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REVIEW ARTICLE

Efficacy of topical agents in oral mucositis prevention: Systematic review and network meta-analysis

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Abstract

Background: Oral mucositis (OM) is considered one of the most common side effects of patients undergoing cancer therapy. OM prevention plays a crucial role in the effectiveness of cancer treatment and the patient's quality of life. Different preventive treatments have been proposed in clinical trials, however with inconclusive results.

Materials and Methods: A systematic review search was conducted in PubMed, Scopus, Web of Science, and Cochrane Database to answer the PICO question: in cancer patients, do specific topical agents compared to standard treatments or placebo reduce the onset and severity of oral mucositis? The risk of bias was assessed, and a network meta-analysis was conducted.

Results: Of 2913 results, 30 randomized clinical trials were considered suitable for inclusion. A total of 2564 patients were analyzed, of which 1284 belonged to the test group and 1280 belonged to the control group. Natural products were the most used, followed mainly by antimicrobial agents, coating agents, and basic oral care measures. Topical sucralfate resulted in the most powerful intervention for the OM prevention (OR = 0.04, 95%C.I. = 0.01–0.25, *p*-value = 0.001).

Conclusion: Due to its cytoprotective action, low cost, ease of administration, and safety, sucralfate could become a potential ally to prevent the onset of OM during cancer therapy.

KEYWORDS
cancer, network meta-analysis, oral mucosa, oral mucositis, prevention, stomatitis, sucralfate, systematic review, therapy

1 | INTRODUCTION

Oral mucositis (OM) is one of the most debilitating side effects of cancer therapy (Elad et al., 2020). The clinical signs of OM range from superficial sore erythema to complete mucosal ulceration, involving the gastrointestinal tract. OM may be accompanied by several complications such as oral pain, xerostomia, dysphagia, loss of taste, nausea, vomiting, loss of appetite, and weight loss (Biswal et al., 2003; Elad et al., 2020; Kostler et al., 2001; McGuire et al., 2013; Ohbayashi et al., 2008; Vagliano et al., 2011; Vokurka et al., 2011). Currently, OM is considered the most severe non-hematological complication affecting cancer patients (Shah et al., 2020). Patients who develop

OM during cancer therapy are more likely to interrupt or postpone the treatment. Additionally, it is associated with a worse prognosis, a poor quality of life, and higher financial costs compared with patients who do not develop OM (Di Fede et al., 2023). The incidence of OM varies widely in the literature; it occurs in almost all the patients receiving radiotherapy (RT) for head and neck (H&N) cancer, approximately 20–40% of patients receiving conventional chemotherapy (CT) (e.g., 5 fluorouracil, carboplatin, cisplatin), and up to 80% in patients receiving high dosage (Daugėlaitė et al., 2019). In patients who receive haematopoietic stem cell transplant (HSCT) approximately 70% develop OM, with over 20% developing severe clinical manifestations (Ohbayashi et al., 2008; Vagliano et al., 2011). Regarding the management, to date, there are various protocols for the prevention and treatment. Given the significant impact that OM has on patients undergoing cancer therapy, the identification of measures and protocols aimed at mitigating oral signs and symptoms via topical application poses a significant challenge.

According to the Cochrane Database of Systematic Reviews, several interventions were found to have some benefit, to prevent or reduce the severity of OM associated with cancer therapy, including aloe vera, amifostine, cryotherapy, granulocyte-colony stimulating factor (G-CSF), intravenous glutamine, honey, keratinocyte growth factor, laser, polymixin/tobramycin/amphotericin (PTA) antibiotic pastille/paste and sucralfate. The strength of the evidence was variable, limited, and specific for certain cancer types and treatments (Worthington et al., 2011).

The Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) conducted systematic reviews to identify the interventions with the strongest evidence to provide specific guidelines to clinicians that are most likely to be effective (Elad et al., 2020).

According to the last version of MASCC/ISOO, the implementation of multiagent combination of oral care protocols (Basic Oral Care, BOC) is beneficial for the prevention of OM during CT, RT, and HSCT. BOC involves all regular procedures carried out by the patient or the healthcare practitioner to minimize the oral bacterial load, including mechanical cleaning (tooth brushing, flossing), oral mouthwashes, and, if necessary, hydration and lubrication measures (Elad et al., 2020).

Therefore, to date, many agents and procedures have been investigated to prevent OM (e.g., anti-inflammatory agents, photobiomodulation therapy, cryotherapy, antimicrobials, coating agents, anesthetics and analgesic agents, growth factors and cytokines, and natural and miscellaneous products); but finally no superior topical agents have been identified (Ariyawardana et al., 2019; Elad et al., 2020; Logan et al., 2020; McGuire et al., 2013; Saunders et al., 2020; Yarom et al., 2020). Many studies compared individual treatments with placebo, thus it is not possible to understand whether experimental agents, when compared to each other, may show benefits in preventing OM onset. The network meta-analysis (NMA) was chosen with the aim of comparing the interventions present in the literature and overcoming this limitation (Tonin et al., 2017).

The present study aims to perform a systematic review and NMA to investigate the efficacy of topical agents in the prevention of oral mucositis in adult patients with solid tumors.

Therefore, we performed a network meta-analysis to compare the efficacy of interventions used for preventing OM, concerning the onset and severity, in cancer adult patients receiving CT, RT, or both.

2 | MATERIALS AND METHODS

2.1 | Protocol

A systematic literature search was conducted independently by two authors (MC and VCAC). Publications were selected and data were analyzed according to the general principles of the Cochrane Handbook for Systematic Reviews of Intervention and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). The protocol was designed a priori and registered on the online database PROSPERO (CRD42023469152).

2.2 | PICO and research question

The research question was designed based on PICO items as follows:

P: Adults with a diagnosis of solid cancer of any anatomical origin.
I: Topical preventive measures (e.g., mouthwash, gel, or topical formulation).
C: Standard treatments, or placebo.
O_1: Number of events (patients developing OM) and the number of total patients in both intervention and control groups.
O_2: Number of severe events (patients developing severe OM) and the number of total events in both intervention and control groups.

The systematic review was based on the following research question: In adults, cancer patients with solid cancer (P), do specific topical preventive measures (I) compared to standard treatments or placebo (C) reduce the onset and severity of oral mucositis (O)?

2.3 | Data sources and search strategy

A selection of studies concerning the preventive topical measures of OM in patients with solid cancer about to start cancer treatment was performed. Records were identified using different search engines: Medline/PubMed, ISI Web of Science, SCOPUS, and Cochrane Library.

For the search strategy, MeSH terms and free text words were combined through Boolean operators as follows: ("oral mucositis" OR "mouth mucositis" OR stomatitis OR mucositis) AND (mouthwash

OR "oral rinse" OR "topical administration" OR "oral administration" OR gel OR "oral care" OR "mouth mucosa") AND (randomized clinical trial OR prospective study) NOT (retrospective study OR review). The last electronic search was performed in November 2023.

2.4 | Eligibility criteria

The inclusion criteria for the studies were as follows:

1. prospective randomized and prospective non-randomized controlled clinical trial (RCT) evaluating as an outcome the prevention of oral mucositis onset in adults (>18 years old).
2. including patients with solid tumors before starting radiotherapy, chemotherapy, or a combination of both protocols.
3. using at least one mouthwash, gel, or topical formulation to prevent oral mucositis.
4. using a placebo or another mouthwash, gel, or topical formulation in the control group.
5. including at least 20 patients in each group.
6. evaluating as an outcome the prevention of oral mucositis onset.

Were excluded:

1. retrospective case–control and cohort studies, case series, case reports, expert opinions, systematic reviews, and meta-analysis.
2. studies including patients with blood tumors.
3. studies using systemic administration for the prevention of OM.
4. including less than 20 patients in each group.
5. focusing on the treatment of oral mucositis.
6. including the prevention of oral mucositis in children and adolescent patients (<18 years old).
7. animal and in vitro studies.

2.5 | Study selection, data collection process, and data items

The selection process was performed in two rounds. In the first round, two independent authors (MC and VCAC) screened the studies reading title and abstract, while in the second phase, a full-text evaluation was performed. In case of disagreement between reviewers, a final decision for the inclusion was taken in a joint session with a third author (RM).

For each study, the following data were extracted using an ad hoc extraction Excel sheet:

- First author, year of publication, and country where the study was performed.
- Study design.
- Tumor type and tumor treatment protocol.
- Total sample size and summary of inclusion criteria used in the study.
- Data about the test group: number of patients, type of intervention, protocol, data about mucositis onset and severity of mucositis.
- Data about the control group: number of patients, type of intervention, protocol, data about mucositis onset, and severity of mucositis.

2.6 | Quality assessment

The analysis of the risk of bias in the studies included was performed according to the Cochrane Risk of Bias in randomized interventional studies tool (RoB 2) in the last version, dated 22 August 2019 (Sterne et al., 2019). The evaluation was specific to estimate the relative effect of two interventions on a target outcome. All participants underwent cancer therapies adopting certain topical preventive measures (intervention) versus other measures or placebo (control) to evaluate the OM onset (primary outcome) and the severity of OM (secondary outcome).

