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Therapeutic alternatives with mouthwashes for management oral mucositis: an integrative review

Alternativas terapêuticas com enxaguantes bucais para o manejo da mucosite oral: uma revisão integrativa

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ABSTRACT

Objective: The aim of this study was to conduct an integrative review to assess the efficacy of the mouthwashes recommended for the prevention and treatment of Oral mucositis (OM) and oropharyngeal mucositis (OPM) in patients undergoing cancer treatment. **Method:** The research question was formulated based on the PICOS strategy: "Are chlorhexidine, allopurinol, benzydamine and propolis mouthwashes effective in preventing and treating OM and OPM in patients undergoing cancer treatment?" Searches were performed in PubMed, Embase, Scopus, Web of Science, OpenGrey and Google Scholar, without publication year or language restrictions. Randomized clinical trials comparing the use of chlorhexidine, allopurinol, benzydamine and propolis with a control group or a group

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that did not undergo any intervention were included. The retrieved articles were analyzed and selected by two reviewers and disagreements were resolved by consultation with a third reviewer. **Results:** After evaluation of the works, 13 of 1183 articles were selected. Mouthwashes containing propolis and benzydamine mouthwashes were promising and effective in the management of mucositis while chlorhexidine or allopurinol did not provide satisfactory results. **Conclusion:** Mouthwashes could be an alternative for treatment or preventing oral mucositis in cancer patients. Services could consider the possibility of incorporating these medications since, in most cases, they are low cost and do not require specialized staff in their use.

Keywords: Antineoplastic therapies. Mouthwashes. Oral Mucositis.

RESUMO

Objetivo: O objetivo deste estudo foi realizar uma revisão integrativa para avaliar a eficácia dos enxaguantes bucais recomendados para a prevenção e tratamento da mucosite oral e da mucosite orofaríngea em pacientes submetidos a terapias antineoplásicas. **Método:** A questão de pesquisa foi formulada com base na estratégia PICOS: "Os enxaguantes bucais a base de clorexidina, alopurinol, benzidamina e própolis são eficazes na prevenção e tratamento da mucosite oral e orofaríngea em pacientes submetidos ao tratamento de câncer?". As buscas foram realizadas nas bases PubMed, Embase, Scopus, Web of Science, OpenGrey e Google Scholar, sem restrições de ano de publicação ou idioma. Ensaios clínicos randomizados comparando o uso de clorexidina, alopurinol, benzidamina e própolis com um grupo controle ou com nenhuma intervenção foram incluídos. Os artigos recuperados foram analisados e selecionados por dois revisores, sendo que os desacordos foram resolvidos em consulta com um terceiro revisor. **Resultados:** Após avaliação dos trabalhos, 13 dos 1183 artigos foram selecionados. Enxaguantes bucais contendo própolis e benzidamina mostraram-se promissores e eficazes no manejo da mucosite, enquanto clorexidina e alopurinol não apresentaram resultados satisfatórios. **Conclusão:** Os enxaguantes bucais podem ser uma alternativa para o tratamento ou prevenção de mucosite oral em pacientes com câncer. Os serviços poderiam considerar a possibilidade de incorporar esses medicamentos, já que, na maioria dos casos, eles têm baixo custo e não requerem pessoal especializado para seu uso.

Palavras-chave: Terapias antineoplásicas. Enxaguantes Bucais. Mucosite Oral.

INTRODUCTION

Oral mucositis (OM) and oropharyngeal mucositis (OPM) are common acute complications in patients undergoing antineoplastic therapy[1]. These conditions result from inflammation and ulceration of the oral mucosa, which becomes edematous, erythematous,

and friable. Consequently, they cause pain, discomfort, and dysphagia[2]. This is considered the most uncomfortable side effect experienced by these patients during treatment[3].

OM and OPM can compromise the patient's nutritional status, such as dehydration and micronutrient deficiencies, and consequently weight loss. Moreover, the various microorganisms residing in the oral cavity can predispose to local and systemic infections, worsening the clinical condition of these patients[4].

As a result, it can limit the progression of chemotherapy and radiotherapy[1]. This generates an economic impact on patients and their families, as well as the healthcare system, whether public or private. The increase in costs is due, for example, to additional treatments with control of secondary infections and previously unplanned hospitalizations[5].

