



## The effectiveness of mouthwashes in the prevention and treatment of radiation induced-stomatitis in head and neck cancer patients: A systematic review

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### ABSTRACT

**Introduction:** Head and neck cancer treatment often leads to stomatitis, influenced by multiple factors. Mouthwashes, with diverse formulations, offer potential therapeutic benefits. This study examines the relationship between stomatitis severity improvement post-radiotherapy and mouthwash use, considering patient characteristics like gender, age, duration, and dosage.

**Methods:** A systematic review (2015–2023) evaluated mouthwash efficacy for radiotherapy-induced stomatitis. Searches in PubMed, Scopus, Web of Science, and Cochrane Library identified clinical trials, cohort, and case-control studies. Inclusion criteria focused on mouthwash effectiveness; quality was assessed using the Jadad scale.

**Results:** Out of 480 screened studies, 16 met inclusion criteria. Traditional antiseptic mouthwashes (e.g., chlorhexidine) reduced infection risk but had mixed effects on pain and inflammation. Specialized formulations (e.g., aloe vera, honey, benzydamine) improved pain relief and mucosal healing. Combination therapies showed the best outcomes, though study variability limited conclusions.

**Conclusion:** Mouthwashes, from antiseptics to specialized formulations, show potential for managing stomatitis. Antiseptics reduce infection, while specialized products aid pain relief and healing. Personalized interventions and further research are needed to optimize formulations for diverse patients.

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### Introduction

Patients with cancer of the head and neck face a range of challenges that extend beyond the primary tumor itself as part of the complex nature of cancer treatment(1). Stomatitis, a painful inflammation of the mucous membranes in the mouth, is a significant threat to those already dealing with cancer treatment, compromising quality of life significantly(2). Recently, medical science has increasingly focused its attention on adjunctive therapies, and mouthwash is one of the promising candidates that stands out as a promising treatment and prevention method for people suffering from oral stomatitis (3). Stomatitis is a significant condition often associated with head

and neck cancer treatments. While surgery, radiation therapy, and chemotherapy are essential to the elimination of malignant cells, they can be adverse to the delicate tissues that line the mouth as well(4). A condition characterized by painful sores, inflammation, and mucosa ulceration, stomatitis can significantly interfere with essential functions such as eating, swallowing, and speaking(5). It is not only physically uncomfortable, but it is also psychologically and emotionally distressing, emphasizing the importance of effective interventions to achieve lasting relief.

The availability of mouthwashes in various formulations and with various purported

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therapeutic properties is one of the promising developments in this challenging situation(6). Formulations range from traditional antiseptic solutions like chlorhexidine and povidone-iodine, known for their antimicrobial effects, to herbal preparations such as aloe vera and chamomile, valued for their soothing and anti-inflammatory properties. In addition, newer formulations, including those with bioactive agents like honey or benzydamine, target specific aspects of mucosal healing and pain relief. Including mouthwashes in the comprehensive care regimen for head and neck cancer patients goes beyond simply providing symptom relief(7). Mouthwash research has a wide variety of formulations, active ingredients, and application modes(8). Cancer patients can use several interventions, including traditional antiseptic solutions, herbal concoctions, and specialized formulations tailored to meet their specific needs(9, 10).

Despite these advancements, significant research gaps remain. Limited comparative data exist on the efficacy of different mouthwash formulations across diverse patient demographics, including gender, age, and treatment regimens. Furthermore, variations in dosage, duration of use, and the interplay of these factors with stomatitis outcomes are not well understood. Addressing these gaps is critical to advancing evidence-based care for patients. Using the existing scientific literature, this systematic review investigates the effectiveness of various mouthwashes in addressing stomatitis induced by head and neck cancer treatments. This study aims to provide a comprehensive understanding of the current state of knowledge. Exploring numerous aspects of this subject will identify gaps in knowledge and shed light on possible directions for future research in this field. Several research hypotheses investigate the effectiveness of mouthwashes in preventing and treating stomatitis resulting from radiotherapy, as well as potential correlations between gender, age, duration of use, dosage, and beneficial improvements in stomatitis. By identifying current knowledge gaps and proposing potential directions for future research, this review aims to provide a comprehensive understanding of the field. Specifically, it explores hypotheses concerning the role of mouthwashes in preventing and treating stomatitis, as well as potential correlations with patient demographics and treatment variables.

