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The efficacy of benzydamine on cancer treatment-induced oral mucositis: A systematic review of randomised controlled trials

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ABSTRACT

Objectives: Mucositis is a well-known complication of oncological therapies, severely affecting the quality of life of patients. Benzydamine appears to be a promising option for the treatment of this condition, particularly in the management of oral mucositis. We can learn more about the potential use of benzydamine for oral mucositis by examining the available published research and what we know from clinical trials that have used this agent. This systematic review aims to evaluate the efficacy of benzydamine for the prevention and treatment of oral mucositis induced by cancer therapy through Randomized Controlled Trials.

Methods: A systematic literature review was performed across seven databases. After screening, this systematic review included nine articles that had been published between 2013 and 2023. The review was conducted in accordance with the Cochrane guidelines (2023). Bias risk is assessed using the Cochrane Collaboration Risk of Bias Assessment Tool. The studies differed in the number of participants, from 26 to 120, giving a total of 593 participants analyzed. The articles in the studies used Benzydamine, herbal formulation, sodium bicarbonate, povidone-iodine, and low-level laser.

Results: Results showed that benzydamine was effective to varying extents. Several studies provided statistically important improvements while others showed no statistically important variations.

Conclusions: This extensive literature review and clinical study offer insight into how benzydamine may work in the management of oral mucositis.

Keywords: Chemotherapy, radiotherapy, oral mucositis, benzydamine, systematic review

Cancer treatment, including chemotherapy (CT) and radiotherapy (RT), is often associated with a range of adverse effects that significantly impact patients' quality of life and adherence to treatment. These adverse effects include cardiotoxicity, nephrotoxicity, myelosuppression, neurotoxicity, hepatotoxicity, gastrointestinal toxicity, mucositis, and alopecia [1-3]. Gastrointestinal issues, including oral mucositis (OM), are particularly common and may lead to early discontinuation of treatment, affecting overall outcomes [4, 5]. OM causes the oral mucosa to become inflamed and ulcerated, which can be painful, make it hard to eat and talk, cause secondary infections, and raise the risk of systemic complications [6, 7]. If not effectively managed, severe OM can result in treatment delays, dose reductions, and even dis-

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continuation of cancer therapy, which may ultimately affect patient outcomes [8].

OM usually happens because CT and RT have direct cytotoxic effects on epithelial cells, which cause inflammation and damage to the tissue. The five steps in the pathophysiology of OM are starting the process, increasing inflammatory pathways, signal amplification, ulceration, and healing [9]. In particular, 40-75% of patients receiving CT or RT for head and neck cancers (HNC) develop OM, with incidence rates reaching 90% in patients receiving concurrent CT [10]. Standardized tools, like the World Health Organization Oral Toxicity Scale (WHO OTS) and the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) [11, 12], are often used to measure how bad OM is.

Researchers have explored various strategies for the prevention and management of OM due to its significant clinical impact. Topical pain killers, anti-inflammatory drugs, cryotherapy, photobiomodulation (also known as low-level laser therapy, or LLLT), and protective coatings are some of the current ways to treat the condition [13]. Despite these efforts, there is no universally accepted standard treatment for OM, and existing interventions provide only partial symptom relief. This highlights the necessity for innovative, evidence-based therapies to ensure efficient patient care [14].

An anti-inflammatory drug (NSAID), benzydamine hydrochloride (HCl), possesses pain-relieving, anti-inflammatory, and antimicrobial properties [15]. It may be an effective treatment for OM. Benzydamine takes effect by inhibiting the synthesis of pro-inflammatory cytokines (TNF-α, IL-1β) and altering prostaglandin biosynthesis. Then, it will hydrate the oral mucosa to help decrease oral pain and swelling [16]. Some medical groups, such as the Multinational Association of Supportive Care in Cancer (MASCC) and International Society of Oral Oncology (ISOO), recommend the use of benzydamine mouthwash for people receiving moderate-dose RT (≤50 Gray [Gy]) without concurrent CT [17]. However, its role when given as part of combination treatments is not clear and requires further exploration, ideally in Randomized Controlled Trials (RCTs).

This systematic review aims to critically appraise the effectiveness of benzydamine for the management of OM due to cancer treatment by pooling findings from RCTs. Organizing the existing evidence should help clarify what medicinal action benzydamine can provide and how it could feature in management plans of OM.