Quality assessment was performed independently by two authors (DR and AILP) and disagreements, if present, were solved in a joint meeting with a third reviewer (RM).

To assess the risk of bias in the included RCTs five aspects were evaluated, as follows:

1. randomization process
2. deviation from intervention
3. missing outcome data
4. measurement of the outcome
5. selection of reported result

The assessment results were scored as high, unknown, and low risk.

2.7 | Network meta-analysis

An arm-based NMA was performed to evaluate the effects of several topical agents, including details about products that have not been directly compared before. An extension of the conventional pairwise meta-analysis, NMA enables comparisons of numerous unique treatments (White, 2015). This approach allows for the synthesis of large amounts of data, the estimation of relative efficacy, and the ranking of interventions according to their impact. The data extraction process's outputs were then integrated (using a network setup command) to work with STATA software.

The assumptions of similarity, transitivity, and consistency were examined (Cipriani et al., 2013). Through a subjective evaluation of the demographic, intervention, comparison, and outcome analyses, the similarity of the included studies was assessed (Reken et al., 2016). Transitivity was assessed further by statistically analyzing the consistency of the outcomes of direct

and indirect comparisons (Salanti, 2012). As a result, network geometry charts and predictive interval plots were created. We looked at links between the various groups and visualized their network using the network geometry display. The nodes represent the groupings, while the edges display the direct comparisons between groups. The relative ranking of the groups was calculated using probability and the surface under the cumulative ranking curves (SUCRA). SUCRA, a simple transformation of the mean rank, considers the location and variation of the relative treatment effects to create a hierarchy of the interventions. As SUCRA levels rise, the treatment ranking gets better. A two-tailed *p*-value of 0.05 was considered significant for hypothesis testing. Data on the number of occurrences over the total number of recorded patients and the overall sample size for each intervention group were extrapolated from clinical studies. The estimated summary effects forest plot, which includes confidence intervals and predictive intervals, displayed the relative mean effects and projections for each comparison. NMA was carried out using the STATA program that Chaimani et al. recommended, utilizing mvmeta network instructions (Antonacci et al., 2023; Chaimani et al., 2013; Hutton et al., 2015; Puhan et al., 2014).

3 | RESULTS

3.1 | Search strategy, screening, and study selection

The last search yielded 2913 results (PubMed = 2338, Scopus = 231, Cochrane = 128, Web of Science = 216). These references were integrated into the EndNote reference software tool (Endnote X9.3.2, Clarivate Analytics). Three hundred and thirty-three duplicates were removed. Then, the screened process of 2580 studies was performed based on the title and abstract, and 2375 were excluded. Subsequently, a full-text evaluation of 205 studies was carried out. Finally, 175 records were excluded, and 30 papers were included in the current review; a detailed flow chart of the selection process is provided in Figure 1.

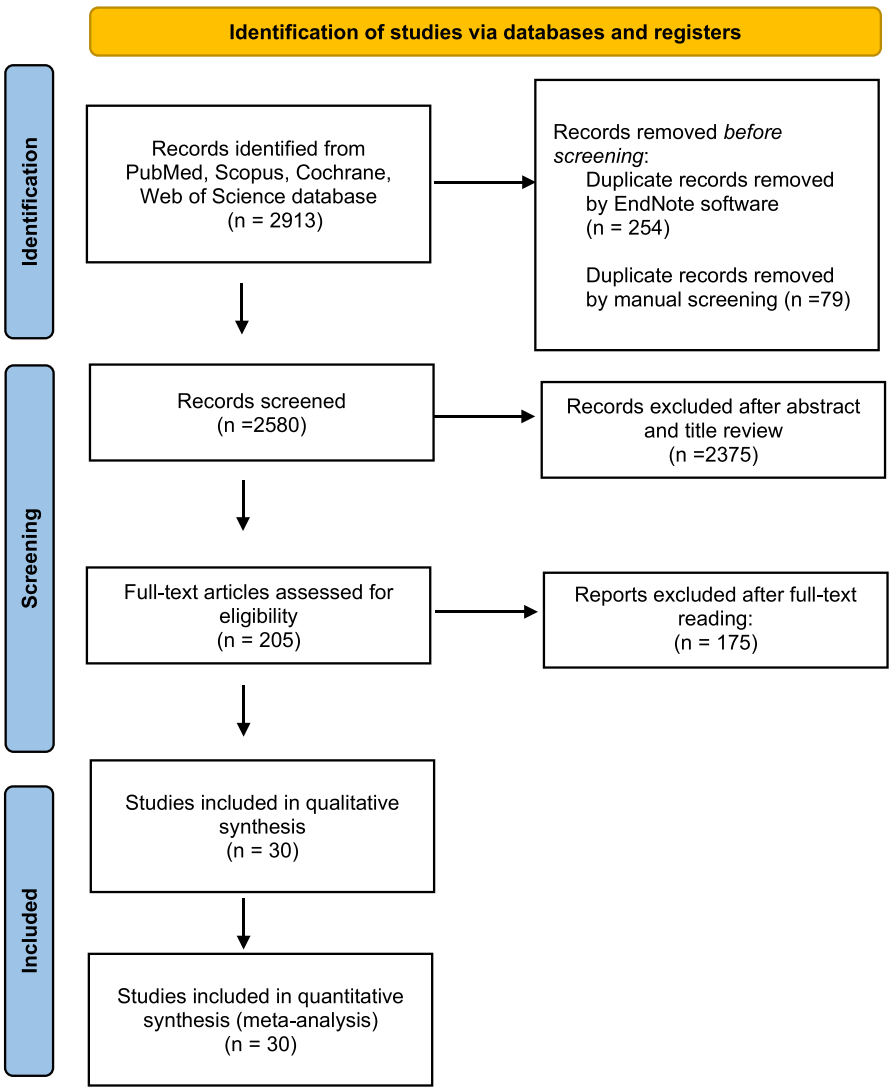

FIGURE 1 PRISMA 2020 flow diagram.

3.2 | General characteristics of the included studies

The included studies were published between 1990 and 2022. Most of the studies were performed in the United States (Dodd et al., 1996; Epstein et al., 2001; Fidler et al., 1996, Foote et al., 1994; Lalla et al., 2020; Loprinzi et al., 1990; Su et al., 2004) and India (Arun et al., 2020; Khanal et al., 2010; Rao et al., 2014; Rastogi et al., 2017; Shah et al., 2020; Sharma et al., 2012), followed by Iran (Ala et al., 2016; Eslami et al., 2022; Kazemian et al., 2009b), Germany (Adamietz et al., 1998; Rahn et al., 1997), Italy (De Sanctis et al., 2019; Piredda et al., 2017), Australia (Veness et al., 2006), Canada (Hawley et al., 2014), Turkey (Mutluay Yayla et al., 2016), Finland (Makkonen et al., 1994), Netherlands (Wijers et al., 2001), UK (Bardy et al., 2012), Cyprus (Charalambous et al., 2018), Brazil (Fernandes et al., 2022), and Thailand (Puataweeponga et al., 2009). One study was performed in Czech Republic and Slovak Republic (Vokurka et al., 2005) and one was a multicenter study performed in the United States, Canada, France, Germany, and United Kingdom (Allison et al., 2014).

All the included studies were RCT with a double (Ala et al.; 2016; Allison et al., 2014; Bardy et al., 2012; Dodd et al., 1996; Eslami et al., 2022; Fernandes et al., 2022; Fidler et al., 1996; Foote et al., 1994; Kazemian et al., 2009b; Lalla et al., 2020; Loprinzi et al., 1990; Makkonen et al., 1994; Puataweeponga et al., 2009; Sharma et al., 2012; Su et al., 2004; Veness et al., 2006; Wijers et al., 2001), triple or single blind design (Rao et al., 2014; Shah et al., 2020); in some studies, the blindness methodology was not specified (Adamietz et al., 1998; Arun et al., 2020; Charalambous et al., 2018; De Sanctis et al., 2019; Hawley et al., 2014; Khanal et al., 2010; Mutluay Yayla et al., 2016; Piredda et al., 2017; Rahn et al., 1997; Rastogi et al., 2017; Vokurka et al., 2005).

In total, 2564 patients were analyzed, of which 1284 belonged to the test group and 1280 belonged to the control group.

In the test group, 821 patients were male (821/1118; 73.4%) and 297 were female (297/1118; 23.1%); in the control group, 786 were male (786/1114; 70.5%) and 328 were female (328/1114; 29.4%) (Adamietz et al., 1998, Ala et al., 2016, Allison et al., 2014, Arun et al., 2020, Bardy et al., 2012, De Sanctis et al., 2019, Dodd et al., 1996, Eslami et al., 2022, Fernandes et al., 2022, Fidler et al., 1996, Foote et al., 1994, Kazemian et al., 2009b, Hawley et al., 2014, Lalla et al., 2020, Makkonen et al., 1994, Mutluay Yayla et al., 2016, Puataweeponga et al., 2009, Rao et al., 2014, Rastogi et al., 2017, Shah et al., 2020, Rahn et al., 1997, Sharma et al., 2012, Su et al., 2004, Wijers et al., 2001, Vokurka et al., 2005). In five studies, the gender of participants was not specified (Charalambous et al., 2018; Khanal et al., 2010; Loprinzi et al., 1990; Piredda et al., 2017; Veness et al., 2006).

