

Turmeric-based Oral Rinses In Oral Mucositis Management: Advances, Mechanisms, And Challenges

Enxaguantes Oraís à Base de Cúrcuma no Tratamento da Mucosite Oral: Avanços, Mecanismos e Desafios

Enjuagues Orales de Cúrcuma En El Tratamiento de La Mucositis Oral: Avances, Mecanismos y Retos

RESUMO

Objetivo: avaliar a eficácia dos enxaguantes orais à base de cúrcuma/curcumina na prevenção e redução da mucosite oral em pacientes submetidos à quimio-radioterapia.

Métodos: realizou-se uma busca sistemática em diferentes bases de dados e literatura cinzenta, considerando estudos publicados entre 2014 e outubro de 2024. Foram selecionados ensaios clínicos e revisões da literatura que investigaram a eficácia dos enxaguantes orais contendo curcumina, excluindo estudos com outras formulações, como cápsulas e géis.

Resultados e Conclusão: quatorze estudos foram incluídos. Os resultados indicam que os enxaguantes com curcumina retardam o aparecimento da mucosite e reduzem sua gravidade, embora não previnam completamente sua incidência. Esses enxaguantes são seguros, de fácil aplicação e bem tolerados. No entanto, limitações metodológicas foram observadas nesses estudos, como amostras reduzidas e variabilidade nas dosagens. Ensaios clínicos robustos são necessários para validar esses achados e otimizar a biodisponibilidade da curcumina, trazendo maior eficácia no tratamento da mucosite oral.

DESCRIPTORIOS: Curcuma; Curcumina; Estomatite; Antissépticos Bucais; Quimiorradioterapia.

ABSTRACT

Objective: to evaluate the effectiveness of turmeric/curcumin-based oral rinses in preventing and reducing oral mucositis in patients undergoing chemo-radiotherapy. **Methods:** we conducted a systematic search across major databases covering studies published from 2014 to October 2024. Randomized clinical trials and literature reviews evaluating the efficacy of curcumin-based oral rinses were selected. Studies using different turmeric formulations (capsules, gels, or combinations with other compounds) were excluded. **Results and Conclusion:** fourteen studies were included. Findings suggest that curcumin-based oral rinses delay the onset of mucositis and reduce its severity, although they do not entirely prevent its occurrence. These rinses are safe, easy to use, and well-tolerated. However, methodological limitations were identified, such as small sample sizes and dosage variability. More robust clinical trials are necessary to validate these findings and improve curcumin bioavailability to enhance its effectiveness in oral mucositis treatment.

DESCRIPTORS: Curcuma; Curcumin; Stomatitis; Mouthwash; Chemoradiotherapy.

RESUMEN

Objetivo: evaluar la eficacia de los enjuagues orales con cúrcuma/curcumina en la prevención y reducción de la mucositis oral en pacientes sometidos a quimiorradioterapia. **Métodos:** se realizó una búsqueda sistemática en bases de datos y literatura gris, considerando estudios publicados entre 2014 y octubre de 2024. Se seleccionaron ensayos clínicos y revisiones sobre la eficacia de los enjuagues con curcumina, excluyendo otras formulaciones. **Resultados y conclusión:** se incluyeron 14 estudios, que indicaron que los enjuagues con curcumina retrasan la mucositis y reducen su gravedad, aunque no previenen totalmente su incidencia. Son seguros, fáciles de aplicar y bien tolerados. Sin embargo, los estudios presentan limitaciones metodológicas, como muestras pequeñas y variabilidad en las dosis. Se requieren ensayos clínicos más robustos para confirmar estos hallazgos y optimizar la biodisponibilidad de la curcumina, mejorando su eficacia en el tratamiento de la mucositis oral.

DESCRIPTORIOS: Curcuma; Curcumina; Estomatitis; Antisépticos Bucales; Quimiorradioterapia.

