understanding of the therapeutic potential of herbal mouthwashes, offering insight into their role in improving the quality of life for cancer patients suffering from OM.

Methods

The present systematic review was conducted following the guidelines of the PRISMA statement to provide a clear narrative and enhance the scope of the study.[28] A thorough literature search was performed using multiple databases and an expanded set of keywords to ensure that eligible studies were identified with the required sensitivity and specificity. This revised methodology includes a broader range of relevant databases, keywords, and synonyms, as well as additional strategies to increase the inclusivity and comprehensiveness of the review, addressing concerns regarding the narrowness of the initial search (Figure 1).

A literature search was conducted across five databases: PubMed, ScienceDirect, Google Scholar, Cochrane Library, and EMBASE. This ensured that a broader range of studies were captured, including those not indexed in commonly used databases. The search included the following broad terms and their synonyms: "herbal mouthwash," "oral mucositis," "cancer," "neoplasm," "head and neck cancer," "chemotherapy," "radiotherapy," "cancer treatment," "antineoplastic therapy," "stomatitis," "phytotherapy," "natural remedies," and "plant-based mouthwash." In addition, the search included cancer-related terms like "chemotherapy-induced mucositis," "radiotherapy-induced mucositis (RIOM)," "oncology care," and "complementary cancer therapies."

The search was restricted to peer-reviewed articles published between 2013 and 2023 to ensure the relevance and timeliness of the findings. Filters were applied to retrieve clinical trials, human studies, and free full-text articles. Review articles, non-English publications, conference abstracts, and articles published before 2013 were excluded. Search results across all databases were imported into Microsoft Excel, where duplicates were identified and removed to avoid potential bias. The remaining articles were screened according to predefined inclusion criteria.

The inclusion criteria were defined using the population, intervention, comparison, and outcome (PICO) model to ensure the review remained focused and relevant. Population (P): Cancer patients with chemotherapy-induced or radiotherapy-induced oral mucositis. Intervention (I): Any herbal-based mouthwash or natural remedy used as a mouth rinse. Comparison (C): Other non-herbal mouthwash, clear water, or placebo. Outcome (O): Onset time, duration of oral mucositis, frequency, and degree of oral mucositis. Targeted clinical evidence consisting of both randomized controlled trials (RCTs) and clinical trials was limited to the articles that estimated the effectiveness of herbal mouthwashes in managing OM in cancer patients and observational studies. Publications in non-English languages, review articles, conference abstracts, articles without full-text access, articles with unpublished results or abstracts only, and studies involving other medications for the treatment of OM were excluded.

As a first step in the abstract and indexing process, we reviewed the titles and abstracts of all the identified articles against inclusion criteria. In cases where the title and abstract failed to disclose if the study was relevant, the full source was examined. After careful assessment, only 11 studies were included in this review to ensure that all the studies met the inclusion criteria. For each eligible study, the following data were extracted: Treatment details with author and year of publication, study design, sample size, type of herbal intervention included in mouthwash, therapeutic properties of the components used in the mouthwash, comparison with the control group, clinical outcomes assessed and side effects noted. The extracted data were organized into categories and summarized in Table S1 for synthesis. Data analysis was qualitative, and results from different studies were compared to evaluate the efficacy of various herbal mouthwashes in reducing the severity and incidence of OM in cancer patients. This synthesis aimed to identify which specific herbal ingredients showed the most promise in managing OM and improving the quality of life in cancer patients undergoing treatment.

Results

The initial database search retrieved 181 results across all three databases. Additionally, two more records were identified through the reference list of some retrieved articles. After removing duplicates, 171 articles remained. Of these, 150 articles were excluded after screening their titles and abstracts, as they did not meet the predefined inclusion criteria. Subsequently, 21 full-text articles were assessed for eligibility. After a thorough evaluation, 10