Based on the available data, the age of the test group patients ranged from 18 to 91 years and the age of the control group patients ranged from 19 to 90 years (Adamietz et al., 1998; Allison et al., 2014; Arun et al., 2020; Bardy et al., 2012; De Sanctis et al., 2019; Fernandes et al., 2022; Makkonen et al., 1994; Puataweeponga et al., 2009; Rahn et al., 1997; Rastogi et al., 2017; Veness et al., 2006; Vokurka et al., 2005; Wijers et al., 2001). Most of the patients were affected by H&N cancer, including oral, salivary glands, oropharyngeal, nasopharyngeal and hypopharyngeal cancer, followed by esophageal, gastric, colorectal, and breast cancer.

Regarding cancer therapy, 17 studies included patients who underwent RT in the H&N district (Adamietz et al., 1998; Arun et al., 2020; Bardy et al., 2012; Charalambous et al., 2018; Eslami et al., 2022; Fernandes et al., 2022; Foote et al., 1994; Hawley et al., 2014; Kazemian et al., 2009b; Khanal et al., 2010; Lalla et al., 2020; Makkonen et al., 1994; Puataweeponga et al., 2009; Shah et al., 2020; Su et al., 2004; Veness et al., 2006; Wijers et al., 2001); eight studies included patients undergoing CT, of which only four specified the medication (5-fluorouracil) (Ala et al., 2016; Allison et al., 2014; Fidler et al., 1996; Loprinzi et al., 1990; Mutluay Yayla et al., 2016; Piredda et al., 2017; Vokurka et al., 2005). In five studies patients were treated by a combination of RT in H&N and CT (De Sanctis et al., 2019; Rahn et al., 1997; Rao et al., 2014; Rastogi et al., 2017; Sharma et al., 2012), of which two with carboplatin and two with cisplatin.

The experimental treatment included topical compounds of different origins. In detail, three studies administered povidone-iodine mouthwash (Adamietz et al., 1998; Rahn et al., 1997; Vokurka et al., 2005), and in one study a paste containing 0.2% polymyxin E sulfate (Colistin sulfate), 0.18% tobramycin and 1% amphotericin B (Wijers et al., 2001).

Two studies evaluated the use of sucralfate mouthwash (Ala et al., 2016; Makkonen et al., 1994), two studies the lactobacillus brevis CD2 lozenges (LB_CD2_lozenges) (De Sanctis et al., 2019; Sharma et al., 2012) and one study analyzed the use of MuGard® (Allison et al., 2014). Basic oral care measures included Chlorhexidine and Dentoxol® (Dodd et al., 1996; Foote et al., 1994; Lalla et al., 2020). Natural products were the most used; four studies analyzed honey topical application (Bardy et al., 2012; Charalambous et al., 2018; Hawley et al., 2014; Khanal et al., 2010), three studies curcumin (Arun et al., 2020; Rao et al., 2014; Shah et al., 2020), two aloe vera (Puataweeponga et al., 2009; Su et al., 2004), one tea (Mutluay Yayla et al., 2016), and grape seed extract (GSE) (Eslami et al., 2022) and two propolis, of which one with galangin plus mouth rinsing (Fernandes et al., 2022; Piredda et al., 2017).

As anti-inflammatory and analgesics agents, two studies analyzed benzydamine mouthwash (Kazemian et al., 2009b; Rastogi et al., 2017) and one study misoprostol (Veness et al., 2006). Only one study evaluated allopurinol mouthwash (Loprinzi et al., 1990).

In the control group, most studies used a placebo (Adamietz et al., 1998; Ala et al., 2016; Arun et al., 2020; Bardy et al., 2012; Charalambous et al., 2018; Dodd et al., 1996; Eslami et al., 2022; Fernandes et al., 2022; Fidler et al., 1996; Foote et al., 1994; Hawley et al., 2014; Kazemian et al., 2009a; Lalla et al., 2020; Loprinzi et al., 1990; Makkonen et al., 1994; Mutluay Yayla et al., 2016; Puataweeponga et al., 2009; Rahn et al., 1997; Rastogi et al., 2017; Sharma et al., 2012; Su et al., 2004; Veness et al., 2006; Vokurka et al., 2005; Wijers et al., 2001). This included sterile or distilled water, NaCl solution, or substance identical in appearance and taste. In six studies, test group was compared to a different experimental

topical agent, different from placebo (Allison et al., 2014; De Sanctis et al., 2019; Khanal et al., 2010; Piredda et al., 2017; Rao et al., 2014; Shah et al., 2020). Rao et al. used povidone-iodine mouthwash (Rao et al., 2014); three studies used sodium bicarbonate mouthwash (Allison et al., 2014; De Sanctis et al., 2019; Piredda et al., 2017), and Shah et al. and Khanal et al. used benzydamine and lignocaine mouthwash, respectively (Khanal et al., 2010; Shah et al., 2020).

Patients in test and control groups developed OM; 757 (757/1284, 58.9%), and 900 (900/1280, 70.3%), respectively. When considering only the patients who developed OM and belonged to the placebo treatment group, an increase in the incidence of OM was observed (71.6% vs. 61.3% for any treatment group). These information are summarized in Table 1.

In 21 studies, also the severity of oral mucositis was described, as reported in Table 2 (Adamietz et al., 1998; Ala et al., 2016; Arun et al., 2020; Bardy et al., 2012; Charalambous et al., 2018; De Sanctis et al., 2019; Eslami et al., 2022; Fernandes et al., 2022; Fidler et al., 1996; Hawley et al., 2014; Kazemian et al., 2009b; Khanal et al., 2010; Loprinzi et al., 1990; Makkonen et al., 1994; Mutluay Yayla et al., 2016; Piredda et al., 2017). Severity was staged according to the World Health Organization (WHO) Classification (Adamietz et al., 1998; Ala et al., 2016; Arun et al., 2020), Radiation Therapy Oncology Group Grading System (RTOG) (Charalambous et al., 2018; Kazemian et al., 2009b; Khanal et al., 2010; Puataweeponga et al., 2009; Veness et al., 2006), and modified RTOG scale (Bardy et al., 2012) and the National Cancer Institute Common Toxicity Criteria (NCI CTC) (De Sanctis et al., 2019; Piredda et al., 2017; Sharma et al., 2012). Only Wijers et al. relied on the van der Schueren scoring system (Wijers et al., 2001). In five studies, the classification was not specified (Eslami et al., 2022; Fidler et al., 1996; Hawley et al., 2014; Loprinzi et al., 1990; Makkonen et al., 1994).

In the test and control group, among the patients who developed OM, 233 and 337 were severe stage, respectively (grade ≥3, 233/757, 30.8%, and 337/900, 37.4%). These information are collected in Table 2.

3.3 | Risk of bias assessment

According to the RoB2 evaluation for randomized trials, 13 RCTs were judged to be at an elevated risk of bias (De Sanctis et al., 2019; Dodd et al., 1996; Eslami et al., 2022; Fidler et al., 1996; Hawley et al., 2014; Kazemian et al., 2009b; Makkonen et al., 1994; Rahn et al., 1997; Rastogi et al., 2017; Shah et al., 2020; Veness et al., 2006; Vokurka et al., 2005; Wijers et al., 2001), 10 were rated as being problematic (Adamietz et al., 1998; Arun et al., 2020; Charalambous et al., 2018; Foote et al., 1994; Khanal et al., 2010; Lalla et al., 2020; Mutluay Yayla et al., 2016; Puataweeponga et al., 2009; Rao et al., 2014; Su et al., 2004), while seven were considered to be a low risk of bias (Ala et al., 2016; Allison et al., 2014; Bardy et al., 2012; Fernandes et al., 2022; Loprinzi et al., 1990; Piredda et al., 2017; Sharma et al., 2012).

The most frequent high-risk items were the lack of blinding process, lack of information on the population included, and the evaluation of the outcome. If research participants' interventions were known to the assessors, and it was not disclosed whether this knowledge could have affected the outcome assessment, the risk of bias was deemed to be high. Studies reporting the incidence of randomized patients with a high number of missing outcome data and analysis conducted on a limited patient sample were considered to be high-risk indicators of the bias of omitted outcome data. Risk of bias is reported in Table S1.

