

# Effects of 9 oral care solutions on the prevention of oral mucositis: a network meta-analysis of randomized controlled trials

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## Abstract

**Background:** Oral mucositis (OM) is a common, disabling, and severe early effect of chemotherapy and radiotherapy that limits the effectiveness of anticancer therapy. The prevention and treatment of OM in patients with malignant tumors is an urgent problem in the field of anticancer therapy.

**Methods:** Databases including PubMed, Embase, Scopus, The Cochrane Library, and Google Scholar were searched to collect published randomized control trials (RCTs) about the effects of different oral care solutions on the prevention of OM from inception to January 2019. We used the Cochrane Handbook to assess the methodological quality of the RCTs. Two of the authors independently extracted the articles and predefined data. Network meta-analysis was then performed using Stata 15.0 software.

**Results:** A total of 28 RCTs involving 1861 patients were included. The results of network meta-analysis showed that chlorhexidine, benzydamine, honey, and curcumin were more effective than placebo ( $P < .05$ ) and that honey and curcumin were more effective than povidone-iodine ( $P < .05$ ). Probability ranking according to the Surface Under the Cumulative Ranking curve showed the following treatments: curcumin, honey, benzydamine, chlorhexidine, allopurinol, sucralfate, granulocyte-macrophage colony-stimulating factor, povidone-iodine, and aloe.

**Conclusion:** Our preliminary results indicate that curcumin and honey may serve as the preferred options for patients to prevent OM. The findings may offer an important theoretical basis for clinical prevention and treatment. However, this conclusion still requires an RCT with a larger sample size for further verification.

**Abbreviations:** CI = confidence interval, GM-CSF = granulocyte-macrophage colony-stimulating factor, IF = inconsistency factor, MASCC/ISOO = Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology, NCI = National Cancer Institute, OM = oral mucositis, OMAS = Oral Mucositis Assessment Scale, RCT = randomized controlled trial, RR = relative risk, RTOG = Radiation Therapy Oncology Group, SUCRA = surface under the cumulative ranking, WHO = World Health Organization.

**Keywords:** cancer, mucositis, network meta-analysis, nursing, oral

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The datasets generated during and/or analyzed during the current study are publicly available.

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## 1. Introduction

Oral mucositis (OM) is described as a common and painful debilitating inflammation of the oral mucosa in patients with cancer that varies from mild mucosal erythema to severe ulcerations.<sup>[1]</sup> OM is one of the main side effects of anticancer treatment with an incidence rate of 40% to 100%, related to tumor type, oral hygiene, treatment method, age, and nutritional status.<sup>[2–4]</sup> Depending on its severity, OM may trigger an inability to tolerate food or fluids, which leads to malnutrition, dehydration, and weight loss.<sup>[5]</sup> Furthermore, it limits the effectiveness of anticancer therapy, increases hospitalization costs, and may even lead to interruption in chemoradiotherapy protocols, which reduces the chances of healing and patients' survival.<sup>[6,7]</sup> Therefore, there is a need to develop therapeutic strategies to prevent and treat OM.

Oral care plays a critical role in the prevention and treatment of OM. Oral care, including regular oral care before and during cancer treatment and gentle flushing with saline or sodium bicarbonate, has long been considered the basis of oral hygiene for patients receiving cancer treatment.<sup>[8]</sup> It is considered important to maintain oral cleansing, reduce the risk of oral infections, and promote oral comfort; the evidence for a role in preventing or treating OM has been both scarce and inconsistent for basic oral care.<sup>[9]</sup> However, the mechanisms by which various

basic oral care strategies may directly affect the pathogenesis of OM are unclear, although most have few complex interactions that may affect the molecular factors that cause mucosal tissue damage.<sup>[10]</sup> Mixed medication mouthwashes, usually consisting of topical coatings, anesthetics, and possibly other agents, have little or no direct effect on the pathogenesis of OM. Finally, some oral rinses are known to have specific biological activity, such as antibacterial drugs chlorhexidine and povidone-iodine, which do not affect the primary pathways involved in mucositis pathogenesis. Despite this, basic oral care is considered the backbone of supportive care for patients receiving cancer treatment.<sup>[9,11]</sup>