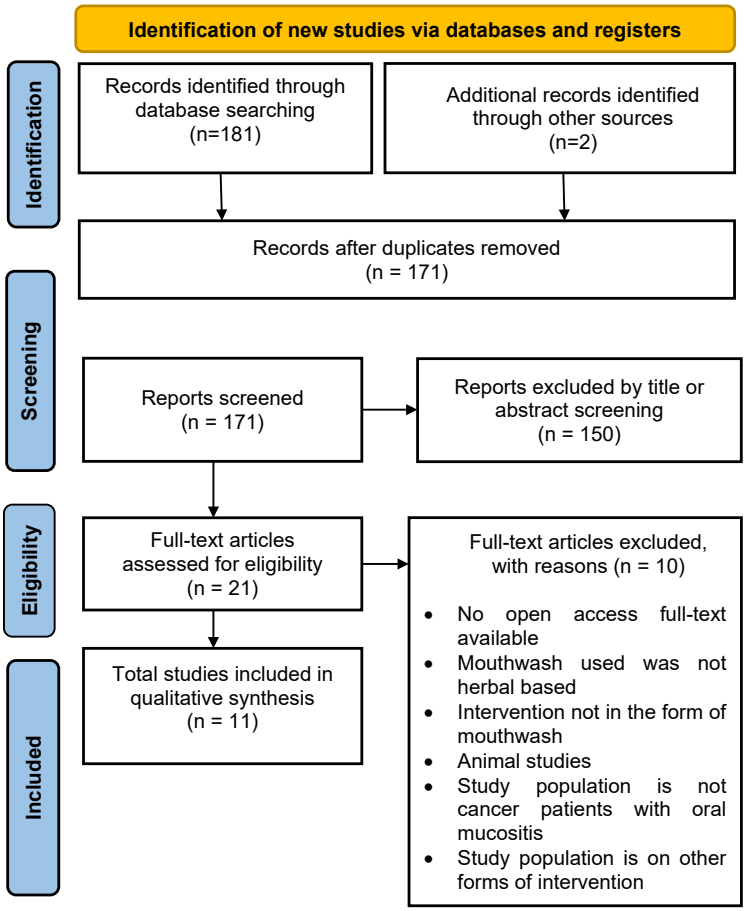

Figure 1. PRISMA flowchart for study selection considering inclusion and exclusion criteria

articles were excluded based on specific selection criteria. Finally, 11 articles were deemed eligible for inclusion in this review. The selection process is visually summarized in the PRISMA flowchart, presented in Figure 1.

Study characteristics

Two studies reported no adverse effects associated with the use of herbal mouthwash.[29] However, the other studies did not provide information on adverse effects. Tavakoli Ardakani et al noted that no allergic reactions to the mouthwash were observed during the study, although this was not explained.[30,31,33,40] The remaining studies reported side effects such as a burning sensation and unpleasant taste, though the burning sensation could be attributed to radiotherapy rather than the herbal mouthwash.[38] In a study by Hasheminasab et al, nausea was reported as a side effect, but no specific details were provided regarding the use of herbal mouthwash.[35]

All 11 eligible studies were published in English between 2013 to 2023. Of these, 10 were RCTs. Seven of the RCTs were double-masked, ensuring that both the researchers and the participants were unaware of which treatments – experimental, standard, or placebo – were administered. One article reported a preliminary study including RCTs that were either single-masked, double-masked crossover, triple-masked, or open-labelled. Most studies compared herbal with non-herbal mouthwash, and four studies compared herbal mouthwash with placebos.[30,31,34] A comprehensive comparative study compared herbal mouthwash with regular mouthwashes and placebo.[31] The remaining studies compared herbal mouthwashes with clear water and basic oral care.[37]

Discussion

There is a growing concern about the use of standard mouthwashes in the treatment of OM. Some of the main components of standard mouthwashes are alcohol and CHX, which is regarded as the "gold standard" of antiplaque mouthwashes due to its ability to prevent plaque formation and its long-lasting broad-spectrum antimicrobial activity.[18] Common side effects of CHX mouthwash include dry mouth, taste disturbances, and tongue discolouration. Less common side effects include oral paraesthesia, burning sensations, and desquamation of the oral mucosa.[19] On the other hand, alcohol-containing mouthwashes have been found to affect oral structures and functions negatively, leading to mucosal soreness, drying of the oral mucosa, and burning

sensations.[41] These adverse effects have contributed to the increasing use of herbal mouthwashes in treating OM due to their better tolerability and fewer adverse effects than standard mouthwashes.