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INTRODUCTION

Oral mucositis (OM) is a common inflammatory condition affecting cancer patients undergoing radiotherapy and chemotherapy. It manifests as painful erythema, erosions, and ulcerations in oral tissues, leading to significant discomfort and weight loss⁽¹⁾. Additionally, OM can result in systemic complications by increasing the risk of opportunistic and secondary infections⁽²⁾.

An estimated 80% of patients receiving radiotherapy for head and neck cancers will develop some degree of OM, with more than 50% of cases classified as moderate to severe (grades 3 and 4)⁽³⁾.

This condition severely impacts the quality of life and adherence to oncological treatments, as its severe forms often render patients unable to tolerate therapy. Moreover, the economic burden is substantial, as the costs of treating symptoms, providing nutritional support, managing secondary infections, and hospitalizations increase significantly⁽⁴⁾.

According to Sonis⁽⁵⁾, the additional cost associated with treating radiation-induced OM in head and neck cancer patients can reach up to \$17,000 per patient. This financial burden significantly affects healthcare systems and patients, emphasizing the need to develop more effective and accessible therapies to alleviate this economic impact and enhance patient care. Currently, there is no universally accepted standard for OM treatment. The most

common clinical management strategies include standardized oral care, anti-inflammatory agents, antimicrobials, analgesics, and topical agents⁽⁶⁻⁷⁾.

Despite extensive research on various therapeutic agents and palliative measures, no single preventive or treatment protocol has proven entirely effective for OM⁽⁸⁾. Consequently, the search for alternative therapies, particularly those involving natural compounds, is gaining traction due to their potentially lower risk of adverse effects and toxicity than conventional treatments⁽⁹⁾.

In this context, turmeric (*Curcuma longa*), a ginger family (*Zingiberaceae*) medicinal herb, has gained attention for its antioxidant, analgesic, anti-inflammatory, antiseptic, antimicrobial, and anticancer properties⁽¹⁰⁾.

Curcumin, the primary bioactive pigment extracted from *Curcuma longa* rhizomes, is widely recognized for its therapeutic benefits. This natural polyphenol is one of the most extensively investigated compounds due to its broad biological effects, including anti-inflammatory and antioxidant activities⁽¹¹⁾.

Rao et al.⁽¹²⁾ showed that turmeric-based mouthwash effectively delayed the onset and reduced the severity of radiation-induced OM. Since then, curcumin has been the focus of many clinical studies to explore its potential in OM prevention and symptom relief.

Given this background, the present study is an integrative review designed to evaluate the scientific literature on the efficacy of turmeric/curcum-

in-based oral rinses for preventing and mitigating OM in cancer patients undergoing chemo-radiotherapy. This review aims to provide an updated understanding of the topic and contribute to developing new therapeutic approaches.

METHODOLOGY

This integrative review explored the current evidence on turmeric/curcumin-based mouthwash for managing oral mucositis in patients undergoing radiotherapy and chemotherapy. We conducted a systematic search across major databases covering studies published from 2014 to October 2024. The search strategy included keywords: turmeric OR curcumin AND "oral mucositis" OR mucositis OR stomatitis AND mouthwash OR mouth rinse OR "oral rinse." Randomized clinical trials and literature reviews were included.