Different oral care solutions have been investigated for the prevention and treatment of OM, such as chlorhexidine, benzydamine, sucralfate, povidone-iodine, and honey, which have been found to prevent mucositis or reduce the severity of mucositis; however, no approach has been completely successful.<sup>[12–14]</sup> Although several systematic reviews and meta-analyses have been conducted to examine the effects of the different oral care solutions, evidence was limited due to the lack of multiple comparisons of classical meta-analysis. Bayesian network meta-analysis is a method combining all available direct and indirect evidences on the relative treatment effects, enabling a unified, coherent analysis of all RCTs.<sup>[15–17]</sup> The objective of this study was to evaluate the effect of different oral care solutions. These treatments were compared from 28 randomized controlled trials (RCTs) by network meta-analysis, which calculates the relative effects for all treatments.<sup>[18]</sup> The aim was to provide hierarchies of the prevention of OM for 9 treatments. This may provide valuable information for OM treatment research in the future.

## 2. Materials and methods

### 2.1. Ethical statement

Ethical approval and informed consent are not required, as the study will be a literature review and will not involve direct contact with patients or alterations to patient care.

### 2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: RCTs; studies that assessed the effects of different oral care solutions on the prevention of OM in patients with cancer who underwent chemotherapy, radiotherapy, or both; OM outcomes reported by trial authors (incidence of mucositis); articles written in English; and the subjects rinsed with different oral care solutions.

The exclusion criteria were as follows: duplicate publications; studies with insufficient data; subjects underwent intravenous, oral, subcutaneous, or inhalation treatment methods; and nonrandomized studies, retrospective studies, review articles, conference abstracts, letters, or case reports.

### 2.3. Literature search

We searched the PubMed, Embase, Scopus, Cochrane Library, and Google Scholar databases for studies related to the prevention of OM that were conducted before January 2019. We also manually searched the bibliographies of relevant literature to further identify any other research related to our analysis. Articles with the following key words and Medical Subject Headings were also searched: “Mucositis,” “Mouthwashes,” “Stomatitis,” “Mouth,”

“Nursing care,” “Oral,” “Ulcer,” “Cancer,” “Chemotherapy,” “Radiotherapy,” and “RCT.”

### 2.4. Data extraction

Two researchers independently extracted information such as patient characteristics, first author, publication year, country of origin, treatment, and incidence of mucositis. A third researcher resolved any disagreement between the reviewers.

### 2.5. Risk of bias assessment

The Cochrane Risk of Bias Tool was used to assess the quality of the included studies by 2 reviewers. The tool is based on assessing random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. The judgment classification in each domain is low risk of bias, unclear risk of bias, or high risk of bias.<sup>[19]</sup>

### 2.6. Statistical analysis

We estimated the relative risk (RR) with 95% confidence intervals (CIs) for dichotomous variables. Statistical analysis was performed using Stata software, version 15.0 (Stata Corporation, College Station, TX).  $P < .05$  was considered statistically significant. Network meta-analysis compares multiple treatments simultaneously by combining direct and indirect evidence of the relative treatment effects.<sup>[20]</sup> We used inconsistency factors (IFs) to estimate heterogeneity in each closed loop, and a 95% CI (IF) value of zero indicated the absence of statistical significance. Funnel plot analysis was used to estimate small-study effects. We ranked the 9 interventions for treating OM according to the Surface Under the Cumulative Ranking curve (SUCRA), which represents the percentage of the area under the curve.<sup>[21]</sup>

## 3. Results

### 3.1. Study characteristics

We identified 2561 articles. We excluded 909 duplicate articles and a further 1518 articles after reviewing titles and abstracts. After screening the full text of the remaining 134 articles, we included 28 articles in our network meta-analysis.<sup>[22–49]</sup> Figure 1 shows a flow chart of the entire sample selection process. Table 1 provides a summary of the studies included in the present meta-analysis. A total of 28 studies were RCTs directly comparing alternative treatments, with a total of 1861 patients.

### 3.2. Quality assessment

Although all the studies involved randomization, 21 trials incorporated an adequate randomization technique. Only 7 articles reported information regarding allocation concealment. Regarding contamination between treatment groups, 18 trials were at a low risk of bias, whereas 18 trials were at a low risk of bias due to selective outcome reporting. Figure 2 shows the Cochrane risk of bias assessment of the included studies.