This review identified 11 studies that evaluated the effects of herbal mouthwashes on OM in cancer patients. The herbal mouthwash studies included clove, liquorice, chamomile, peppermint, aloe vera (AV), turmeric, curcumin, *Plantago ovata*, *Achillea millefolium*, sage, thyme, and silymarin. The outcomes evaluated included the time of OM onset, duration, incidence, severity, the need for pain medication, and the patient's quality of life. Chamomile (*Matricaria recutita*) has antibacterial, anti-inflammatory, and wound-healing properties. Peppermint has anti-inflammatory, analgesic, and antimicrobial effects, while AV possesses anti-inflammatory, analgesic, antimicrobial, and wound-healing properties. It is hypothesized that the anti-inflammatory properties of AV result from its ability to reduce leukocyte adhesive molecules, decrease TNF-α levels, and inhibit cyclooxygenase.[42] *Achillea millefolium* has antibacterial, anti-inflammatory, and wound-healing properties, with its wound-healing effects linked to reducing platelet aggregation, enhancing collagen synthesis, and eliminating free radicals.[42] Since OM is characterized by inflammation, the anti-inflammatory properties of these herbs can help reduce inflammation and improve OM symptoms.

Chemotherapy and RT damage the cell lining of the oral mucosa, making it more susceptible to infection. Additionally, these therapies reduce white blood cell (WBC) count and function, which impairs the body's ability to fight infection.[43] These herbs' antibacterial and antimicrobial effects aid in fighting infection and promoting healing. Herbs with analgesic properties, such as those reported in studies by Tavakoli Ardakani et al and Hajisalem et al, showed that they can relieve pain and improve the quality of life of OM patients.[38,39] Additionally, herbs with wound-healing effects can help reduce the duration of OM. Five studies included in this review utilized chamomile, peppermint, AV, and *Achillea millefolium*, all of which demonstrated significant reductions in the severity and incidence of OM, proving the efficacy of these herbal agents as treatment options for OM.[31,36–39]

This review also evaluated studies that examined the effects of other herbal mouthwashes, including turmeric, curcumin, *Plantago ovata*, sage, thyme, and clove. Turmeric, derived from *Curcuma longa*, is known for its analgesic, anti-inflammatory, and wound-healing properties. At the same time, curcuma, a phenolic compound found in turmeric, offers anti-inflammatory, antioxidant, and wound-healing benefits.[44] The antioxidant property of curcumin helps protect the oral mucosa from damage caused by the increasing ROS generated by anticancer therapies.[45] Studies by Rao et al and Shah et al suggest that turmeric and curcumin delay the onset of anticancer therapy-induced OM, particularly RIOM.[33,34] *Plantago ovata*, sage, thyme, and clove also significantly delayed OM onset or reduced its duration, incidence, and severity. These findings support the potential utility of herbal mouthwashes as a treatment for OM.[33-35,37] Moreover, different formulations of herbal mouthwashes affect OM in various ways, depending on the specific herbs and their concentrations. Herbs such as chamomile and AV, with their anti-inflammatory, antimicrobial, and analgesic properties, help reduce inflammation, pain, and OM severity, while wound-healing herbs promote mucosal repair.

Licorice (*Glycyrrhiza glabra*) is a valuable medicinal plant with anti-inflammatory and antibiotic properties. Amin et al studied the effect of liquorice root extract mouthwash and combined mouthwash on the incidence and severity of chemotherapy-induced mucositis.[30] This implies that mouthwash containing liquorice may help prevent the development of severe infection and higher-grade OM but may not be as effective in preventing higher grade 1 and grade 2 OM based on the above-mentioned studies. Najafi et al also pointed out that the size of the ulcerative lesions and irritation score of oral mucosa was significantly higher in the intervention group than in the placebo group, which indicates that liquorice might not have a profound effect in reducing OM. In the Byelorussian study of Sattari et al, where mouthwash containing liquorice was used, no difference in the incidence or severity of OM was observed.[30] This suggests that liquorice may not be an effective herbal intervention for OM.