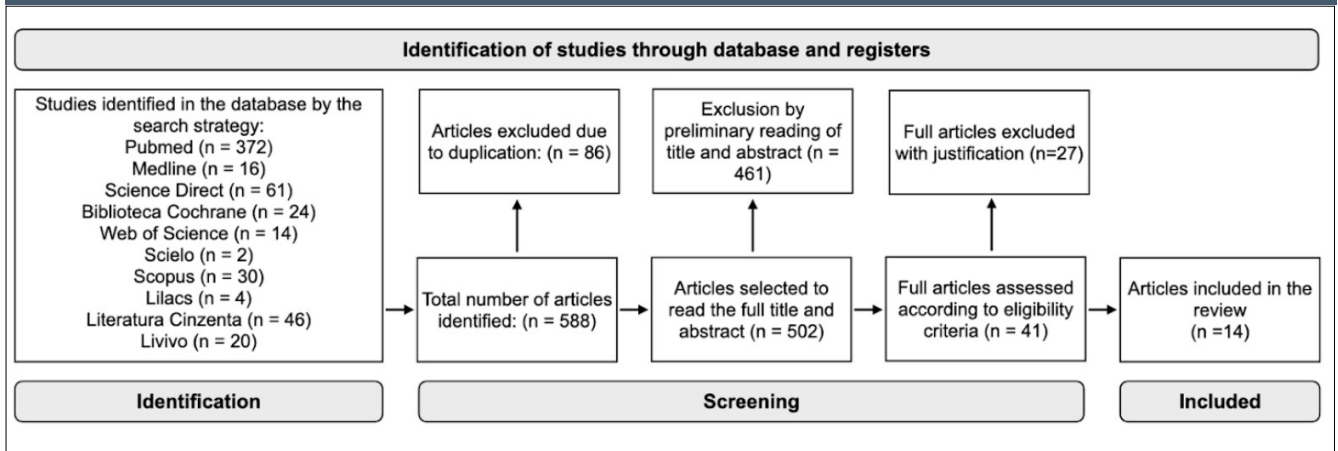
We used Rayyan to remove duplicate references to ensure accuracy. Two independent reviewers screened studies, with a third resolving disagreements. Full-text articles meeting the criteria were reviewed, resulting in 14 selected studies. We included research evaluating the efficacy of turmeric/curcumin-based mouthwash compared to placebo or other treatments and excluded studies on non-mouthwash curcumin formulations or combinations with other compounds. PRISMA guidelines ensured a transparent selection process (Figure 1).

Integrative Review

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Figure 1. PRISMA Diagram.



Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n7

RESULTS

We identified 14 studies after performing the selection method. Table

1 lists the Clinical Trials and Table 2 shows the review studies.

Table 1. Main points covered in Clinical Trial studies.

Study Limitations	Small sample, short 5-day duration, single-center study, subjective OM and pain assessment.	Small sample, single-center, no blinding in the turmeric group, no pain or quality of life assessments.	Small sample, high loss to follow-up, dropout rate affected reliability, results influenced by MO's self-limiting nature and radiotherapy dose response.	Insufficient details about blinding.	Small sample size. Confounding factors (radiation site/dose) affecting OM severity	
Results and Conclusions	Turmeric Mouthwash: Reduced OM severity Saline Mouthwash: Also reduced OM Comparison: Significant difference on days 4 and 5.	Turmeric: Delayed and reduced OM severity, fewer intolerable cases (14/39), and less weight loss.	Curcumin Mouthwash: Delayed OM onset, similar efficacy to benzydamine in preventing severe OM, well tolerated. Average Start off OM 7 days (benzydamine), 21 days (curcumin), with a 50% lower risk in the curcumin group	Turmeric mouthwash was more effective in reducing OM severity than benzydamine mouthwash	Curcumin reduced severity/burning vs. placebo. By the study's end, 33% (mouthwash) and 15% (nanocapsules) were ulcer-free; all placebo-developed OM. Pain and WHO scores were similar.	
Intervention Characteristics	Control	Saline solution (0.9 g/100 mL water), rinse 50mL 3x/day for 5 days.	Povidone-iodine mouthwash. Rinse 10 mL 2x/ day for 7 weeks.	<i>Benzydamine 0.15% mouthwash. 10 mL 3 x/ day for 6 to 7 weeks.</i>	<i>Benzydamine Mouthwash</i>	<i>Placebo Mouthwash (10 mL 3 x/day for 21 days).</i>
	Intervention	Turmeric mouthwash (1.5 g/50 mL water), rinse 50 mL 3x/day for 5 days.	Turmeric mouthwash (400 mg/80 mL water), rinse 10 mL 6x/day for 7 weeks.	<i>Nanocurcumin 0.1% mouthwash. 10 mL mouthwash 3x/day for 6 to 7 weeks.</i>	<i>Turmeric mouthwash (400 mg/80 mL water), gargle 6x/day for 7 weeks.</i>	<i>Rinse with curcumin 0.1% (10 mL, 3x/day, 21 days) + nanocapsules (40 mg/day, up to 21 days).</i>