### 3.3. Evidence network

As shown in Figure 3, the lines in the evidence network represent a direct comparison between the 2 directly related interventions. Interventions without connections are compared indirectly

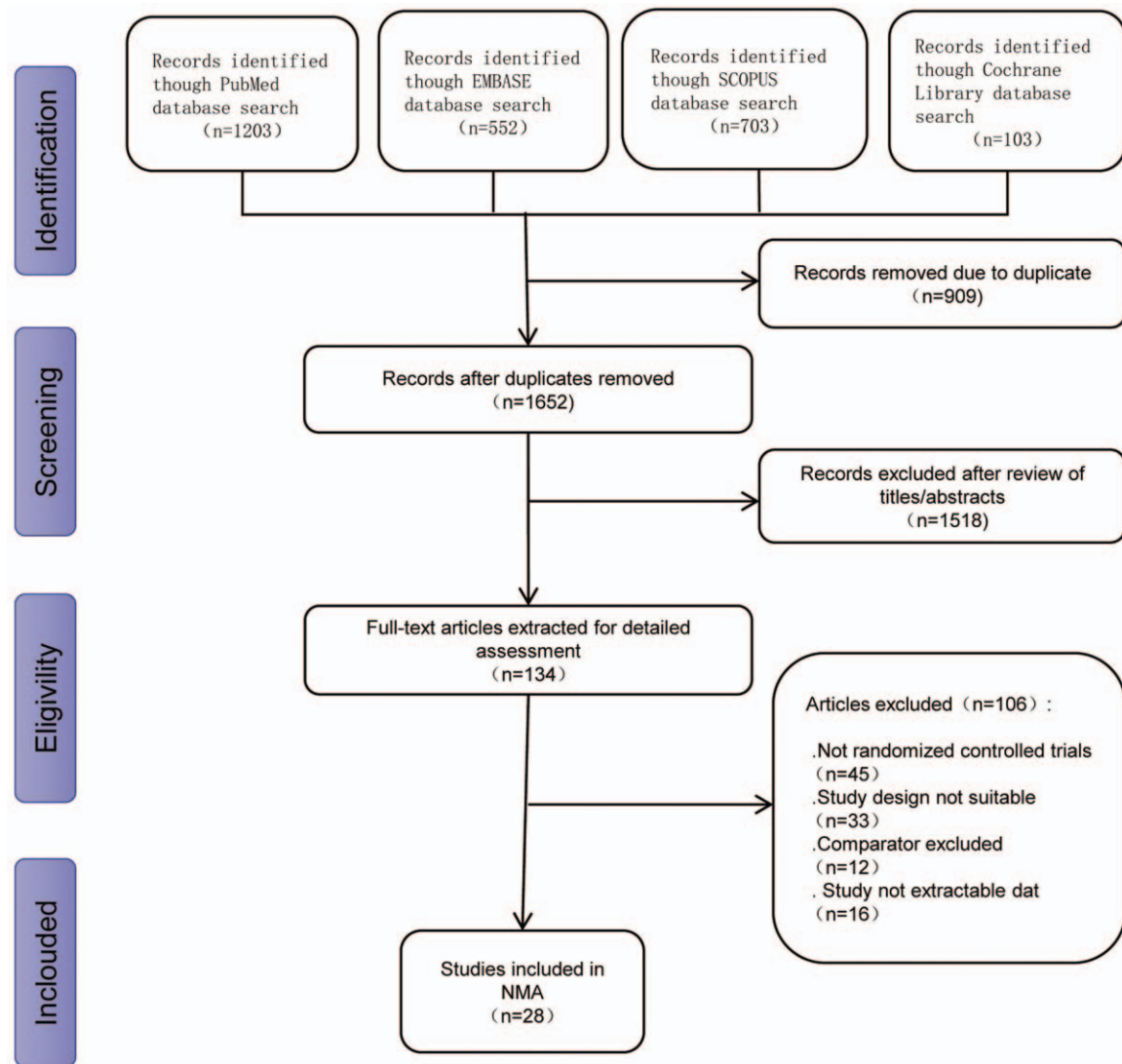


Figure 1. Flow diagram of study selection.

through the network meta-analysis. The width of the lines represents the number of trials, and the size of the node represents the total sample size of multiple treatments.