METHODS

This study followed Cochrane guidance (2023) and was registered in PROSPERO (International Prospective Register of Systematic Reviews) as CRD42023494747 [20].

Study Design

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. The specific research question was developed based on the PICO (Population, Intervention, Comparison, and Outcome) framework to guarantee both clarity and systematic ordering [19]:

(1) Population (P): Adult patients (≥ 18 years) undergoing CT and/or RT for cancer.

(2) Intervention (I): Mouth rinse with Benzydamine HCl, a NSAID, for OM management.

(3) Comparison (C): Control or comparative interventions, e.g., placebo (or) alternative such as herbal therapies, sodium bicarbonate, povidone-iodine, and LLLT.

(4) Outcome (O): Efficacy of benzydamine to reduce OM severity, duration, and impact on quality of life.

Guided by this framework, the main research question was: "Does benzydamine HCl reduce the severity and/or improve the management of OM in adult cancer patients undergoing CT and/or RT?

Search Strategy

This was followed by a systematic search of the literature using seven major databases, which included MEDLINE, PubMed, Science Direct, Scopus, Springer Link, Taylor & Francis, and Web of Science. The search was restricted to RCTs before 2023. The keywords and medical subject headings (MeSH) terms were as follows: “Oral mucositis,” “Benzydamine,” “Non-steroidal anti-inflammatory agents,” “Cancer treatment,” “Oncology treatment,” “Radiotherapy,” “Chemotherapy,” “Randomized controlled trials”

Two researchers (DG, ZY) independently screened all records for inclusion and resolved inconsistencies by consensus with a third reviewer (FT).

Eligibility Criteria

The eligibility criteria for this systematic review were determined using the PICO framework to develop a structured selection process. Eligibility criteria included RCTs that assessed the efficacy of benzydamine in treating OM in adult cancer patients. Studies had to compare benzydamine against placebo or other treatment and report quantifiable outcome measures, including OM severity, duration, pain levels, or quality of life. Furthermore, studies published in languages other than English or before 2012 were excluded to align with the goals of the study.

On the other hand, nonrandomized trials, retrospective analyses, case reports, and reviews were excluded, as these study designs do not provide sufficient evidence for this review. Studies that involved either animal models or OM not related to cancer were excluded, as we were primarily interested in understanding the potential role of benzydamine in cancer-related mucositis. Additionally, studies in languages other than English were excluded due to practical limitations of translation and interpretation.

Study Selection Process

Study selection was performed in three steps:

(1) Identification articles were obtained from seven databases according to the pre-specified search strategy.

(2) Screening: Titles and abstracts were screened for relevance by two independent reviewers (DG, ZY) after omitting duplicates.

(3) Screening, eligibility, and inclusion: All full-text articles were screened to determine eligibility, and the inclusion of articles was reached by consensus with a third reviewer (FT).

A PRISMA flow diagram illustrated the process of study selection, with the number of included/excluded studies at each stage of the process.

Data Extraction and Risk of Bias Assessment

(1) A standardized data extraction pro forma was used to obtain:

(2) Study details (author, year, country)

(3) Sample size and patient features.

(4) Intervention details (e.g., dosage, duration, route).

(5) Comparator interventions.

(6) Primary and secondary outcomes (OM severity, pain, quality of life).

(7) What statistical analysis was performed?

Bias risk assessment was conducted applying the Cochrane Collaboration Risk of Bias (RoB2) tool, which assesses bias in five domains:

(1) Randomization process

(2) Anomalies from planned interventions

(3) Missing outcome data

(4) Measurement of outcomes

(5) Selective reporting bias.

Each study was rated as low risk, some concerns, or high risk of bias. Bias was assessed independently by two reviewers (DG, ZY), and disagreements were resolved by FT.

Ethical Considerations

This systematic review was focused on previously published papers and did not involve any direct human or animal participants. Thus, ethical approval was not required.

Statistical Analysis

Qualitative synthesis was performed to summarize the study findings. Because of heterogeneity in study designs, interventions, and outcome measures, a meta-analysis was not conducted. Results were descriptively analyzed by evaluating the effect of benzydamine in comparison with control interventions.