The prevention and treatment of antineoplastic therapy-induced OM and OPM have been extensively discussed in literature. Some studies have investigated measures to reduce the severity of these conditions and possible complications. However, there seems to be no consensus regarding a specific protocol to be adopted. Among the methods investigated, photobiomodulation therapy (PBMT) has shown good results in the management of OM[6,7].

A preliminary randomized clinical study evaluated three photobiomodulation (PBMT) protocols for OM and OPM. The study focused on adults undergoing chemotherapy (CT) or hematopoietic stem cell transplantation (HSCT). The three investigated PBMT protocols showed good results in managing OM. They effectively prevented and reduced OM. This leads to less odynophagia and reduced dependence on parenteral nutrition. There were no adverse effects reported. PBMT is safe and effective[8]. Nevertheless, it requires specialized personnel and equipment and cannot be performed by the patients themselves[6,7].

In view of the adverse effects of traditional drugs, increasing attention has been given to a range of natural agents because of their anti-inflammatory, antibacterial, antioxidant, immunomodulatory, sedative, and healing activities. These agents may be effective in the prevention and treatment of OM and OPM[9].

An example of this is some mouthwashes. They are easy to use, and suitable for healthcare services. They can be used safely by patients and are accessible to most of the population. Additionally, such therapies are expected to promote the re-epithelialization of tissue lesions and to have a pleasant taste and low toxicity[9].

Thus, there is a need for new therapies that not only promote symptom relief but also act as a therapeutic alternative. The aim of this integrative review was to evaluate the efficacy of mouthwashes in preventing and treating OM and OPM in cancer patients.

MATERIAL AND METHODS

Study design

An integrative review, also known as a qualitative systematic review or qualitative evidence synthesis, is a method that synthesizes existing literature to provide a comprehensive understanding of a health phenomenon or problem, facilitating the incorporation of this knowledge into practice. This approach involves the identification and analysis of independent studies on the same topic. While including studies with varying designs can complicate the analysis, such diversity in the sampling process can enhance the depth and comprehensiveness of the review's conclusions[10,11,12].

To aid in writing integrative review manuscripts, the use of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[13] checklist, available in Portuguese, is recommended. Although designed to improve the reporting of systematic reviews and meta-analyses, PRISMA can be effectively adapted for integrative reviews, as demonstrated in this study[10].

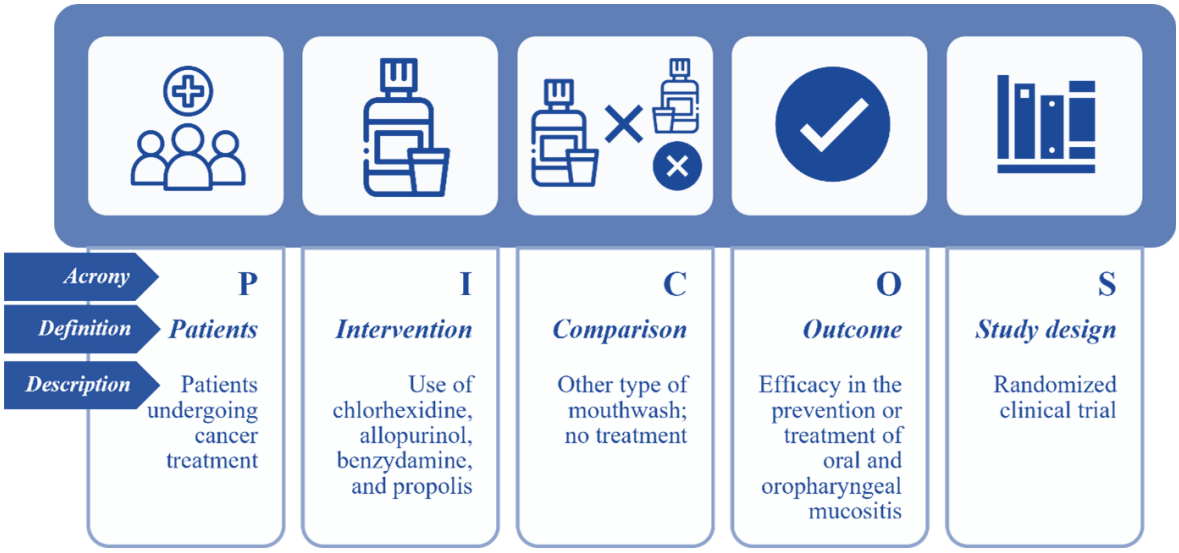
This integrative review compiles data from articles to evaluate and understand the efficacy of various mouthwashes in the prevention and treatment of oral mucositis (OM) and oropharyngeal mucositis (OPM) in cancer patients. The mouthwashes assessed include chlorhexidine, allopurinol, benzydamine, and propolis.