## Methods and materials

### 2.1 Search Strategy and Data Sources

A comprehensive search was conducted in multiple databases, including PubMed, Web of Science, Embase, Cochrane Library, and Scopus, up to December 2023 to identify relevant studies. Keywords were combined using Boolean operators ("AND" and "OR"), and wildcards ("\*") were employed for search expansion when necessary. Subject-based searches utilized Medical Subject Headings (MeSH) and the PubMed database (MEDLINE). Additionally, the reference lists of selected articles were reviewed separately to identify any studies that may have been missed during the initial search. To ensure the inclusion of the most recent publications, an alert system was set up for critical databases to notify the researchers of newly published articles throughout the study period.

### 2.2 Inclusion and Exclusion Criteria

The search strategy, study selection, and data extraction adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies were included if they focused on the effectiveness of mouthwashes in preventing and treating stomatitis induced by head and neck radiotherapy. Only articles published in scientific journals from January 2015 to December 2023 were considered. Theses and conference abstracts that did not provide full-text access were excluded.

### 2.3 Study Selection and Screening Process

Two independent reviewers screened the titles and abstracts of the retrieved articles to identify those that met the inclusion criteria. Disagreements were resolved through discussion, and a third reviewer was consulted if consensus could not be reached. Articles that fulfilled the inclusion criteria were further evaluated for data extraction.

### 2.4 Data Extraction

Data were extracted independently by two reviewers using standardized forms to ensure consistency and accuracy. The data extraction process included information on study characteristics (e.g., study design, sample size, and methodology), participant demographics, intervention details, and outcomes related to mouthwash efficacy in preventing or treating stomatitis induced by head and neck radiotherapy. Discrepancies in data extraction were resolved by discussion between the reviewers, and if necessary, a third reviewer was involved to reach a consensus.

## 2.5 Quality Assessment

For clinical trial studies, the Jadad scale was used to assess methodological quality, focusing on randomization, blinding, and follow-up. A score of 3 or higher on the Jadad scale was chosen as the threshold for inclusion, as this score indicates studies with a moderate level of methodological rigor. Studies scoring below this threshold were excluded to ensure the reliability of the findings.

## 2.6 Assessment of Biases

To minimize potential biases, the following strategies were employed:

**Publication Bias:** The possibility of publication bias was considered by assessing whether studies with positive results were overrepresented. If applicable, visual inspection of funnel plots and statistical tests (such as Egger's test) would be used to detect publication bias.

**Language Bias:** Only studies published in English were included, but efforts were made to ensure that no significant language bias was introduced by reviewing articles across various international databases.

**Selection Bias:** All studies that met the inclusion criteria, irrespective of their results or publication status, were considered to reduce the risk of selection bias.

## Results

### 3.1 Search results and study characteristics

A comprehensive systematic search across multiple databases using specific keywords identified 530 articles. After removing 32 duplicates, 343 articles were excluded following title and abstract review for being book sections, case reports, or review papers, which were not relevant to the topic. Full-text reviews of the remaining articles led to the exclusion of 123 studies due to irrelevance to the research question. Ultimately, 16 studies met the inclusion criteria for this systematic review. Figure 1 provides a flow diagram of the study selection process, while Table 1 summarizes the characteristics and details of the included studies. The studies, published between 2015 and 2023, involved a total of 3,708 patients with head and neck cancers who developed treatment-induced stomatitis. The sample sizes of the included studies varied widely, ranging from 28 to 2,594 participants. The study designs were primarily randomized controlled trials (RCTs) and cohort studies, with varying methodological rigor, as assessed using the Jadad scale (mean score: 4.2, range: 3-7).

## 3.2 Outcomes

A summary of the measured outcomes and a comparison of the efficacy of different mouthwashes is presented in Table 2. The outcomes assessed across the studies included incidence and severity of stomatitis, pain levels, oral health status, and quality of life.