RESULTS

Study Selection

The first database search yielded 1,564 articles from MEDLINE (n=22), PubMed (n=339), Science Direct (n=171), Scopus (n=619), Springer Link (n=228), Taylor & Francis (n=147), and Web of Science (n=38). The titles and abstracts of the remaining articles, after removing duplicates, were screened for relevancy. Fifteen studies were found eligible for full-text review; however, full texts could not be retrieved for 2 studies [21, 22]. After full-text evaluation, four further studies were excluded for inappropriate study design [23, 24], lack of randomization [15], or inclu-

sion of participants under 18 years of age [25]. As a result, this systematic review included nine RCTs published between 2013 and 2023. Study selection is demonstrated in the PRISMA flow diagram (Fig. 1).

Characteristics of Included Studies

The nine studies included had a total of 593 participants (ranging from 26 to 120 per study). Three studies were conducted in Iran, three in India, two in Thailand, and one in Egypt. The studies evaluated therapeutic interventions such as benzydamine, herbal formulations (turmeric, sumac-rose water, curcumin, aloe vera), sodium bicarbonate, povidone-iodine, and LLLT. There was variability in assessment tools, intervention duration, and primary outcomes between studies, limiting comparability (Table 1).

Interventional Methods and Study Findings

The studies included in the systematic review investigated various intervention strategies for OM in malignant tumors. Results: In one study from Iran (2023), 56 RT patients were randomized to receive either benzydamine 0.15% mouthwash or sumac-rose water spray, administered 4--8 times/day. High-grade