Research question and Search strategy

The following research question was formulated based on the PICOS strategy (Figure 1):“Are chlorhexidine, allopurinol, benzydamine and propolis mouthwashes effective in preventing and treating OM and OPM in patients undergoing cancer treatment?”

Searches were performed in the databases PubMed, Embase, Scopus, Web of Science, OpenGrey and Google Scholar, without publication year or language restrictions, on 30 October 2023 and updated on 30 January 2024. The search strategy was based on a combination of the keywords *(“mouthwash” OR “mouthwashes”) AND (“stomatitides” OR “stomatitis” OR “oral mucositis” OR “oral mucositides” OR “oromucositides”).* The references retrieved were exported to Endnote Online (Clarivate Analytics, London, UK). Duplicates were removed.

Figure 1 - Description of the PICOS strategy for formulation of the research question



Source: Authors (2024)

Inclusion and exclusion criteria

The inclusion criteria were randomized clinical trials that evaluated the use of mouthwashes containing chlorhexidine, allopurinol, benzydamine and propolis for the prevention or treatment of OM or OPM. Clinical trials without a control group, studies in which patients had undergone previous interventions, studies in which patients rinsed the mouth and swallowed the mouthwash, *in vitro* studies, and animal studies were excluded.

Study selection and data extraction

Two reviewers analyzed and selected each article. In the case of disagreement, a third reviewer was consulted. Article selection was conducted in two steps. First, all titles/abstracts of the records retrieved in the electronic search were evaluated. Records whose title/abstract met the eligibility criteria were directly included in this systematic review. In the case of records whose titles/abstracts contained insufficient information for a decision, the full text was retrieved and evaluated independently by the same two authors in the second step. Records whose full text met the eligibility criteria were also included.