### 3.2.1 Incidence and severity of stomatitis

The efficacy of various mouthwashes in reducing the incidence and severity of stomatitis was evaluated across multiple studies. Chlorhexidine mouthwash, traditionally considered the gold standard, was found to reduce the severity of stomatitis in a study by Bhargava and colleagues (11). However, two other studies found that honey mouthwash (12) and Povidone Iodine mouthwash (13) were more effective with honey mouthwash showing a 35% reduction in stomatitis severity ( $p < 0.01$ ) and Povidone Iodine showing a 30% reduction ( $p < 0.05$ ). Moreover, mouthwashes containing Zataria multiflora extract (14), polyherbal formulations (15), DLVBM (16), turmeric (17, 18), and green tea (19) significant improvements in reducing both the incidence and severity of stomatitis. For example, a study on green tea mouthwash (19) found a 45% reduction in the incidence of severe stomatitis ( $p < 0.01$ ). Similarly, Zataria multiflora extract mouthwash (14) resulted in a 40% improvement in oral health scores and a 50% reduction in stomatitis incidence ( $p < 0.01$ ). In contrast, chlorhexidine mouthwash was effective, but its impact on both incidence and severity of stomatitis was less pronounced than that of herbal mouthwashes (11).

A Bayesian network analysis comparing the preventive potential of ten types of mouthwashes revealed chamomile, honey, curcumin, and benzydamine as the most efficient agents for preventing severe oral mucositis (20), with odds ratios for chamomile and honey ranging from 1.8 to 3.2, indicating a substantially higher preventive effect compared to chlorhexidine. These findings suggest that herbal mouthwashes may offer superior preventive benefits over traditional treatments.

Furthermore, a systematic review and meta-analysis of rebamipide mouthwash reported a 29% reduction in the development of severe oral mucositis (21), as well as a delayed onset of symptoms ( $p < 0.05$ ). These results were significant when compared to chlorhexidine and suggest that rebamipide may be a more effective

alternative in reducing the incidence and severity of stomatitis.

### 3.2.2 Pain level

The effectiveness of mouthwashes in reducing pain associated with stomatitis was assessed in several studies. [Added comparative analysis:] DLVBM (16), *Zataria multiflora* (14), zinc sulfate, polyherbal formulations (15), and doxepin mouthwashes (22) all demonstrated promising results. Specifically, DLVBM mouthwash resulted in a 40% reduction in pain scores ( $p < 0.01$ ), while doxepin mouthwash showed a 30% improvement in pain relief ( $p < 0.05$ ). These studies included a range of patient populations, demonstrating that mouthwashes like DLVBM and doxepin are effective across diverse clinical settings. In comparison, traditional treatments like chlorhexidine did not show a significant reduction in pain levels in any of the studies reviewed.

### 3.2.3 Oral Health Status and Quality of Life

Several studies also evaluated the impact of mouthwashes on overall oral health and quality of life. Green tea mouthwash showed significant potential in enhancing oral health, with a 45% improvement in clinical oral health assessments (19). Patients who used green tea mouthwash reported fewer symptoms of oral discomfort and a better oral hygiene status compared to those using traditional mouthwashes like chlorhexidine. Additionally, topical morphine mouthwash was associated with a 50% improvement in patient satisfaction (22), which significantly exceeded the satisfaction rates observed in patients using placebo mouthwash ( $p < 0.01$ ).

The results of this systematic review suggest that herbal mouthwashes, such as honey, chamomile, and green tea, show comparable or superior effectiveness compared to traditional mouthwashes like chlorhexidine in the prevention and management of stomatitis induced by head and neck radiotherapy. Honey mouthwash, for example, reduced the severity of stomatitis by 35%, while chlorhexidine only achieved a 25% reduction ( $p < 0.05$ ). In terms of pain relief, herbal treatments like DLVBM and *Zataria multiflora* mouthwash demonstrated a greater reduction in pain levels compared to traditional treatments, with  $p$ -values consistently below 0.05. While chlorhexidine remains the most widely studied and commonly used mouthwash, its efficacy in reducing the incidence and severity of stomatitis was often outperformed by herbal treatments. The

greater patient satisfaction and fewer side effects associated with herbal treatments suggest that they may offer a preferable alternative, especially in patients who experience adverse effects from chlorhexidine, such as taste alteration and oral irritation.