3.4 | Network meta-analysis

Thirty studies were considered comparing 19 different topical agents in preventing OM. All the comparisons are depicted in the network plot in Figure 2. By plotting risk of bias, most of the comparisons resulted as high risk of bias. Only five comparisons were at low risk of bias, such as placebo versus, respectively, propolis, allopurinol, and LB_CD2_lozenges and sodium bicarbonate mouthwash versus propolis and MuGard. The placebo represented the main group and was set as reference. Most of the compared treatments were investigated only in one study, as by node representation, while povidone iodine and honey were the most investigated treatment groups, being represented by four studies, respectively. As for single comparison weight, placebo versus honey represented the main one, followed by povidone iodine.

Overall inconsistency resulted in absent at global (p-value = 0.722) and local level (p-value ranging between 0.294 and 1.0). Visualization of the inconsistency was figured in the network forest plot, in which effect sizes by study were graphically represented (Figure S1).

Among the 19 interventions, 13 did not show a preventive effect for the occurrence of mucositis, as their confidence interval crossed the null-effect line (black vertical line, p-value >0.05). Sucralfate resulted in the most powerful treatment for the preventive purpose of mucositis (OR = 0.04, 95%C.I. = 0.01–0.25, p-value = 0.001). MuGard and Curcumin yielded similar results with a milder effect (OR = 0.07). LB_CD2_lozenges, GSE, and benzydamine showed as well effective prevention. To note of all these treatments, the predictive intervals never crossed the null effect line, showing promising similar results in future trials (Table 3 and Figure 3). These comparisons were further inspected based on SUCRA scores. Top ranked treatment resulted in the use of sucralfate, with a mean rank of 2 among all the interventions and a SUCRA value of 0.9 and the probability of being the best treatment in 53.5% of cases. A numerical summary of the SUCRA and the probability for each treatment to be the most suitable is summarized in Table 4 and Figure S2.

When considering only those patients developing severe grade mucositis, 20 studies were included comparing 15 different treatments. All the comparisons are depicted in the network plot in Figure 4. By plotting risk of bias, most of the comparisons resulted as high risk of bias. The same comparisons were at low risk of bias,

TABLE 1 Characteristics of included studies.

N	Authors	Year	Country	Study design	N. Patients (total)	Tumor type	Cancer treatment	N. Patients test group
1	Adamietz IA	1998	Germany	RCT	40	H&N cancer	RT in H&N district	20
2	Ala S	2016	Iran	RCT	51	Gastric and colon cancers	CT (5-FU)	25
3	Allision RR	2014	USA, Canada, France, Germany, UK	RCT	78	H&N cancer	CT	37
4	Arun P	2020	India	RCT	61	H&N cancer	RT in H&N district	30
5	Bardy J	2012	UK	RCT	127	H&N cancer	RT in H&N district	64
6	Charalambou M	2018	Cyprus	RCT	72	H&N cancer	RT in H&N district	36
7	De Sanctis V	2019	Italy	RCT	68	H&N cancer	RT in H&N district and CT	32
8	Dodd MJ	1996	USA	RCT	222	Breast and colon cancer and other	CT	112
9	Eslami H	2022	Iran	Double blinded RCT	78	H&N cancer	RT in H&N district	39
10	Fernandes PM	2022	Brazil	Double blinded RCT	60	H&N cancer	RT in H&N district	32
11	Fidler P	1996	USA	Double blinded RCT	164	n/a	CT (5-FU)	82
12	Foote RL	1994	USA	Double blinded RCT	52	n/a	RT in H&N district	25
13	Hawley, P.	2014	Canada	RCT	106	H&N cancer	RT in H&N district	54➔40
14	Kazemian A.	2009	Iran	Double blind RCT	81	H&N cancer	RT in H&N district	39
15	. Khanal B	2010	India	RCT	40	Oral carcinoma	RT in H&N district	20
16	Lalla RV	2020	USA	Double-blind RCT	108	H&N cancer	RT in H&N district	55
17	Loprinzi CL	1990	USA	Double blind RCT	77	Colorectal cancer	CT (5-FU)	39
18	Makkonen TA	1994	Finland	Double blind RCT	40	H&N cancer	RT in H&N district	20
19	Mutluay Yayla E	2016	Turkey	RCT	60	Colon, rectal, breast, esophageal and gastric	CT (5-FU)	30
20	Piredda RN	2017	Italy	RCT	60	Breast cancer	CT	30
21	Puataweepong P	2009	Thailand	Double blind RCT	61	H&N cancer	RT in H&N district	30
22	Rahn R	1997	Germany	RCT	40	H&N cancer	RT in H&N district and CT (carboplatin)	20
23	Rao S	2014	India	Investigator- blinded RCT	80	H&N cancer	RT in H&N district and CT (carboplatin)	40➔39
24	Rastogi M	2017	India	RCT	120	H&N cancer	RT in H&N district and CT (cisplatin)	63
25	Shah S	2020	India	Triple-blinded RCT	68	H&N cancer	RT in H&N district	33
26	Sharma A	2012	India	Double-Blind RCT	200	H&N cancer	RT in H&N district and CT (cisplatin)	101➔93
27	Su CK	2004	USA	Double-Blind RCT	58	H&N cancer	RT in H&N district	28
28	Veness MJ	2006	Australia	Double-blind RCT	83	H&N cancer	RT in H&N district	42➔41
29	Vokurka S	2005	Czech Republic, Slovak Republic	Prospective, Randomized, Multicenter Study	132	n/a	CT	67
30	Wijers OB	2001	Netherlands	Double-blind RCT	77	H&N cancer	RT in H&N district	39

Note: Placebo: placebo was sterile or distilled water or substance identical in appearance and taste consisting of the vehicle only and basic oral care or NaCl solution.

Abbreviations: CT, chemotherapy; GSE, Grape Seed Extract; LB CD2 lozenges, Lactobacillus brevis CD2 lozenges; PTA, paste contained 0.2% Polymyxin E sulfate (Colistin sulfate), 0.18% Tobramycin, and 1% Amphotericin B; RT, radiotherapy; SB mouthwash, Sodium bicarbonate mouthwash.

Test group intervention	M/F	Age (range, median or mean age ± SD)	N. Of events (%)	N. Patients control group	Control group intervention	M/F	Age (range, median or mean age ± SD)	N. Of events (%)
Povidone-Iodine	17/3	35–84	14 (70%)	20	Placebo	17/3	37–75	20 (100%)
Sucralfate	15/10	56.3	6 (24%)	26	Placebo	20/6	57.2	25 (96.2%)
MuGard®	29/8	38–81 (58)	22 (59%)	41	SB mouthwash	37/4	38–73 (58)	35 (85%)
Curcumin	15/15	30–80	28 (93.3%)	31	Placebo	13/18	30–90	31 (100%)
Honey	53/11	39–85 (59)	51 (80%)	63	Placebo	46/17	38–83 (58)	47 (75%)
Honey	n/a	n/a	36 (100%)	36	Placebo	n/a	n/a	36 (100%)
LB CD2 lozenges	26/6	34–74 (58.4)	13 (40.6%)	36	SB mouthwash	27/9	39–77 (60)	15 (41.7%)
Chlorhexidine	75/37	55.43 ± 15.04	26 (23.2%)	110	Placebo	75/35	57.90 ± 13.62	28 (25.4%)
GSE	20/19	48.66 ± 15.48	13 (33.3%)	39	Placebo	20/19	51.84 ± 19.36	26 (66.7%)
Propolis	22/10	37–80	32 (100%)	28	Placebo	23/5	42–86	28 (100%)
Chamomile	43/39	65.5	33 (40%)	82	Placebo	50/32	65.5	37 (45%)
Chlorhexidine	19/6	67	25 (100%)	27	Placebo	22/5	58	26 (96%)
Honey	44/10	56.8	40 (100%)	52➔41	Placebo	43/9	59.5	41 (100%)
Benzydamine	27/13	n/a	17 (43.6%)	42	Placebo	27/14	n/a	33 (78.6%)
Honey	n/a	n/a	20 (100%)	20	Lignocaine	n/a	n/a	20 (100%)
Dentoxol®	42/13	61.21 ± 13.48	22 (40.7%)	53➔51	Placebo	31/22	61.88 ± 12.19	26 (51%)
Allopurinol	n/a	n/a	31 (79.5%)	38	Placebo	n/a	n/a	22 (57.9%)
Sucralfate	16/4	23–87 (62)	20 (100%)	20	Placebo	9/11	41–88 (69)	20 (100%)
Tea	11/19	52.6 ± 8.2	2 (6.7%)	30	Placebo	13/17	48.7 ± 10.0	1 (3.3%)
Propolis with galangin plus mouth rinsing	n/a	52.4 (12.7)	2 (6.7%)	30	SB mouthwash	n/a	50.9 (10.6)	4 (13.4%)
Aloe vera	27/3	60 (38–91)	29 (97%)	31	Placebo	20/11	54 (31–84)	31 (100%)
Povidone-Iodine	17/3	35–84	14 (70%)	20	Placebo	17/3	37–75	20 (100%)
Curcumin	34/6	56.8 ± 11.73	14 (35.9%)	40	Povidone-Iodine	30/10	55.08 ± 13.14	34 (85%)
Benzydamine	56/7	20–86	25 (39.7%)	57	Placebo	49/8	19–76	36 (63.1%)
Curcumin	28/5	53.76 ± 13.51	23 (69,7%)	35	Benzydamine	26/9	55.03 ± 13.74	32 (91.4%)
LB CD2 lozenges	94/7	52.35 ± 9.433	67 (72%)	99➔95	Placebo	91/8	50.09 ± 10.038	88 (92%)
Aloe vera	22/6	57	18 (64%)	30	Placebo	23/7	55	21 (70%)
Misoprostol	n/a	39–81 (57)	41 (100%)	41	Placebo	n/a	21–77 (57)	41 (100%)
Povidone-Iodine	44/23	55 (26–70)	47 (70%)	65	Placebo	37/28	52 (20–72)	46 (71%)
PTA	25/14	20–78 (55.7)	26 (66.7%)	38	Placebo	20/18	32–79 (57.4)	30 (79%)

such as placebo versus, respectively, propolis, allopurinol, and LB_CD2_lozenges and the comparisons of sodium bicarbonate mouthwash versus propolis. The placebo represented the main group and was set as reference group. Most of the compared treatments were investigated only in one study, as by node representation, while LB_CD2_lozenges and Honey were the most investigated treatment groups, being represented by three studies, respectively.