### 3.4. Inconsistency test

Figure 4 shows an inconsistency plot for assessing the heterogeneity among studies in the closed loop of the network meta-analysis. It was composed of 7 loops with a 95% CI (IF) value of zero, which indicates that our network analysis data were consistent. In addition, all *P* values were >0.05, indicating that the indirect and direct comparisons of the various treatments were consistent.

### 3.5. Network meta-analysis

The results of network meta-analysis showed that chlorhexidine, benzydamine, honey, and curcumin were more effective than placebo (chlorhexidine: RR=0.39; 95% CI, 0.18–0.82; benzydamine: RR=0.30; 95% CI, 0.13–0.68; honey: RR=0.25; 95%

CI, 0.11–0.56; curcumin: RR=0.08; 95% CI, 0.01–0.60) and that honey and curcumin were more effective than povidone-iodine (honey: RR=0.32; 95% CI, 0.11–0.97; curcumin: RR=0.10; 95% CI, 0.02–0.60). Other comparisons were not statistically significant (Fig. 5).

### 3.6. Ranking probability

A ranking graph of the distribution of probabilities on remission is presented in Figure 6. Based on SUCRA, curcumin had the highest SUCRA rank, which was the first efficacy possibility. The SUCRA result showed the following efficacy ranking: curcumin > honey > benzydamine > chlorhexidine > allopurinol > sucralfate > granulocyte-macrophage colony-stimulating factor (GM-CSF) > povidone-iodine > aloe > placebo (Fig. 6).

### 3.7. Publication biases

The funnel plot suggested that the results for chlorhexidine might be affected by publication bias and small-study effects, which





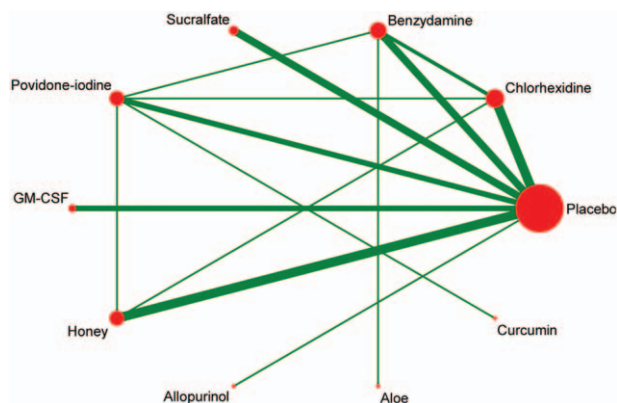


Figure 3. Evidence network of the RCT in the network meta-analysis.

might have a significant impact on the estimated treatment effect (Fig. 7).

#### 4. Discussion

OM is a common, disabling, and severe early effect of chemotherapy and radiotherapy. The prevention and treatment of OM in patients with malignant tumors is an urgent problem in the field of anticancer therapy. Recently, oral care was suggested to play a role in OM progression. Many RCTs and meta-analyses have been conducted for the prevention and treatment of OM with different oral care solutions. However,

traditional meta-analysis is not conclusive in assessing >2 oral care solutions. Our study is the first to assess different oral care solutions for OM in patients receiving anti-cancer treatment based on network meta-analysis. Network meta-analysis is used to compare multiple interventions through direct and indirect comparisons.

A total of 28 RCTs involving 1861 patients and 9 oral care solutions were included. This article may present current evidence for OM treatment research in the future.

The results of network meta-analysis showed that chlorhexidine, benzylamine, honey, and curcumin were more effective than placebo ( $P < .05$ ) and that honey and curcumin were more effective than povidone-iodine ( $P < .05$ ). SUCRA showed the following result: curcumin, honey, benzylamine, chlorhexidine, allopurinol, sucralfate, GM-CSF, povidone-iodine, and aloe.

Members of the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) recently completed the process of updating the MASCC/ISOO Clinical Practice Guidelines for the prevention and treatment of mucositis.<sup>[50]</sup> These guidelines were originally published in 2004,<sup>[51]</sup> and then updated in 2007<sup>[9]</sup> and 2014.<sup>[52]</sup> In agreement with our data, the current guidelines recommend that benzylamine mouthwash be used to prevent OM in patients with cancer (level I). Furthermore, the panel suggests that chlorhexidine and GM-CSF mouthwash not be used to prevent OM in patients receiving radiation therapy for head and neck cancer (level II).<sup>[52]</sup> This guide roughly aligns with our findings. In this context, due to inadequate evidence, no guideline was possible in relation to other agents of natural origin reviewed, including honey, aloe vera, and Chinese herbs.<sup>[52]</sup>