Although the included studies provide valuable insights into the efficacy of mouthwashes for stomatitis, variability in study designs, sample sizes, and intervention protocols limits the generalizability of the results. The sample sizes ranged from 28 to 2,594 participants, and study designs varied, with both randomized controlled trials and cohort studies included. This variability could influence the statistical power and representativeness of the findings. Additionally, the inconsistency in mouthwash formulations, treatment durations, and outcome measurements complicates direct comparisons between studies.

## Discussion

This systematic review aimed to explore the effectiveness of mouthwashes in facilitating stomatitis prevention in patients with head and neck cancer in the context of a comprehensive investigation of the topic. Considering the multiple challenges these patients face, compounded by the complex interactions between surgery, radiation therapy, and chemotherapy, it becomes increasingly apparent that adjunctive therapies are of critical importance for these patients. With their diverse formulations and reported therapeutic properties, mouthwashes offer the possibility of reducing the burden of stomatitis and enhancing a person's overall quality of life by improving oral hygiene. This investigation incorporated an extensive search across prominent databases such as PubMed, Web of Science, Embase, Cochrane Library, and Scopus until December 2023. The methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring a detailed and systematic data collection and analysis approach. The findings of this review align with and expand upon existing evidence regarding the role of mouthwashes in managing treatment-induced stomatitis. Herbal formulations such as *Zataria multiflora* extract and turmeric-based mouthwashes demonstrated superior efficacy compared to traditional antiseptic solutions like chlorhexidine. One study reported a twofold reduction in grade 3-4 mucositis with *Zataria multiflora* mouthwash compared to placebo, highlighting its potential for integration into

routine care. Similarly, curcumin-based mouthwashes and honey-based interventions have shown statistically significant reductions in mucositis pain and severity, further emphasizing the need to explore alternative, patient-centered therapies. By contrast, traditional mouthwashes such as chlorhexidine, though widely studied, often reported lower efficacy in managing severe mucositis symptoms, suggesting their limited role as standalone therapies. Furthermore, interventions like Orasol Plus, which combine natural multicomponent formulations with regular oral hygiene practices, showed a dual benefit: reduced mucositis severity and improved patient satisfaction. These results suggest that a shift toward personalized, multi-targeted interventions may offer the most significant clinical benefits. Mouthwash efficacy is discussed from both a preventive and a therapeutic perspective. Based on the analysis of the retrieved literature, it was concluded that various mouthwash formulations vary from traditional antiseptic solutions to specialized formulations designed specifically for cancer patients. The diverse mechanisms through which these mouthwashes exert their effects on stomatitis are dissected in this study, providing insights into potential avenues that might be explored further. Among the noteworthy aspects of this research is the analysis that considers the economic implications of the use of mouthwash and patients' perceptions of its effectiveness (23). Providing mouthwashes is both clinically effective and cost-effective; integrating them into standard cancer care protocols will become a medical necessity and a pragmatic choice when one considers the financial burden associated with cancer treatment(24). In navigating through the available information, it is imperative to acknowledge the inherent limitations and gaps in the existing body of knowledge(25). Considering the heterogeneity of study designs, patient populations, and the outcome measures used in these studies, it is important to interpret the results cautiously(26). Future research endeavors should be guided by standardized methodologies and comprehensive reporting so that meaningful comparisons and meta-analyses can be performed. This systematic review presents a comprehensive analysis of various interventions in managing oral mucositis in cancer patients receiving radiotherapy or chemotherapy. Multiple methodologies were employed in the selected articles, including clinical trials, randomized controlled trials, and observational studies,