Overall inconsistency was absent at global (p-value = 0.870) and local levels (p-value ranging between 0.870 and 0.998). Visualization of the inconsistency was figured in the network forest plot, in which effect sizes by study were graphically represented (Figure S3).

All the interventions did not show a statistically significant preventive effect for the occurrence of severe high-grade mucositis, as their confidence intervals were crossing the null-effect line (black vertical line, p-value >0.05). Aloe vera and curcumin showed a promising active effect, despite their large confidence and predictive intervals, which could indicate a null effect in future trials (Figure 5).

4 | DISCUSSION

The present systematic review with NMA of prospective RCT was conducted to evaluate the prevention measures of OM onset and severity in adults under therapy for solid tumors.

Solid tumors represent more than 90% of human cancers and cancer-related mortalities (Wu et al., 2022).

According to Global Cancer Statistics 2020, breast cancer was the most common cancer, with an estimated 2.3 million new cases (11.7%), followed by lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%) cancers (Sung et al., 2021).

Oral mucositis is a distressing side effect of cancer therapy and may be associated with intense pain and increased consumption of painkillers (e.g., opioids), need for parental nutrition, and increased risk of infection and sepsis. All these conditions may result in increased non-adherence to cancer treatment and a reduction of patients' quality of life. Therefore, efforts are needed to reduce the severity of stomatitis or, if possible, to prevent it.

According to a recent study, old age, female gender, high body weight, reduced clearance of drugs and genetic susceptibility are mucositis-related development risk factors (Pulito et al., 2020).

Nevertheless, in our study, a higher prevalence of males was observed compared to females in both groups. This could be related to a higher incidence of cancer diseases in males, especially gastrointestinal tract tumors (Rawla & Barsouk, 2019). Furthermore, most of the included studies were conducted in the United States and India; this datum also reflects the global prevalence of cancer (Sathishkumar et al., 2022; Sung et al., 2019).

To date, there is no gold standard for the prevention and treatment of OM, the MASCC/ISOO Clinical Guidelines are used as a reference for managing patients undergoing oncologic therapies (Elad et al., 2020). According to the last edition, several interventions may be beneficial for the prevention of OM, such as basic oral care, chlorhexidine and benzydamine mouthwash, photobiomodulation therapy, and honey.

Beyond the multimodal approach, to date, no topical agents capable of preventing the development of OM have not yet been reported.

The present study showed that sucralfate significantly reduced the incidence of OM onset following cancer treatment, contrary to what is reported in MASCC/ISO guidelines, where the use of sucralfate is not recommended for either the prevention or treatment of OM. However, the MASCC/ISO guidelines do not individually analyze the effectiveness of topical sucralfate, but rather the effect of combined topical and systemic sucralfate. Furthermore, according to the MASCC/ISO guidelines, the new studies on sucralfate did not pertain to the clinical settings indicated in the 2014 guidelines, which did not evaluate the new formulation of sucralfate (i.e., polymerized cross-linked sucralfate) (Elad et al., 2020) In 2013, the Food and Drug Administration approved the use of polymerized cross-linked sucralfate for the prevention and treatment of different types of oral lesions, including OM (McCullough, 2019).

To our knowledge, to date, no meta-analysis has reported the topical use of sucralfate to prevent the OM onset. Sucralfate is a non-absorbable aluminum salt of sulfated disaccharide that has been shown to be effective in the treatment and prevention of gastric and duodenal ulcers. It exhibits a high affinity for gastric mucosal proteins, especially in the case of mucosal damage, binding to the gastric mucosa and creating a physical protective barrier that protects it (Jensen & Funch Jensen, 1992). Due to its cytoprotective action, sucralfate has also been used to prevent OM brought on by cancer therapies (Etiz et al., 2000). In addition to the formation of a protective physical barrier which has been shown to promote ulcer healing, there are other reasons that may justify the prevention of OM onset. In fact, it is now believed that the main pharmacological actions of sucralfate are linked to the stimulation of the mucosal defense and repair mechanisms, possibly related to the stimulation of the local production of prostaglandins (Jensen & Funch Jensen, 1992). Some studies have also observed a reduction of pathogens colonization of the upper digestive tract of patients treated with sucralfate suspension (Shenep et al., 1988). This has led to the hypothesis that this is due to the action of sucralfate interfering with the adhesion to mucous membranes or with any antibacterial properties of sucralfate (Shenep et al., 1988; Tryba & Mantey-Stiers, 1987). Ala et al. reported a considerable difference both in the frequency and the severity of OM in the sucralfate group compared to control group (Ala et al., 2016).

Etiz et al. performed a histopathological evaluation of sucralfate effectiveness in the prevention of OM induced by RT in patients with H&N tumors and biopsies obtained from the buccal mucosa demonstrated a reduction in altered vascular calibration and permeability and leukocyte emigration in sucralfate group (Etiz et al., 2000).

Following sucralfate, MuGard and Curcumin mouthwashes yielded similar results in OM prevention onset. Also, J. N. Carneiro-Neto et al. reported that MuGard had a positive effect in the control

TABLE 2 Severity of oral mucositis in included studies.

N	Authors	Year	N. Patients (total)	Test group intervention	N. Patients test group	N. Of events (%)	Criteria to assess oral mucositis	Severity of oral mucositis in test group	Control group intervention	N. Patients control group	N. Of events (%)	Severity of oral mucositis in control group
1	Adamietz	1998	40	Povidone-Iodine	20	14 (70%)	WHO Classification	Grade 1: 5 Grado 2: 5 Grado 3: 4	Placebo	20	20 (100%)	Grade 2: 7 Grade 3: 12 Grade 4: 1
2	Ala S	2016	51	Sucralfate	25	6 (24%)	WHO Classification	Grade 1: 1 Grade 2: 1 Grade 3: 2 Grade 4: 2	Placebo	26	25 (96.2%)	Grade 1: 10 Grade 2: 2 Grade 3: 4 Grade 4: 9
3	Arun P	2020	61	Curcumin	30	28 (93.3%)	WHO Classification	Grade 1: 22 Grade 2: 6	Placebo	31	31 (100%)	Grade 1: 6 Grade 2: 21 Grade 3: 4
4	Bardy J	2012	127	Honey	64	51 (80%)	RTOG modified Scale	Grade 3: 51	Placebo	63	47 (75%)	Grade 3: 47
5	Charalambou M	2018	Cyprus	Honey	36	36 (100%)	RTOC criteria	Grade 1: 30 Grade 2: 5 Grade 3–4: 1	Placebo	36	36 (100%)	Grade 1: 4 Grade 2: 16 Grade 3–4: 16
6	De Sanctis V	2019	68	LB CD2 lozenges	32	13 (40.6%)	NCI Common Toxicity Criteria	Grade ≥3: 13	SB mouthwash	36	15 (41.7%)	Grade ≥3: 15
7	Eslami H	2022	78	GSE	39	13 (33.3%)	n.d.	Grade 1: 10 Grade 2: 3	Placebo	39	26 (66.7%)	Grade 1: 7 Grade 2: 19
8	Fernandes PM	2022	60	Propolis	32	32 (100%)	WHO Classification	Grade 1: 15 Grade 3: 17	Placebo	28	28 (100%)	Grade 1: 10 Grade 3: 18
9	Fidler P	1996	164	Chamomile	82	33 (40%)	n.d.	Grade 1: 21 Grade 2: 4 Grade 3: 5 Grade 4: 3	Placebo	82	37 (45%)	Grade 1: 18 Grade 2: 12 Grade 3: 6 Grade 4:1
10	Hawley, P.	2014	106	Honey	54➔40	40 (100%)	RTOG, WHO and Oral Mucositis Assessment Scale scales	Grade <3: 26 Grade ≥3: 14	Placebo	52➔41	41 (100%)	Grade <3: 23 Grade ≥3: 18
11	Kazemian A.	2009	81	Benzydamine	39	17 (43.6%)	RTOG Grading System	Grade ≥3: 17	Placebo	42	33 (78.6%)	Grade ≥3: 33
12	Khanal B	2010	India	Honey	20	20 (100%)	RTOG Grading System	Grade 1: 15 Grade 2: 4 Grade 3: 1	Lignocaine	20	20 (100%)	Grade 1: 0 Grade 2: 5 Grade 3: 14 Grade 4: 1