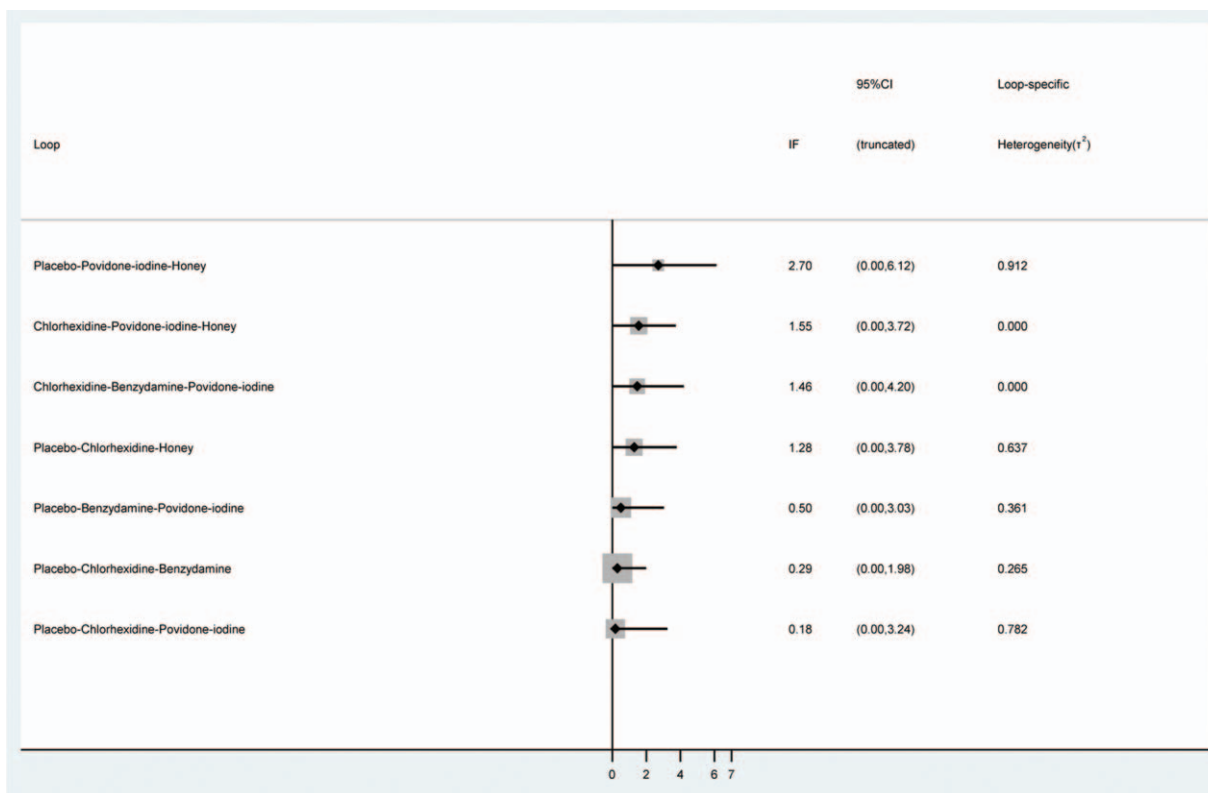


Figure 4. Inconsistency test for direct and indirect comparisons of the enrolled studies in the network meta-analysis.