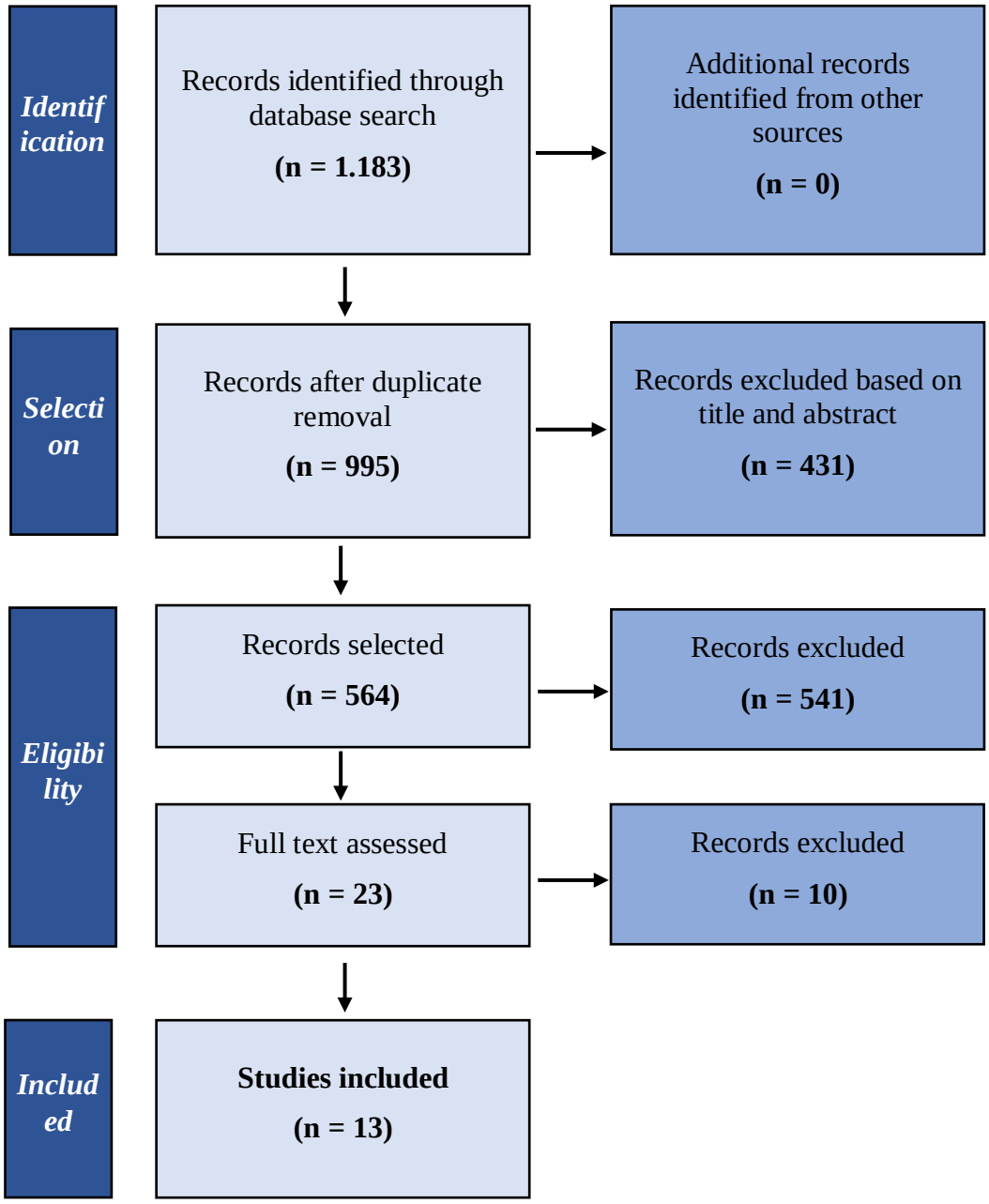
Author, year/place of publication, comparison groups, objective of the study, initial and final sample, diagnosis, treatment, variables analyzed, and results of data comparisons were extracted and entered the database of the software Microsoft Excel® for Windows®.

RESULTS

Study selection

The searches retrieved 1.183 articles. After the removal of duplicate articles, 995 titles/abstracts were evaluated in the first step and 431 records were excluded. The methodology was evaluated in the remaining 564 articles. Screening of based on the eligibility criteria resulted in the selection of 23 articles for full-text reading. Thirteen of these articles met the eligibility criteria and were included in this integrative review (Figure 2). The studies are described in chronological order in Chart 1.

Figure 2 - PRISMA flow diagram of the article selection process.



Source: Authors (2024)

Chart 1 - Studies described in chronological order

N.	*Author, country and Years*	*Comparison groups and objective*	*Initial and final sample*	*Diagnosis and Treatment*	*Variables analyzed*	*Results of comparisons*
1	**Loprinzi *et al.*[14]** United State 1990	**TG: allopurinol** **CG: placebo** Prevention	77 (77)	**Colorectal cancer** Chemotherapy: 5-FU and Leucovorin	OM degree evaluated using two methods: 1) physician judgment of mucositis severity, graded from 0 to 4 according to NCCTG toxicity guidelines; 2) patient questionnaires to rate their own degree of mucositis	There was no significant difference in OM degrees between TG and CG: mean physician-judged toxicity grade was 1.8 for TG and 1.3 for CG (p=0.07); mean patient-graded toxicity was 1.9 for TG and 1.5 for CG (p=0.15).
2	**Abbasi Nazari *et al.*[15]** Iran 2007	**TG: allopurinol** **CG: placebo** Prevention and treatment	24 (24)	**Oral, nasopharyngeal or hypopharyngeal cancer** Radiotherapy	OM degree (WHO) in the first, second, third, fourth, fifth, and sixth week of radiotherapy	There was no significant difference in mucositis severity between TG and CG in the first or second week (p=0.227 and p=0.121, respectively). TG had lower scores in the third, fourth, fifth and sixth week of treatment (p<0.05 for each week).
3	**Kumar *et al.*[16]** India 2008	**Three TG:** 1) 0.12% chlorhexidine 2) 1% povidone-iodine 3) salt/sodium bicarbonate **CG: Plain water** Prevention and treatmen	80 (76)	**Malignant head and neck neoplasms** Radiotherapy	OM degree (WHO) was assessed at baseline and at weekly intervals during radiation therapy for 6 weeks	TG: significant difference between the povidone-iodine group and all other groups No statistically significant difference in mean mucositis scores between TG and CG