(Continues)

TABLE 2 (Continued)

N	Authors	Year	N. Patients (total)	Test group intervention	N. Patients test group	N. Of events (%)	Criteria to assess oral mucositis	Severity of oral mucositis in test group	Control group intervention	N. Patients control group	N. Of events (%)	Severity of oral mucositis in control group
13	Loprinzi CL	1990	78	Allopurinol	39	31 (79.5%)	n.d.	Grade1: 9 Grade 2: 12 Grade 3: 9 Grade 4: 2	Placebo	38	22 (57.9%)	Grade 1: 4 Grade 2: 8 Grade 3: 10
14	Makkonen TA	1994	40	Sucralfate	20	20 (100%)	n.d.	Grade 1: 6 Grade 2: 14	Placebo	20	20 (100%)	Grade 1: 4 Grade 2: 15
15	Mutluay Yayla E	2016	60	Tea	30	2 (6.7%)	WHO Classification	Grade1: 1 Grade 2: 1	Placebo	30	1 (3.3%)	Grade 1: 1
16	Piredda RN	2017	60	Dry extract of propolis with 8–12% of galangin plus mouth rinsing with SB	30	2 (6.7%)	Modified National Cancer Institute Scale version 4.0 (NCI-CTCAE v4 modified)	Grade 1: 2	SB mouthwash	30	4 (13.4%)	Grade 1: 2 Grade 2: 2
17	Puataweepong P	2009	61	Aloe Vera	30	29 (97%)	RTOG Grading System	Grade 1: 13 Grade 2: 15 Grade 3: 1	Placebo	31	31 (100%)	Grade 1: 4 Grade 2: 19 Grade 3: 7 Grade 4: 1
18	Sharma A	2012	200	LB CD2 lozenges	101➔93	67 (72%)	NCI CTC version 2.0	Grade 1: 10 Grade 2: 8 Grade 3: 2 Grade 4: 47	Placebo	99➔95	88 (92%)	Grade 1: 10 Grade 2: 5 Grade 3: 8 Grade 4: 65
19	Veness MJ	2006	83	Misoprostol	42	41 (100%)	RTOG Grading System	Grade 1: 4 Grade 2: 19 Grade 3: 18	Placebo	41	41 (100%)	Grade 1: 5 Grade 2: 18 Grade 3: 17 Grade 4: 1
20	Vokurka S	2005	132	Povidone-Iodine	67	47 (70%)	WHO Classification	Grade 1: 15 Grade 2: 16 Grade 3: 13 Grade 4: 3	Placebo	65	46 (71%)	Grade 1: 17 Grade 2: 12 Grade 3: 14 Grade 4: 3
21	Wijers OB	2001	77	PTA	39	26 (66.7%)	van der Schueren scoring system	Grade 1: 11 Grade 2: 7 Grade 3: 3 Grade 4: 5	Placebo	38	30 (79%)	Grade 1: 8 Grade 2: 10 Grade 3: 8 Grade 4: 4

Abbreviations: NCI, National Cancer Institute; RTOG, Radiation Therapy Oncology Group; RTOG/EORTC, Radiation Therapy Oncology Group and the European Organization for Research and Treatment Cancer; WHO, World Health Organization.

of OM, oral pain, and dysphagia during cancer therapy. This study, however, did not exclusively analyze the effect of MuGard, but of a protocol in which MuGard was used in combination with other measures, such as antiseptic mouthrinse with chlorhexidine and cetylpyridinium chloride, benzydamine bioadhsive oromucosal gel and diode laser therapy (Carneiro-Neto et al., 2017). Moreover, in patients affected by cancer therapy-induced OM, curcumin has been reported to be safe, effective, well-tolerated, and to reduce discomfort while also delaying the OM onset and severity (Dharman et al., 2021). In a systematic review and meta-analysis on the efficacy of curcumin for the prevention and amelioration of RT or CT-induced OM in H&N cancer patients performed by Daharman S. et al. it has been reported that curcumin did not prevent the overall incidence of OM but delayed the onset, and reduced the incidence of grade 3 manifestations (Dharman et al., 2021). In recent years, polyphenols, including GSE and curcumin, have attracted the attention of researchers due to their broad spectrum of properties, as well as their low side effects (Magrone et al., 2019). Their wide range of biological activities includes antioxidant, antifungal, anti-inflammatory, anti-aging, chemoprotective, and anticancer properties which makes them potentially useful in various fields of medicine, including oncology (Luo et al., 2021; Rudrapal et al., 2022).

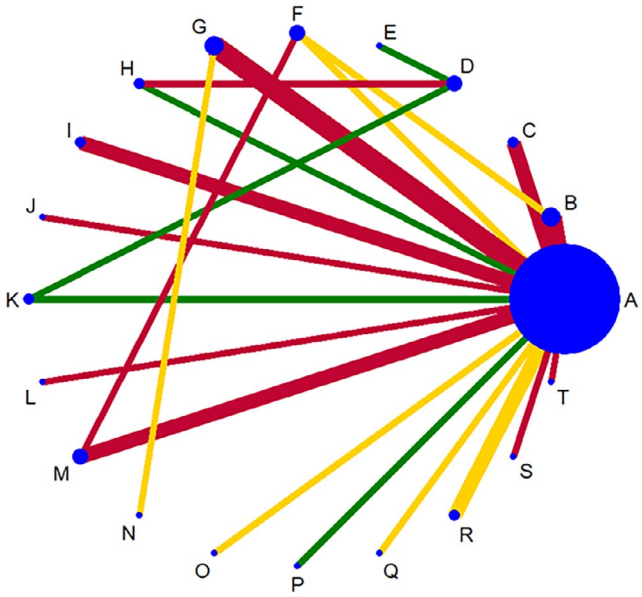

FIGURE 2 Network plot representing direct comparisons of the 20 diverse treatments. A: Placebo; B: Povidone Iodine; C: Sucralfate; D: Sodium bicarbonate mouthwash; E: MuGard; F: Curcumin; G: Honey; H: LB CD2 lozenges; I: Chlorhexidine; J: Grape Seed Extract; K: Propolis; L: Chamomile; M: Benzydamine; N: Lignocaine; O: Dentoxol; P: Allopurinol; Q: Tea; R: Aloe Vera; S: Misoprostol; T: Polymyxin Tobramycin Amphotericin paste.

In third place, we found that also LB_CD2_lozenges, GSE, and benzydamine showed as well effective prevention. Based on numerous studies documenting the beneficial effects of probiotics in the oral cavity due to their anti-inflammatory and immunomodulatory properties, our study on LB_CD2 lozenges demonstrates their effective preventive action in cancer care-related contexts as well (Azad et al., 2018; Cristofori et al., 2021; Liu et al., 2022). Their potential benefits in preventing toxic side effects induced by cancer therapy, including OM, could prompt their introduction into clinical practice.

TABLE 3 Estimated lnORs for all the interventions compared to placebo.

	Ln (odds ratio)	Std. err.	*p*-Value	Ln [95% Conf. Interval]	
Povidone Iodine	−0.36222	0.56334	0.52	−1.466347	0.7419064
Sucralfate	−3.336137	0.99589	0.001	−5.288046	−1.384229
Sodium bicarbonate mouthwash	−1.322041	0.703321	0.06	−2.700525	0.0564436
MuGard	−2.702636	0.905569	0.003	−4.477519	−0.9277539
Curcumin	−2.612959	0.551234	<0.001	−3.693357	−1.53256
Honey	0.2625381	0.426623	0.538	−0.5736285	1.098705
LB CD2 lozenges	−1.483111	0.478978	0.002	−2.42189	−0.5443318
Chlorhexidine	−0.0740799	0.353093	0.834	−0.76613	0.6179703
Grape Seed Extract	−1.386294	0.498804	0.005	−2.363932	−0.4086567
Propolis	−1.709636	1.039415	0.1	−3.746852	0.3275796
Chamomile	−0.2197709	0.342912	0.522	−0.8918652	0.4523235
Benzydamine	−1.167111	0.320663	<0.001	−1.795598	−0.5386234
Lignocaine	0.262538	2.073066	0.899	−3.800597	4.325673
Dentoxol	−0.4446858	0.415036	0.284	−1.258142	0.3687705
Allopurinol	1.036092	0.532211	0.052	−0.0070227	2.079207
Tea	0.7282385	1.260251	0.563	−1.741808	3.198285
Aloe Vera	−0.3570406	0.549043	0.516	−1.433144	0.719063
Misoprostol	1.50E−10	2.016489	1	−3.952246	3.952246
Polymyxin Tobramycin Amphotericin paste	−0.6286087	0.540143	0.245	−1.687269	0.4300514