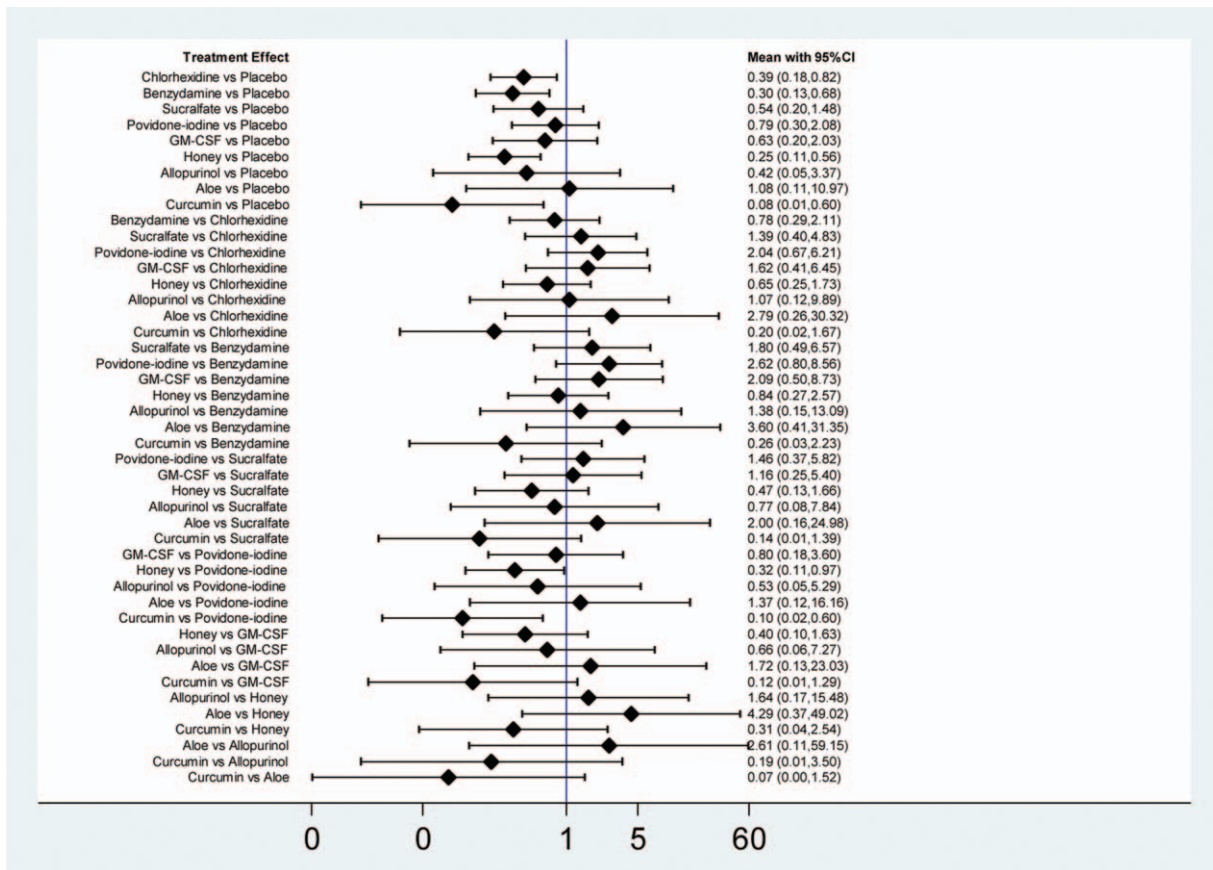


Figure 5. Results of the network meta- analysis.

However, there were 8 articles included in our study that reported curcumin (Chinese herbs) and honey as oral care solutions. Only 2 articles were published before 2014, and 6 were published after 2014. Increasingly more studies confirm the role of natural medicines in the prevention and treatment of OM. Our research may provide a basis for updating the guidelines.

Active components are extracted from the rhizomes of the turmeric plant. In recent years, numerous studies have demonstrated the potentially important effects of curcumin as a potential therapeutic agent, such as antioxidant, anticancer, and antiulcer activities.<sup>[53,54]</sup> Of the total of 28 articles included, only 1 reported treatment with curcumin. However, numerous studies have shown that curcumin plays an important role in OM. Patil et al<sup>[55]</sup> also confirmed that the effect of curcumin may be better in the management of radiochemotherapy-induced OM compared with chlorhexidine. Meanwhile, this effect may be due to the different study populations used. A non-RCT found that curcumin combined with honey also has significant advantages for OM.<sup>[56]</sup> Elad et al<sup>[57]</sup> assessed the tolerability of a curcumin mouthwash for the prevention of OM in pediatric patients, and no adverse events were documented. Large-scale, long-term studies are needed to evaluate the role of curcumin in the treatment of OM.