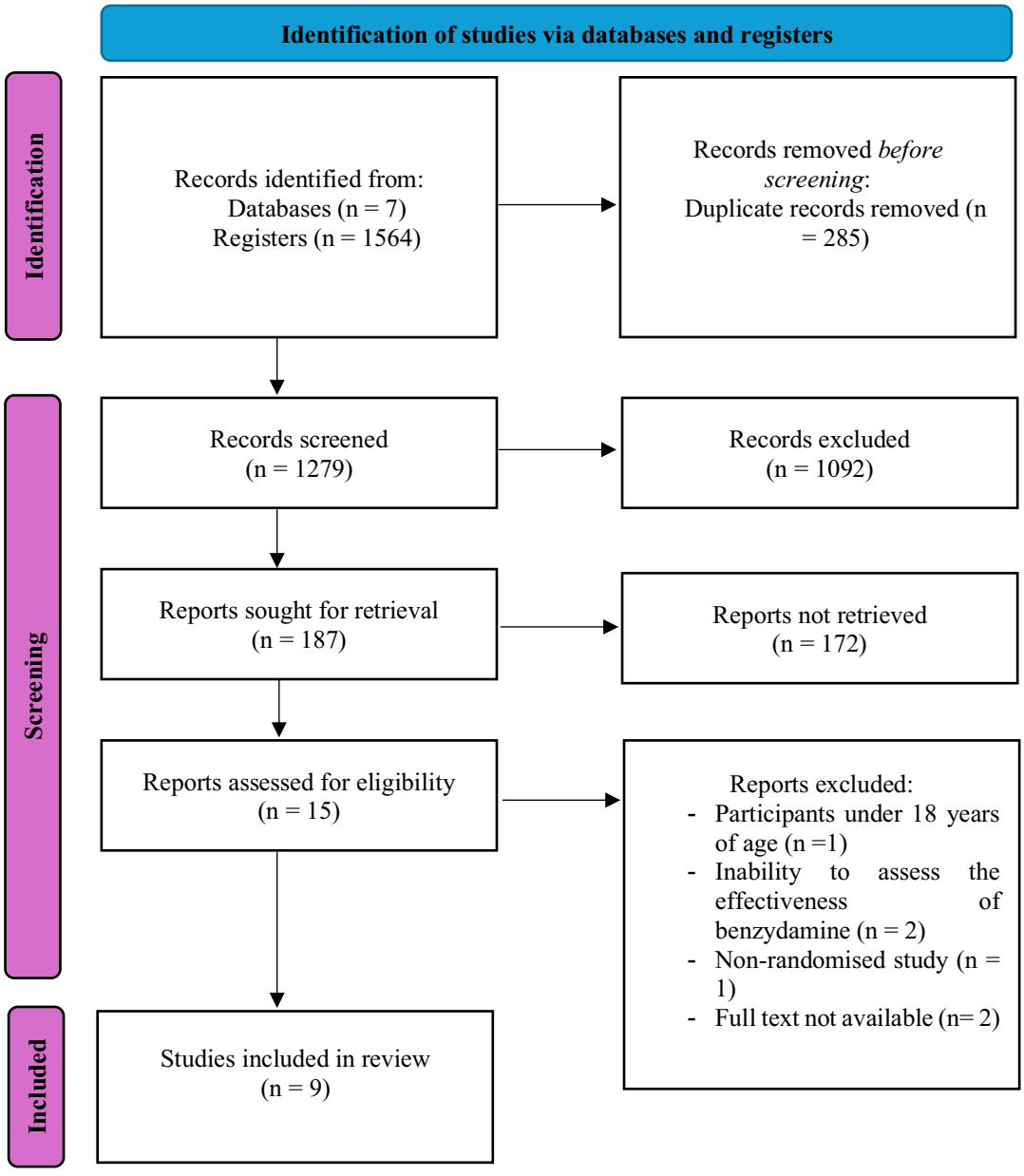

Fig. 1. PRISMA flow diagram for the studies.

Table 1. Characteristics of studies included

Author	Study design	Sample size	OM assessment tool and assessment period	Primary outcome measures	Secondary outcome measures	Administration	Intervention	Control	Type of cancer treatment	Results
Ameri et al. [26]	Phase II, triple-blind, RCT	HNC n=56	RTOG grading	OM occurrence, site and grade	OP grade	Rinse mouth with mouthwash 4 to 8 times a day, starting one day before treatment and continuing until one week after treatment has finished.	Sumac-rose water 30 ml spray bottle	Benzydamine 0.15%	Total RT dose of 50 Gy or more	The control group had more OM occurrence (P>0.05).
		-Sumak-rose group n=28	OP numerical rating scale		Quality of life				CT during RT in both groups	In the intervention group, the occurrence of OP (P=0.001) and high-grade OM (P<0.05) was delayed.
		-Benzydamine group n=28	EORTC QLQ All-H&N 35							At the fifth week of therapy and beyond, the control group had more high-grade OM, worse quality of life, and significantly higher proportions of involved subsites (P<0.05).
			Patients were evaluated on the first treatment day, then weekly and one week after the end of treatment.							The control group had a higher mean OP score during the whole therapy period. In the third week of therapy, this difference became statistically significant (P=0.01).
Chitapanarux et al. [27]	Multi-centre, RCT	Non-metastatic HNC n=60	OMAS	OM severity	Pain intensity	Rinsing with 15 ml of solution for two minutes four times a daily, starting before therapy and continuing until two weeks after the end of therapy	Benzydamine 0.15%	Sodium bicarbonate, two teaspoons of baking soda with one litre of water	At least 60 Gy platinum-based CT with RT	The median value of OMAS scores was found to be statistically significantly lower in the intervention group every week between the second and eighth weeks of treatment (P<0.01). During treatment and at follow-up, the two groups did not differ significantly in regard to the median value of pain scores (P>0.05).
		Benzydamine group n=30	Pain score (0-10)							
		Sodium bicarbonate group n=30	Patients were assessed before therapy, weekly during therapy, at the end of therapy and 4 weeks after therapy.							
Kannarunimit et al. [28]	Prospective RCT	HNC curatively treated with concurrent CT n=71	OMAS	OM grade		Rinsing the mouth for 30 seconds 4 times a day starting from the first day of therapy	Benzydamine	Povidone-iodine 0.1%	Radiation dose totalled 66-70 Gy	The intervention group presented more OM occurrence (P<0.05).
		Benzydamine group n=37	NCI-CTCAE version 5.0							The incidence of OM grade III-IV according to NCI-CTCAE version 5.0 was 51.4% in the intervention group and 26.5% in the control group during the assessment period (P<0.05). At the same mucositis grade, the highest incidence of OM according to this scale occurred at the 7th week of therapy (P=0.01).
		Povidone iodine group n=34	Patients were assessed once a week for 7 weeks and 4 weeks following completion of treatment.							
Mohamed et al. [29]	RCT	HNC treated or not treated with RT n=90	WHO OTS	OM severity	OP intensity	Rinsing the mouth with alcohol-free mouthwashes twice a day among the oral hygiene recommendations in the first group	Benzydamine	Oral care	Radiation dose is 70 Gy in total in 7 weeks, 5 days a week	According to WHO OTS, fewer OM scores were recorded in group 3 during the therapy period. While the difference between the groups was not significant at week 4 (P>0.05), highly significant differences were recorded at weeks 2 and 6 (P<0.001) and week 7 (P<0.005).
		In the first group, oral care n=30	NCI-CTCAE			In the second group, rinsing the mouth with 15 ml of benzydamine solution 4-8 times a day with 2 minutes until the end of treatment	LLLT		RT alone or in combination with CT	The third group showed lower NCI-CTCAE scores throughout therapy. The difference between the groups was highly significant at weeks 3, 4 and 5 (P<0.05) and weeks 2, 6 and 7 (P<0.001).
		In the second group, benzydamine 0.15% n=30	VAS			Laser irradiation three times a week during therapy to the third group				In the third group, pain scores were lower during therapy.
		In the third group, LLLT n=30	Patients were assessed before therapy and every week until the therapy was completed.							
Rastogi et al. [30]	Non-blinded, prospective, RCT	HNC n=120	WHO OTS	OM grade	-	Rinsing the inside of the mouth with 10 ml of mouthwash for at least 1 minute 4-6 times a day during treatment	SW+Benzydamine 0.15%	SW (half a tablespoon salt per 1 litre water)	Radiation dose ≥60 Gy	According to WHO OTS (p<0.05) and NCI-CTCAE version 4.0 (P<0.05), group A patients had more grade III OM than group B patients.
		SW+Benzydamine 0.15%:	NCI-CTCAE version 4.0							According to WHO OTS (p>0.05) and NCI-CTCAE version 4.0 (P>0.05), the degree of OM between groups C and D was not statistically significant.
		-Group B (RT) n=30	Patients were assessed weekly during therapy and up to 4 weeks after completion of therapy.							
		-Group D (CT) n=30								
		SW mouthwashes:								
		-Group A (RT) n=30								
		-Group C (CT) n=30								