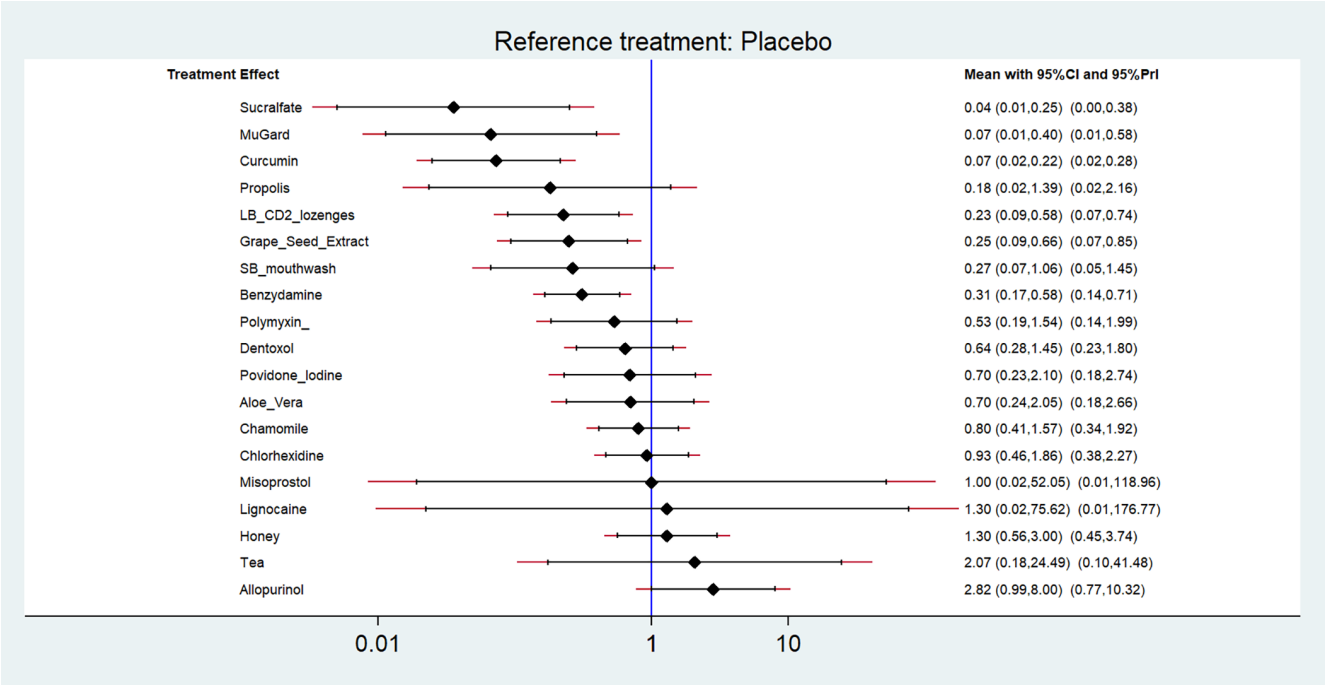

FIGURE 3 Treatment effect as odds ratios with respective 95% confidence intervals and predictive intervals. CI, confidence interval; LB_CD2_lozenges, Lactobacillus brevis CD2 lozenges; Polymyxin_, Polymyxin Tobramycin Amphotericin paste; PrI, Predictive Intervals; SB_mouthwash, Sodium bicarbonate mouthwash.

The effectiveness of these agents may stem from the fact that the initial phase of OM pathogenesis is characterized by cellular damage, increased expression of inflammatory cytokines, primary damage response, and activation and amplification of the inflammatory cascade (Shetty et al., 2022). According to MASCC/ISOO guidelines, probiotics containing Lactobacillus spp. may offer potential benefits in preventing radiation therapy RT-induced or RT-CT-induced diarrhea in patients with pelvic malignancies (Elad et al., 2020).

Referring to GSE, a previous study carried out on animals demonstrated the effectiveness of GSE in injuries caused experimentally (Saleh et al., 2017). Ahmed Saleh et al. found that administering GSE during chemotherapy reduced tongue damage without affecting microbe colony counts. Conversely, pretreatment with GSE resulted in the best outcomes, with occasional atrophic regions in filiform papillae and minimal inflammation (Saleh et al., 2017).

Regarding the efficacy of benzydamine in preventing oral mucositis, our findings align with MASCC/ISOO guidelines recommending benzydamine mouthwash for oral mucositis prevention in patients with H&N cancer undergoing moderate-dose RT, as well as in those receiving RT-CT (Elad et al., 2020).

Also, the oral microbiota represents another crucial aspect in the onset of different oral disease, including OM (Bruno et al., 2023; Mauceri et al., 2022). Microbial dysbiosis, along with invasion and colonization of the oral mucosa, have been identified as key contributors to the pathophysiology of OM (Mauceri et al., 2023; Sonis, 2017).

According to MASC/ISOO Clinical Practice Guidelines, BOC remains an important best practice for patients undergoing cancer treatment, including patient education, multiagent combination oral care protocols, professional oral care, and different types of oral rinse, such as saline solution, sodium bicarbonate, and chlorhexidine. However, only chlorhexidine mouthwash is not endorsed for OM prevention in patients undergoing H&N RT (Elad et al., 2020).

Unfortunately, not all patients affected by OM can afford this multidimensional management, whether due to health, economic, or social conditions.

In our revision BOC and oral rinses with antimicrobial agents as the only preventive measures did not show any effectiveness. We hypothesize that these procedures should still be recommended to patients undergoing cancer treatment as, although they do not prevent the onset of OM, they might limit the severity.

In the present study, the only agent that did not demonstrate efficacy in preventing OM, but instead showed worse outcomes compared to the control group, was allopurinol (Loprinzi et al., 1990). In fact, the effects of allopurinol on the oral mucosa should not be underestimated, as it has been demonstrated to also be responsible for the formation of oral lichenoid reactions, which, according to the latest WHO classification, are known to belong to the group of oral potentially malignant disorders (Perez et al., 2020; Warnakulasuriya et al., 2021).

Regarding to the severity of OM, no interventions analyzed showed a statistically significant preventive effect, which appears to be conditioned by other factors including sex, smoking habits, age, and nutritional status (Brown & Gupta, 2020; Chen et al., 2021).

TABLE 4 Summary of probability and SUCRA and relative mean rank for each intervention.

	Treatment																		
Rank	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
Best	0	0	53.5	0	21.6	13.8	0	0	0	0.2	3.4	0	0	3.5	0	0	0.1	0	3.9	0
2nd	0	0	21.8	0.5	29.2	31.2	0	0.4	0	1.2	8.2	0	0.1	3.5	0	0	0.2	0	3.7	0
3rd	0	0.2	11.8	2.9	24.4	27.5	0	2.8	0	5.8	14.0	0	1.4	3.6	0.1	0	0.5	0.2	4.3	0.5
4th	0	0.9	5.4	9.1	12.5	14.5	0	11.4	0	11.9	17.1	0	5.3	3.9	0.3	0	1.2	0.7	4.4	1.4
5th	0	1.6	2.8	14.5	5.7	6.5	0	20.7	0.1	14.2	12.1	0.1	9.2	3.4	0.5	0	1.3	1.3	3.4	2.7
6th	0	2.4	2	16.3	2.4	3.9	0	22.7	0.1	14.0	8.8	0.2	13	2.9	1.2	0	1.1	1.9	3	4.2
7th	0	3.2	1	14.2	1.5	1.7	0.1	17.6	0.2	16.0	7.1	0.5	17	2.9	2.7	0	1.3	3.2	3.2	6.5
8th	0	5.2	0.6	11.8	1	0.7	0.2	11.4	0.8	13.8	5.7	1.4	20.6	2.9	4.7	0	1.8	5.2	3.1	9
9th	0	7.7	0.4	9	0.6	0.3	0.5	6.7	2.3	10.0	5.2	3.9	16.5	2.6	8.8	0	2.6	7.5	3.4	12.1
10th	0.1	10.2	0.3	6.5	0.5	0	1	3.4	4.2	6.2	4.1	7	10.3	3.2	13.1	0.1	2.9	10.2	3.6	13.1
11th	0.8	11.1	0.1	4.7	0.2	0	2.5	1.4	7.5	3.1	3.1	11.6	4.4	3.1	15.3	0.2	3.1	11.5	3.4	13
12th	3.3	10.6	0.1	3.4	0.2	0	4	0.7	10.2	1.9	2.4	14.1	1.7	2.9	15.2	0.4	3.6	12.1	3	10
13th	10.8	9.6	0	2.2	0.1	0	5.5	0.4	12.9	0.8	1.8	16.2	0.5	2.8	11.5	0.7	3.4	9.7	2.8	8
14th	21.7	7.9	0	1.4	0.1	0	7.7	0.1	13.2	0.5	1.5	13.6	0.1	2.6	9	0.8	3.2	8	2.7	5.8
15th	27.1	7.1	0	1.2	0	0	9.4	0.1	13.3	0.3	1.1	11.8	0	2.3	6.6	1.5	3.3	7.4	2.9	4.5
16th	22	7.6	0	0.9	0	0	16.3	0	13.2	0.1	1.3	8.5	0	3.1	5	2.9	4.5	7.2	3.3	4
17th	10.7	6.7	0	0.6	0	0	22.4	0	12.2	0.1	1.3	6.4	0	5	3.6	8.2	7.9	6.9	5.3	2.7
18th	3	5.2	0	0.5	0	0	19.6	0	7.1	0.0	1.0	3.4	0	8.3	1.8	23.1	12.6	4.7	7.9	1.9
19th	0.4	2.4	0	0.2	0	0	9	0	2.4	0.0	0.6	1.1	0	12.3	0.6	36.5	20.5	1.9	11.5	0.6
Worst	0	0.5	0	0	0	0	1.8	0	0.3	0.0	0.2	0.1	0	25.2	0	25.7	24.7	0.5	20.9	0.1
MEAN RANK	15	12.4	2	7.5	2.8	2.9	16.1	6.4	14.3	6.8	6.3	13.3	7.6	13.7	11.9	18.6	16.3	12.4	13.1	10.7
SUCRA	0.3	0.4	0.9	0.7	0.9	0.9	0.2	0.7	0.3	0.7	0.7	0.4	0.7	0.3	0.4	0.1	0.2	0.4	0.4	0.5