Previous reviews and meta-analyses have reported that honey is beneficial to prevent the development of severe mucositis, compared with controls.<sup>[58,59]</sup> This study updated previous data as it added 3 recent clinical trials to the previous systematic

reviews and meta-analyses. The additional studies used chlorhexidine and povidone-iodine as the controls, and these studies have shown that honey plays an important role in OM. However, the apprehension that honey would enhance the radiation-related caries in cancer patients topically applying them during the course of the radiation is a major concern as this would enhance dental caries and compromise the quality of life of the cancer survivors.<sup>[60,61]</sup> In contrast, when compared with honey, turmeric may not have long-term adjunct effects as studies have shown it to be also beneficial in the treatment of various periodontal diseases.<sup>[62,63]</sup> Clinically, although clinically chlorhexidine is a therapy that may be routinely used or recommended in cancer patients with OM, the current evidence does not support the routine prescription and cost of chlorhexidine for the prevention or treatment of OM until further studies are performed. Well, in this study, probability ranking according to SUCRA indicates that curcumin and honey have great potential in preventing OM until further studies are performed.

The outcome measurement of mucositis is fairly uniform with the Radiation Therapy Oncology Group, World Health Organization, National Cancer Institute, and OM Assessment Scale. These evaluation standards were the scales used in most of the studies included. These scales are fairly similar, all with grades 0 and 1 indicating tolerable or less severe mucositis and grades 2 to 4 indicating intolerable or severe mucositis. In consequence, to standardize the outcome indicators, the occurrence of OM was defined as a grade of >1. The benefit of using a standardized