Sample	40 patients	79 patients	17 patients	88 patients (45 patients
Study	Non-Randomized Clinical Trial	Randomized Clinical Trial	Triple-blind Randomized Clinical Trial	Randomized Clinical Trial	Single-blind, randomized, controlled clinical trial
Author /Year	Saldanha, 2014 ⁽¹³⁾	Rao et al., 2014 ⁽¹²⁾	Shah et al., 2020 ⁽¹⁴⁾	Thomas et al., 2023 ⁽¹⁵⁾	Ramezani et al., 2023 ⁽¹⁶⁾

Table 2. Main points covered in Review-type studies

Limitations of the Study	High variability in study design, interventions, outcomes, treatments, dosages, controls, and follow-ups. Small sample size and limited RCTs.	Small samples, moderate methodological quality, and potential bias.	Limited human applicability (mainly animal studies). More trials are needed for dose, route, and safety. Low oral bioavailability reduced efficacy.	Limited to specific patient groups. Further research needed in diverse populations. High variability in dose, duration, design, and formulation.	Need for well-designed, high-quality, large-scale RCTs. Few studies. A small number of patients tested, making it difficult to be certain of the results. Influence of chemotherapy regimens not considered.	High heterogeneity in formulations, concentrations and evaluation criteria. Low number of studies. Lack of detailed information on chemotherapy/ radiotherapy received and other side effects.	Need for more blinded randomized clinical trials. Small sample sizes limit conclusions about efficacy.	Confounding factors, such as radiation site and dose, that affect the severity of OM.	Non-uniform methods of administration and doses of curcumin in clinical trials. Lack of consistent assessment criteria for OM across studies. Inclusion of only six small samples from randomized clinical trials in the article.
Therapeutic Results	Delays onset of OM. Reduces severity Reduces pain score	Prevents Severe OM	Nanoformulations improve bioavailability. Nanoformulations improve bioavailability	Reduces the severity of OM. They are safe and well tolerated	Efficacy was greater than placebo (P<0.05).	Reduces pain and severity of OM, significantly decreasing erythema and ulcer size.	Reduces the severity of OM. Reduces the pain score Promotes the healing of ulceration	Reduces the severity of OM. Reduces Pain Score Reduces weight loss by improving symptoms such as dysphagia	Reduces the incidence of severe OM. Reduces weight loss by improving symptoms such as dysphagia
Study design	Systematic Review with Meta-Analysis	Systematic Review with Meta-Analysis	Integrative Review	Integrative Review	Systematic Review with Meta-Analysis	Systematic Review	Systematic Review	Systematic Review with Meta-Analysis	Systematic Review with Meta-Analysis
References	Dharma, 2021 ⁽¹⁷⁾	Zhang et al., 2020 ⁽¹⁸⁾	Akbari et al. 2020 ⁽¹⁹⁾	Hegde et al., 2023 ⁽²⁰⁾	Yu et al. 2020 ⁽²¹⁾	Normando et al., 2019 ⁽²²⁾	Wahyuni et al. 2021 ⁽²³⁾	Wu et al. 2024 ⁽²⁴⁾	Zhang; Tang; Wei, 2021 ⁽²⁵⁾

DISCUSSION

Neoadjuvant radiotherapy (RT), alone or in combination with chemotherapy (CT), improves cancer patient survival but often induces

oral mucositis (OM), a major clinical challenge⁽²⁶⁻²⁷⁾. The World Health Organization (WHO)⁽²⁸⁾ classifies OM severity from grade 0 (intact mucosa) to grade 4 (severe ulcers and intense pain).

RT and CT cause direct genetic damage, leading to DNA strand breaks, apoptosis of basal epithelial cells, and reactive oxygen species production, activating nuclear factor kappa B (NF-κB). NF-κB regulates

pro-inflammatory cytokines and adhesion proteins, playing a key role in OM pathogenesis. Curcumin, turmeric's primary active compound, has emerged as a promising therapeutic due to its ability to inhibit NF- κ B activation, suppress pro-inflammatory cytokines like TNF- α , IL-6, and IL-8, and exhibit antibacterial properties, preventing bacterial adhesion in OM models⁽²⁹⁻³¹⁾.