Note: A: Placebo; B: Povidone Iodine; C: Sucralfate; D: Sodium bicarbonate mouthwash; E: MuGard; F: Curcumin; G: Honey; H: LB CD2 lozenges; I: Chlorhexidine; J: Grape Seed Extract; K: Propolis; L: Chamomile; M: Benzydamine; N: Lignocaine; O: Dentoxol; P: Allopurinol; Q: Tea; R: Aloe Vera; S: Misoprostol; T: Polymyxin Tobramycin Amphotericin paste.

In addition to the topical measures mentioned above, it has been reported that also photobiomodulation (PMB) therapy using low-level laser may confer beneficial effects in OM prevention in patients undergoing HSCT and receiving H&N RT with or without CT, which was not evaluated in the present NMA (Elad et al., 2020).

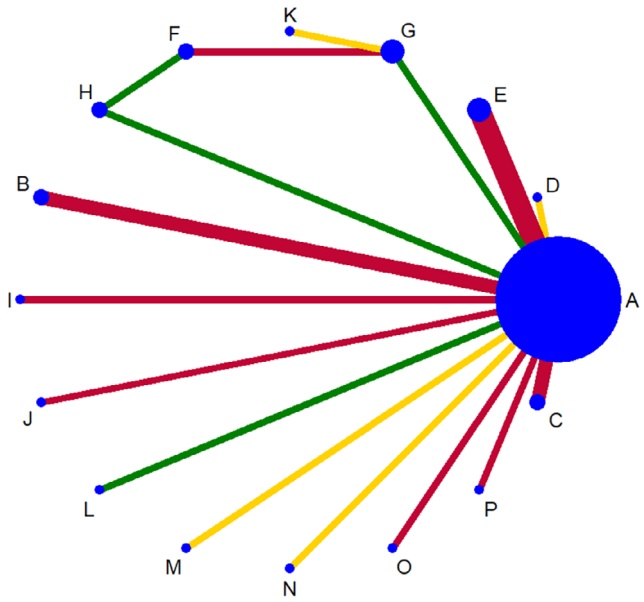

FIGURE 4 Network plot representing direct comparisons of the 15 diverse treatments. A: Placebo; B: Povidone Iodine; C: Sucralfate; D: Curcumin; E: Honey; F: Sodium bicarbonate mouthwash; G: LB CD2 lozenges; H: Propolis; I: Chamomile; J: Benzydamine; K: Lignocaine; L: Allopurinol; M: Tea; N: Aloe Vera; O: Misoprostol; P: Polymyxin Tobramycin Amphotericin paste.

The present study, for the first time, aims to identify the topical agents available for the prevention of OM; nonetheless, it possesses several limitations. First, the included studies are heterogeneous in terms of the interventions, patients' characteristics, including different therapeutic modalities adopted (CT, RT, or both), and the assessment of OM. Second, the preventive interventions were all different and consisted of topical measures rather than systemic, making them difficult to dose and quantify as they depend on the patient's ability and compliance. Third, the absence of a standard classification for measuring the severity of OM has made it challenging to compare across studies, thereby preventing the attainment of statistically significant data. Included studies had a high risk of bias due to key elements in designing an RCT, including errors in the randomization and blinding process and usually patients undergoing treatment for OM are not screened by trained oral specialists. All these factors could affect research results and the respective conclusions. It is recommended to consider these parameters in future and standardized studies.

5 | CONCLUSIONS

In contrast to the significant advances in the cancer therapies field, resulting in extended lifespans for cancer patients, analogous progress has not been achieved in the prevention or treatment of cancer therapy-induced OM. Our study suggests that sucralfate mouthwash might be recommended in the management of cancer therapy considering its low cost, easy administration, satisfactory compliance, and lack of association with significant adverse effects. Given its cytoprotective properties, the sucralfate use represents a highly promising outcome that we expect to be confirmed by future studies.

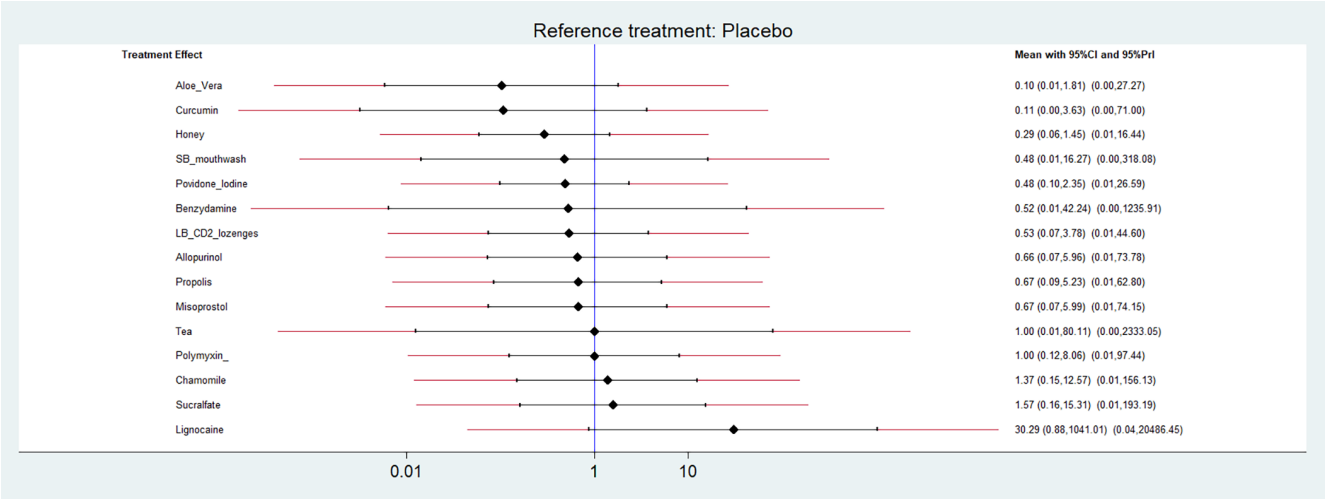

FIGURE 5 Treatment effect as odds ratios with respective 95% Confidence Intervals and Predictive Intervals. CI, confidence interval; LB_CD2_lozenges, Lactobacillus brevis CD2 lozenges; Polymyxin_, Polymyxin Tobramycin Amphotericin paste; PrI, Predictive Intervals; SB_mouthwash, Sodium bicarbonate mouthwash.

AUTHOR CONTRIBUTIONS

Martina Coppini: Investigation; writing – original draft; methodology; visualization; data curation; formal analysis. **Vito Carlo Alberto Caponio:** Investigation; writing – review and editing; methodology; visualization; formal analysis; validation. **Rodolfo Mauceri:** Validation; conceptualization; writing – review and editing; visualization; supervision. **Maria Eleonora Bizzoca:** Visualization; data curation; formal analysis. **Luigi Laino:** Visualization; formal analysis; validation. **Alejandro I. Lorenzo-Pouso:** Visualization; formal analysis; data curation. **Diana Russo:** Visualization; formal analysis; data curation. **Giuseppe Troiano:** Visualization; formal analysis; data curation. **Fábio França Vieira E. Silva:** Visualization; formal analysis; data curation. **Lorenzo Lo Muzio:** Visualization; formal analysis; data curation; project administration; validation. **Giuseppina Campisi:** Conceptualization; writing – review and editing; visualization; validation; resources; supervision; project administration.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. The protocol was designed a priori and registered on the online database PROSPERO (CRD42023469152).

INFORMED CONSENT STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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