4	**Shabanloei *et al.*[17]** Iran 2009	**Two TG:** 1) allopurinol 2) chamomile CG: normal saline Prevention	83 (83)	**Different malignant diseases** Chemotherapy	OM degree (WHO) for 16 days and self-reporting tools to evaluate pain	No significant difference in the variability or total intensity of stomatitis was found between the allopurinol and chamomile groups from the first to the fourth time. Stomatitis pain intensity differed significantly in the allopurinol group compared to the normal saline group.
5	**Panahi *et al.*[18]** Iran 2010	**TG: allopurinol** **CG: placebo** Prevention	33 (30)	**Different malignant diseases** Chemotherapy with 5-FU	OM degree (WHO) on days 1, 3 and 7 after chemotherapy.	The results did not show a significant difference in the occurrence (p=0.256) or severity (p=0.386) of mucositis between the two groups.
6	**Mehdipour *et al.*[19]** Iran 2011	**TG:** 0.2% zinc sulfate **CG:** chlorhexidine Prevention and treatment	30 (30)	**Acute leukemia** Chemotherapy	Spijkervet Scale to grade oral mucositis every week for 8 weeks	There was no significant difference between groups in the first week of treatment (p=0.124). The trend of changes in the OM index assessed during the study was similar in both groups; however, a significant difference was observed in weeks 2 and 3 (p=0.025), with OM being less severe in patients using zinc sulfate, suggesting efficacy of the product
7	**Choi *and* Kim[20]** South Korea 2012	**TG:** chlorhexidine (CHX) **CG:** Sodium bicarbonate (SB)	68 (48)	**Acute leukemia** Chemotherapy	OM degree (WHO) every day from the day chemotherapy started to the 28th day or to the day of discharge from the hospital	No significant differences were noted in the incidence rates of oral mucositis between the two groups. However, the incidence rate of ulcerative oral mucositis was significantly lower in the SB group

		Prevention and treatment				(25.0%) than in the CHX group (62.5%, p=0.008). The onset of ulcerative mucositis was significantly later in the SB group (16.1 days) than in the CHX group (11.4 days, p=0.013. No significant differences were observed in the mean duration of oral mucositis between the SB group (11.8 days) and CHX group (13.7 days).
8	**Ahmed** [21] Iraq 2013	**TG:** benzydamine, olive leaf extract (OLE) **CG:** placebo Prevention	40 (25)	**Acute myeloid leukemia and lymphoblastic leukemia** Chemotherapy	OMAS and WHO scales on days 1, 8, and 15	The lowest mean OMAS scores were recorded in the OLE group, followed by the benzydamine and placebo groups, respectively. Changes in the OMAS scores were highly significant (p<0.01).
9	**Akhavan-Karbassi *et al.*** [22] Iran 2016	**TG:** propolis **CG:** placebo (sterile water) Treatment and prevention	40 (40)	**Head and neck neoplasms** Chemotherapy with different chemotherapeutic agents	OM degree (WHO) at baseline and on days 3 and 7	In the placebo and propolis groups, mucositis grades were significantly lower on day 7, while on day 3, a significant difference was only observed in the propolis group. There were significant differences in oral mucositis between the propolis and placebo groups (p=0.007).
10	**Gupta *et al.*** [23] India 2018	**TG:** benzydamine (0.15%) **CG:** "candid b lotion (30 ml), cotrimazole (1% w/v),	60 (60)	**Head and neck cancer** Radiotherapy	OM degree (WHO) every week for 2 weeks after the completion of radiotherapy	No significant difference between the two groups.