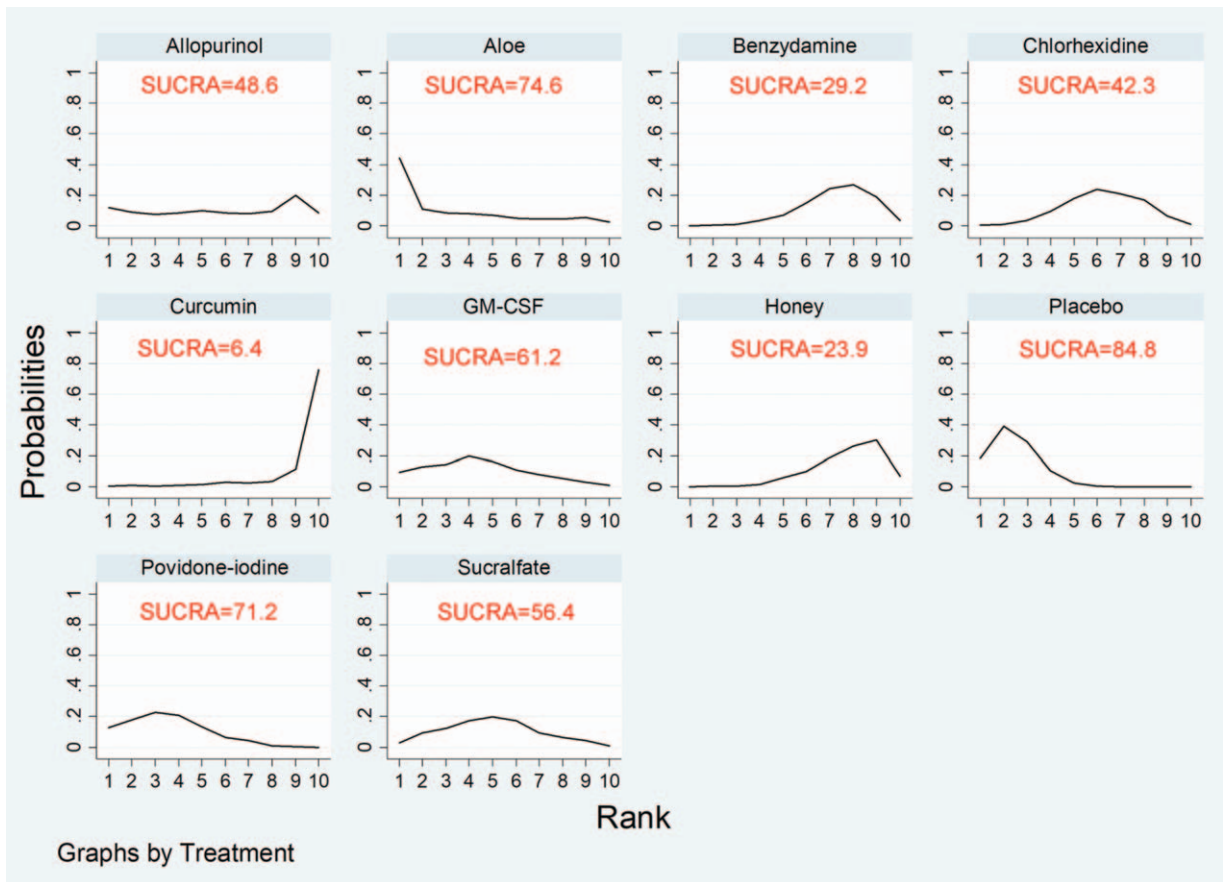


Figure 6. SUCRA probabilities of the different oral care solutions on prevention of oral mucositis. SUCRA = surface under the cumulative ranking.

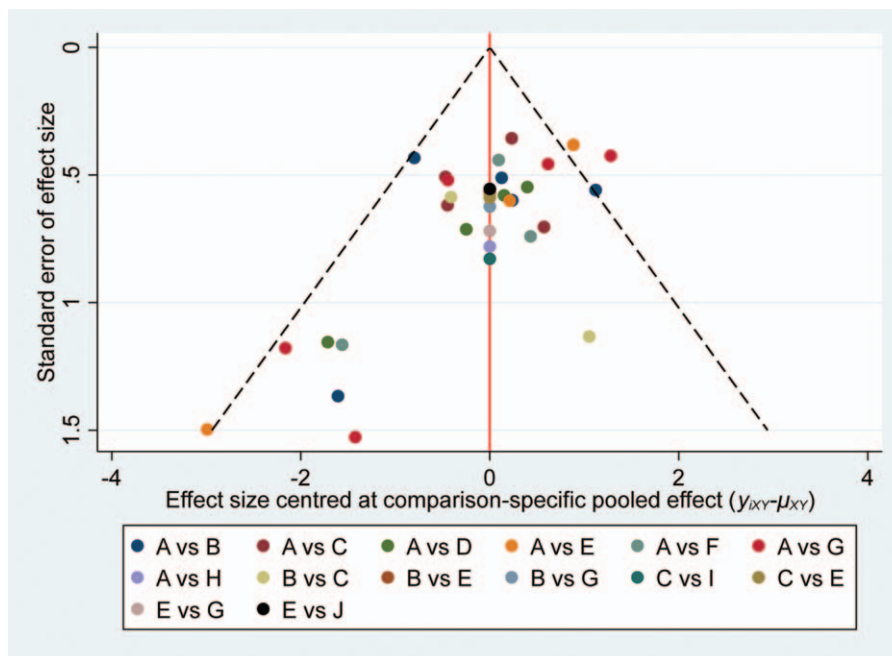


Figure 7. The comparison-adjusted funnel plot of multiple treatments for oral mucositis. A=Placebo, B=Chlorhexidine, C=Benzydamine, D=Sucralfate, E=Povidone-iodine, F=GM-CSF, G=Honey, H=Allopurinol, I=Aloe, J=Curcumin.

reporting system will facilitate better pooling of results from different studies.<sup>[64]</sup>

This network meta-analysis has several limitations. First, we focused on the occurrence of OM in patients with cancer and did not consider other outcomes, such as the severity of mucositis and side effects of different mouthwashes because these data were not available. Second, due to the lack of data to yield outcomes (such as incidence rate) in most trials included in our article, we could only extract the change according to various international groups (RTOG, WHO, NCI, and OMAS) to evaluate the effectiveness of various treatments. Third, some of the treatments, including curcumin, allopurinol, and aloe, were respectively covered by just 1 study, and the number of patients involved in some treatments was relatively small. In addition to the variety of agents, chemotherapy regimens may also affect the prognosis of patients while included in this network meta-analysis.

## 5. Conclusion

In summary, our preliminary results indicate that curcumin and honey may serve as the preferred options for patients to prevent OM. The findings may offer an important theoretical basis for clinical prevention and treatment. Hence, in the future, well-designed, high-quality, large-scale RCTs are necessary.

## Author contributions

**Conceptualization:** Ya-Ying Yu, Xin Zhou.

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**Supervision:** Zu Zhong Zhang.

**Validation:** Zu Zhong Zhang.

**Visualization:** Zu Zhong Zhang.

**Writing – original draft:** Ya-Ying Yu.

**Writing – review & editing:** Xin Zhou.

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