Two studies confirmed the absence of adverse effects from using herbal mouthwashes, indicating that they may be better tolerated than standard mouthwashes.[29,36] However, most studies did not report adverse effects, possibly because they were not designed to assess safety outcomes. It is also possible that herbal mouthwashes were well-tolerated and produced no or minimal adverse effects or that publication bias favored positive results. Further research is needed to confirm the safety of herbal mouthwashes. Further research should focus on conducting larger, well-designed studies to confirm the safety and efficacy of herbal mouthwashes for OM treatment. Additionally, future studies should identify the optimal formulations and dosages by investigating the most promising herbal ingredients. Clinical trials should then evaluate these formulations regarding safety, efficacy, mechanism of action, long-term effects, and possible interactions with cancer treatments.

Current literature indicates that there is potential for using these herbs in conjunction with conventional treatments as a complementary therapy for patients with OM due to cancer. It remains possible that other topical agents, including herbal agents such as curcumin

and aloe Vera, which both have anti-inflammatory and agents used to treat wounds such as cryotherapy or low-level laser agents, can help improve the effectiveness of current treatments.[23] Moreover, a combination of herbal mouthwashes with agents that reduce oxidative stress, such as superoxide dismutase (SOD) or vitamin E, could provide additional protection against the damage induced by chemotherapy and radiotherapy.[46] These findings suggest that integrated treatment approaches, combining herbal and conventional therapies, could offer a more comprehensive management strategy for OM. Future research should explore the potential for such synergistic combinations in clinical settings.

Strengths and Limitations

To summarize, the evidence gathered for this review collectively supports the potential utility of herbal mouthwashes in treating OM with fewer adverse effects, offering a promising alternative to standard mouthwashes. The efficacy of herbal mouthwashes appears to depend largely on the specific formulations and the herbs used. However, the effectiveness of liquorice-containing mouthwash in reducing the incidence and severity of OM seems limited, as it did not significantly outperform the control group. Therefore, further research is necessary to confirm whether herbal mouthwashes are indeed safe and effective, particularly when compared to standard treatments such as CHX or alcohol-based mouthwashes.

Although the findings of this review are promising, the quality of the evidence is limited by the relatively small number of available studies that assess the effects of herbal mouthwashes on OM in cancer patients. As a result, it is difficult to conclusively determine whether herbal mouthwashes can serve as a viable alternative to standard medical care. Additionally, the studies reviewed varied significantly in their composition, preparation methods, and herbal mouthwash dosages, making direct comparisons challenging. The lack of standardization across formulations further complicates the interpretation of the results.

Furthermore, most studies did not provide sufficient information on potential adverse effects, limiting the ability to fully assess herbal mouthwashes' safety. Without detailed reports of adverse effects, it is difficult to determine whether these products are indeed safer than conventional mouthwashes. Moreover, this review did not perform a comprehensive risk of bias and quality assessment for the included studies, which may limit the accuracy and reliability of the findings presented. Lastly, the long-term effects of herbal mouthwashes and their interactions with cancer therapies could also be highlighted as areas requiring further exploration. Many of the studies included in the review likely focus on short-term outcomes, but the potential for long-term adverse effects or interactions with ongoing cancer treatments (chemotherapy, radiotherapy) is a vital consideration. Lastly, excluding non-English studies introduces the possibility that relevant studies were missed, potentially leading to incomplete evidence in this review.

Conclusion

In conclusion, oral mucositis (OM) is a debilitating side effect of cancer treatments, often resulting in pain, difficulty eating and drinking, and diminished quality of life. While conventional mouthwashes such as CHX and alcohol-based formulations are widely used, their associated adverse effects have led to interest in herbal alternatives. This review, which included 11 studies, 10 of which were RCTs, suggests that herbal mouthwashes containing ingredients like chamomile, aloe vera, peppermint, turmeric, and *Plantago ovata* offer promising benefits in reducing the incidence, severity, and duration of OM, with several studies reporting a decreased need for painkillers. However, the current evidence is limited by the small number of studies, variability in formulations, and insufficient safety data. Further large-scale, well-designed trials are necessary to confirm the efficacy and safety of herbal mouthwashes, determine optimal dosages, and standardize formulations. Such research is essential for establishing herbal mouthwashes as a viable alternative or adjunct to conventional OM treatments in cancer patients.

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Competing Interests

The authors declare no conflict of interest.

Data Availability Statement

Not applicable.

Ethical Approval

Not applicable.

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Supplementary Files

Supplementary file 1 contains Table S1.

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