		beclomethasone dipropionate (0.025% w/v), tetracycline (500 mg) and glycerin (30 ml). Treatment				
11	**Chitapanarux *et al.*[24]** Thailand 2018	**TG:** benzydamine hydrochloride (0.15%) **CG:** sodium bicarbonate (0.15%) Prevention	60 (60)	**Head and neck cancer** Radiotherapy and platinum-based chemotherapy	OMAS scale, evaluated weekly during and at the end of radiotherapy	The median OMAS scores were significantly lower in the study group every week between the second and eighth week of cancer treatment. The corresponding p values for these weeks in chronological order were 0.003, <0.001, <0.001, <0.001, <0.001, 0.01, and 0.04. The maximum OMAS score across the whole period in the benzydamine group was 25, substantially lower than the maximum score of 37 in the sodium bicarbonate group.
12	**Afrasiabifar *et al.*[25]** Iran 2020	**TG:** combined solution of grape vinegar and rose water **CG:** chlorhexidine Treatment	60 (53)	**Carcinomas, adenocarcinomas and others** Chemotherapy (any drug)	OM degree (WHO) at baseline and on days 7, 14, and 21	Comparison between groups using Fisher's exact test showed no significant differences in the number of patients with treated oral mucositis in either group (p>0.05). The changes in chemotherapy-induced disease severity after the use of the combined solution of grape vinegar and rose water were similar to those observed for chlorhexidine.

13	**Santaella *et al*.**[26] Brazil 2020	**TG:** polyhexanide (0.2%) (Prosept®) **CG:** chlorhexidine Prevention and treatment	40 (23)	**Different neoplasms** Chemotherapy (any drug); Radiotherapy plus chemotherapy	OM degree (WHO) evaluated in three stages: immediately before starting radiotherapy and/or chemotherapy sessions; during antineoplastic treatment (radiotherapy: after 15 to 20 sessions; chemotherapy: after 5 to 7 days), and after the end of the antineoplastic treatment cycle	There was no significant difference between groups in the assessments regarding the development of mucositis.

TG: treatment group; **CG:** control group.

5-FU: 5-fluorouracil; OM: oral mucositis; NCCTG: North Central Cancer Treatment Group; WHO: World Health Organization; OMAS: Oral Mucositis Assessment Scale

Characteristics of the included studies

All studies were published in English and were conducted in eight different countries. The largest number of studies was from Iran (n=4), followed by India (n=2). The other countries, including the United States, South Korea, Papua New Guinea, Iraq, Thailand, and Brazil, contributed one study each (n=6).

The total sample of this review consisted of 629 patients who used the mouthwashes evaluated in the included studies. Chlorhexidine was analyzed in five studies (total sample of 230 patients), allopurinol in four (214 patients), benzydamine in three (230 patients), and propolis in one study (40 patients).

The sample size of the studies ranged from 83 participants in the largest group analyzed to 23 participants in the smallest group.

Nine studies evaluated chemotherapy-induced mucositis, three studies analyzed radiotherapy-induced mucositis, and the patients underwent both treatments in one study.

Five of the included studies aimed to evaluate interventions for mucositis prevention alone. Another five studies aimed to examine the prevention and treatment of OM, and only three studies the treatment of OM. Among the interventions for prevention, four studies did not report results that would permit us to consider the interventions effective. In two studies, the interventions used for treatment proved to be effective. Among the studies that evaluated interventions for simultaneous prevention and treatment, four reported effective interventions for prevention and treatment and one effective intervention for treatment.

Regarding the agents used as controls, five studies used placebo. The remaining eight studies used the following products as control: povidone-iodine, sodium bicarbonate, chamomile, normal saline, zinc sulfate, olive leaf extract, magic mouthwash, combined solution of grape vinegar and rose water, and polyhexanide.

The severity of OM was assessed using scales that measure the degree of this condition based on specific characteristics. The WHO mucositis grading scale was the most frequently employed instrument, used in 11 of the studies included in the systematic review. Only one study[19] used the Spijkervet Scale for OM grading, and another study[14] graded OM using the NCCTG toxicity guidelines, and a questionnaire completed by the patients to rate their own symptoms.