We conducted a comprehensive analysis of studies published up to October 2024 to address this topic. The findings indicate that the topical application of curcumin on mucosal surfaces represents a promising treatment strategy, as it delays the onset of oral mucositis and reduces its severity, even though it does not entirely prevent the condition. The formulation in mouthwash has advantages due to its ease of application, practicality, and good patient tolerability^(15-18, 22, 24).

Despite these pharmacological benefits, curcumin faces challenges related to its therapeutic efficacy due to its limited bioavailability, low solubility in aqueous solutions, and rapid metabolism⁽³²⁾. Different formulations, such as micelles, nanoparticles, liposomes, and solid dispersions, have been explored *in vitro* and *in vivo* to enhance curcumin bioavailability in clinical studies⁽²⁰⁾.

Most studies investigating curcumin's anti-inflammatory effects have shown promising results. However, these findings should be interpreted cautiously due to the high heterogeneity among studies. Variations in curcumin dosages and differences in control groups, which applied distinct therapeutic approaches, complicate the direct comparison of results. Furthermore, the small sample sizes in many studies limit the generalizability of the findings^(14, 17, 19, 21).

Including both randomized and non-randomized clinical trials also increases the risk of bias, which can affect the quality of the evidence.

The patient response to radiotherapy, influenced by the radiation dose received and the self-limiting nature of OM, contributes to variability in outcomes⁽¹⁴⁾. Other confounding factors include the radiation site and applied dose, directly impacting treatment efficacy⁽¹⁶⁾.

Limited curcumin bioavailability remains a significant challenge, hindering its clinical application. Its low solubility and rapid metabolism in the body restrict absorption, reducing its therapeutic efficacy, especially in short-term treatments where fast results are required⁽³³⁾.

Recent research has focused on improving curcumin formulations to address these limitations. One promising approach is bio-enhanced formulations, which combine curcumin with other curcuminoids. These formulations have yielded positive results in reducing OM severity, dysphagia, and pain⁽³⁴⁾. Additionally, using nanoformulations of curcumin in mouthwashes has demonstrated greater efficacy, indicating new possibilities for treatment⁽¹⁴⁾.

Future multicenter studies with standardized and innovative curcumin formulations are essential to strengthening the evidence regarding its efficacy in OM treatment. Well-designed clinical trials with rigorous variable control are necessary to minimize bias risks. The adoption of strict methodological criteria is crucial to ensuring comparability across studies. Precise study protocols and adequate standardization can achieve a more reliable assessment of curcumin's impact on oral mucositis prevention and treatment.

CONCLUSION

This review's results demonstrate the efficacy of turmeric-based mouthwash in preventing and reducing the severity of oral mucositis in cancer patients undergoing chemoradio-

therapy. However, to strengthen the reliability and applicability of these studies, high-quality randomized, double-masked clinical trials must be conducted. These studies should include larger samples to increase representativeness and minimize statistical errors. In addition, rigorous control of variables such as radiation time, application location, curcumin doses administered, use of placebo, and blinding is necessary to avoid bias.

A more extended follow-up period is also recommended to assess long-term effects. Different methods should be investigated to determine their treatment effectiveness, which is essential to ensure more consistent clinically relevant results. In addition, it is essential to develop new curcumin formulations that minimize the challenges of its bioavailability and reduce adverse effects. In this context, nanoformulation of curcumin appears to be a promising strategy, capable of increasing its bioavailability and reducing its rapid degradation in the body.

Finally, a rigorous cost-benefit study, with logistical feasibility and access analyses, could better support introducing this type of product in Public or Private Health Systems. Such studies would allow us to assess the economic viability of using curcumin and expand its reach and accessibility, especially for populations with lower purchasing power. This economic viability could represent a significant advance in providing more effective, low-cost therapies for treating OM.

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