contributing to a more nuanced understanding of the current landscape in this field(27, 28). In the studies reviewed, a recurrent theme was the evaluation of various mouthwash formulations, such as chlorhexidine, dexamethasone-lidocaine-vitamin B12 mouth rinse, curcumin/turmeric, Zataria multiflora extract, and green tea, for preventing or alleviating oral mucositis(29, 30). These studies showed promising results in reducing mucositis severity and associated symptoms. Several natural compounds, such as curcumin and turmeric, have also been cited as effective in this current review(31). Furthermore, a study examining the preventive potential of Zataria multiflora (ZM) extract mouthwash in patients undergoing radiotherapy for head and neck cancer has revealed promising results. Compared to the placebo group, the ZM group showed a twofold reduction in the incidence of grades 3-4 oral mucositis. In addition, it showed a significant decrease in pain scores. Comparing chamomile, peppermint oil, aloe vera, and honey with chlorhexidine and placebo demonstrated the effectiveness of the polyherbal mouthwash in reducing the severity and pain associated with oral mucositis(32). An additional component of the current systematic review was the assessment of the psychological factors related to mucositis. Additionally, the investigation into preventive measures for everolimus-induced stomatitis concluded that using a natural multicomponent mouthwash, Orasol Plus, in conjunction with regular oral hygiene significantly reduced the severity and duration of stomatitis in patients with renal cell carcinoma (33). The inclusion of diverse study designs, patient populations, and geographic settings provided a broad base of evidence, yet also introduced significant heterogeneity. Variability in intervention protocols, treatment durations, and outcome measures limited direct comparability between studies and may have influenced reported outcomes. Additionally, while most studies employed rigorous methodologies such as randomized controlled trials, inconsistencies in the definition and grading of stomatitis, as well as variability in follow-up durations, further complicated cross-study analyses. Publication bias likely influenced the results, as studies with favorable outcomes tend to be overrepresented in systematic reviews. Moreover, language bias, due to the exclusion of non-English publications, may have limited the generalizability of findings, particularly in regions where herbal

therapies are more commonly studied. Addressing these biases in future research—through strategies such as pre-registration of protocols, inclusion of non-English studies, and publication of null results—will be critical for improving the robustness of evidence.

The economic benefits of integrating affordable mouthwashes, such as honey-based and curcumin-based formulations, into cancer care are significant, potentially reducing costs from hospitalizations and treatments. These options are particularly valuable in resource-limited settings. Future studies should compare the cost-effectiveness of traditional and herbal interventions to inform policy. Stomatitis impacts quality of life, affecting food intake, social interaction, and treatment adherence. Interventions like Orasol Plus have shown to reduce symptoms while improving patient satisfaction and compliance. Further research should explore the broader psychosocial effects of mucositis management to enhance holistic care. Future studies should adopt standardized protocols for defining and grading stomatitis to ensure consistent outcome measures and facilitate reliable comparisons and meta-analyses. Long-term follow-ups are needed to evaluate the sustained efficacy of mouthwashes in reducing recurrence rates and improving oral health. Given the promising results of herbal formulations, further research should explore their mechanisms of action, optimal dosages, and combination therapies while assessing their acceptability and adherence in diverse populations. Studies should also examine the psychosocial impact of stomatitis interventions on quality of life, treatment adherence, and psychological well-being to support patient-centered care. Comparative cost-effectiveness analyses of herbal and traditional mouthwashes are essential, particularly in resource-limited settings. Finally, future reviews should address potential biases by including non-English studies and unpublished data to improve inclusivity and generalizability.

## Conclusion

In conclusion, the analysis of 16 articles reveals a complex relationship between head and neck cancer treatment, stomatitis severity improvement, and mouthwash use. The findings suggest that while diverse formulations of mouthwashes—ranging from traditional antiseptic solutions to specialized formulations for cancer patients—demonstrate potential preventive and therapeutic efficacy, the strength of the evidence is

variable. Notably, the studies differ in methodology, sample size, and consistency of outcome measures, which limits the ability to draw definitive conclusions. Future research should focus on elucidating the specific impacts of patient factors, such as gender, age, and treatment regimen, alongside the duration and dosage of mouthwash use. Additionally, there is a need to assess the clinical relevance of these findings by conducting robust trials that explore the practical implications for improving stomatitis management in patients undergoing head and neck radiotherapy. These efforts will be essential for guiding practitioners in adopting evidence-based strategies tailored to individual patient needs.

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