Considering the observed effectiveness of the mouthwashes studied in this review, we observed that benzydamide was effective in two studies of the three found. Propolis was used in only one study and showed effectiveness in patients undergoing chemotherapy. Chlorhexidine was used in five studies and did not show effectiveness and allopurinol showed effectiveness only after 3 weeks of treatment (Chart 2).

Chart 2 - Efficacy of medications in the studies analyzed

Benzydamine 3 articles		
Chemotherapy and radiotherapy (1)	Chitapanarux *et al.*[24]	Showed efficacy
Chemotherapy (1)	Ahmed[21]	Showed efficacy
Radiotherapy (1)	Gupta *et al.*[23]	Did not show efficacy
Propolis 1 article		
Chemotherapy (1)	Akhaven-Karbassi *et al.*[22]	Showed efficacy
Chlorhexidine 5 articles		
Chemotherapy (3)	Mehdipour *et al.*[19] Choi and Kim[20] Afrasiabifar *et al.*[25]	Did not show efficacy
Radiotherapy (1)	Kumar *et al.*[16]	Did not show efficacy
Chemotherapy and radiotherapy (1)	Santaella *et al.*[26]	Did not show efficacy
Allopurinol 4 articles		
Chemotherapy (3)	Loprinzi *et al.*[14] Shabanloei *et al.*[17] Panahi *et al.*[18]	Did not show efficacy
Radiotherapy (1)	Abassi-Nazari *et al.*[15]	Efficacy after 3 weeks

Source: Authors (2024)

DISCUSSION

One of the most severe non-hematological complications of cancer therapy, OM, commonly manifested in patients undergoing cancer treatment, and could be a limiting factor in cancer treatment. Thus, the prevention and treatment include relieving painful symptoms and preventing the spread of infections since the lesions are a gateway for pathogenic microorganisms[1-6].

Despite being the best alternative in the treatment and prevention of mucositis photobiomodulation needs trained professional and appropriate equipment thus healthcare teams, on some occasions, need cheaper and simple alternatives to be implemented in patients' cancer care.

In the studies analyzed, propolis and benzydamine hydrochloride mouthwashes suggest being effective in reducing OM and OPM, while allopurinol and Chlorhexidine mouthwash did not show significant results.

Allopurinol is a medication commonly used to treat gout; a condition marked by painful episodes of inflammation in different joints due to excess uric acid in the body. The drug works by inhibiting xanthine oxidase, an enzyme essential in uric acid production, causing a decrease in uric acid levels in the blood. This inhibition provides relief from pain and inflammation[17,18].

Allopurinol was evaluated in four articles[14,15,17,18]. Three studies analyzed patients undergoing chemotherapy[14,17,18], and one study evaluated patients undergoing radiotherapy[15]. The clinical trial investigating patients undergoing radiotherapy[15] found no differences in the severity of OM between the group treated with allopurinol and the control group during the first 2 weeks of treatment. However, there were significant differences between the groups from weeks 3 to 6, with significant improvement in mucositis in the allopurinol group. In contrast, the studies involving patients undergoing chemotherapy found no significant difference between the group that used allopurinol, and the other compounds analyzed[14,15,17,18].

Benzydamine is a local analgesic and anti-inflammatory agent used to treat a variety of painful and inflammatory conditions, especially those affecting the mouth and throat. Its

mechanism of action involves inhibiting prostaglandin synthesis, which helps reduce pain and swelling (anti-inflammatory and analgesic)[29].

Three studies evaluated the activity of benzydamine[21,23,24]. One including patients undergoing chemotherapy[21], one radiotherapy[23], and other one including patients undergoing radiotherapy and chemotherapy[24]. Two studies[21,24] found benzydamine hydrochloride to be effective in the prevention and treatment of OM. This suggests that the agent could be useful in managing OM in patients undergoing chemotherapy. However, due to the diversity of studies conducted, more research is needed before it can be safely incorporated into hospice services.

The studies included a wide range of cancer treatments, such as radiotherapy and chemotherapy. As a result, the mucositis risk may be influenced by various factors. These factors can be divided into patient-related variables and therapy-related variables. Patient-related factors include age, diagnosis, and mouth condition before and during therapy. Are variables related to therapy include the type of drug, dose and frequency of treatment, in addition to the use of concomitant therapy. Mucositis related to chemotherapy is more acute and resolves on average two weeks. While radiation-induced mucositis is dose dependent and often lasts up to three or four weeks[1].

Chlorhexidine is a potent antiseptic agent that acts against a broad spectrum of bacteria, both gram-positive and gram-negative. The compound is often incorporated in oral health products because of its effectiveness in reducing plaque formation and in treating gingivitis. Due to its bactericidal and bacteriostatic activity, chlorhexidine is frequently used in hospital environments for skin disinfection before surgical procedures[30].

Chlorhexidine is the most widely used and recommended mouthwash for patients undergoing cancer treatment because of its bactericidal, fungicidal, and virucidal properties. Five studies analyzed chlorhexidine[16,19,20,25,26]. Of these, one study investigated patients undergoing radiotherapy[16], one study examined patients undergoing chemotherapy and radiotherapy[26], and three studies investigated patients undergoing chemotherapy[19,20,25]. However, chlorhexidine was not superior in any of these studies compared to other compounds.

One study[20] compares the efficacy of sodium bicarbonate solution and chlorhexidine in oral care for patients during induction chemotherapy. The study found sodium bicarbonate

to be more effective than chlorhexidine mouthwash. This reinforces the need for the patient's care team to carefully assess the indication of mouthwashes.

Propolis is a resin collected by bees from different plants to protect the hive. This resin has antimicrobial, anti-inflammatory, antioxidant, and anticarcinogenic properties. It is therefore a product with different therapeutic applications [31]. The history of propolis use extends into traditional medicine, where it is used to boost immunity and to treat different infections and inflammatory conditions. Only one study evaluated the effectiveness of propolis[22]. It found that propolis reduced chemotherapy-induced OM. This suggests that it is a promising drug in mucositis management. Nonetheless, more studies are needed due to the limited data analyzed.

The lack of standardization impairs the direct comparison of studies and the determination of the relative efficacy of mouthwashes. Therefore, further studies with a robust design that provide more detailed information about the results are needed to obtain stronger scientific evidence.

The diversity of interventions explored reflects the complexity of mucositis. Highlights the importance of multifaceted approaches to the treatment and prevention of OM in cancer patients. Regarding the results obtained, most studies provided qualitative data on the improvement of OM with the use of mouthwashes. It is noteworthy that the studies evaluated did not identify important adverse effects of the interventions implemented for the prevention or treatment of OM and OPM.

The literature presents arguments favoring the use of Integrative Reviews. However, there is a lack of specific guidelines for their conduct. Our study adapted the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA)[13], following certain points from its checklist. The absence of a specific protocol for this type of review can be a limitation of Integrative Reviews and our study. Nevertheless, our approach strives to offer valuable insights within these constraints.

The methods used in the studies varied widely in terms of study design, active ingredients in the mouthwashes, and substances used for comparison. It is important to note that most studies did not observe a significant reduction in OM. This could be a consequence of the variety of studies with different types of cancer and the wide variety of chemotherapy drugs and doses administered. In some studies, the authors included patients with diverse

diseases that required different antineoplastic treatments, which may interfere with the development and severity of OM and OPM. Additionally, the inclusion of only comparative studies may have limited the generalization of the findings.

The studies provided valuable information on alternatives to prevent and treat OM in cancer patients. And thus, it contributes to developing more effective approaches using these substances, improving the quality of life for patients undergoing antineoplastic treatment. These drugs are easily accessible at public or private hospitals. Do not require the recruitment of additional technical staff. Could be prescribed by the multidisciplinary team and are low cost.

It is important to note that each patient is unique and may respond differently to treatment. Thus, further studies are needed to evaluate the possibility of incorporating these drugs in definitive protocols for the management of OM and OPM in cancer patients.

CONCLUSION

Mouthwashes containing chlorhexidine or allopurinol were not effective in preventing and treating OM. Benzydamine and propolis show promising results in the prevention and treatment of OM in patients undergoing cancer treatment. The use of benzydamine and propolis can contribute to improving the patient's quality of life and to reducing the negative impacts of mucositis during antineoplastic treatment.

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