Table 1 contunied. Characteristics of studies included

Author	Study design	Sample size	OM assessment tool and assessment period	Primary outcome measures	Secondary outcome measures	Administration	Intervention	Control	Type of cancer treatment	Results
Sahebjamee et al. [31]	Triple-blind, RCT	HNC n=26	WHO OTS	OM grade	-	Rinsing the mouth 3 times a daily with 5 ml of solution from the first day of treatment until the end of treatment	Aloe vera	Benzydamine 0.15%	RT dose of at least 50 Gy in a single fraction	Mucositis grade and changes in mucositis grade over time were not significantly different between the two groups (P>0.05).
		Aloe vera group n=13	Patients were assessed once before therapy, then once a week during the 6-week therapy period, totalling 8 times.							
		Benzydamine group n=13								
Shah et al. [32]	Parallel-arm, triple-blind RCT	HNC n=68	WHO OTS	OM prevention and severity	-	Rinsing the mouth three times a daily for six weeks with 10 ml of solution	Curcumin 0.1 %	Benzydamine 0.15%	Radiation dose 60-70 Gy	In the intervention group, the risk of immediate onset of OM was found to be 50% lower than in the control group and delayed the onset of mucositis by 2 weeks (p=0.001).
		Benzydamine group n=35	Patients were assessed until the end of the 6th week.							Both mouthwashes were equally effective in preventing the onset of severe forms of OM.
		Curcumin group n=33								
Sheibani et al. [17]	Double-blind, RCT	HNC n=51	OM degree scale (4-point scale)	OM severity	-	Rinsing the mouth with 15 ml of solution for 2 minutes 4-8 times a day for 2 weeks, starting from before therapy until 2 weeks after the end of therapy	Benzydamine 0.15%	Placebo	Radiation dose≥5000 cGy, 5 days per week	OM severity did not differ between the two groups until the end of the third week and after the study was completed (p>0.05).
		Benzydamine group n=26	Patients were assessed before therapy and weekly until 2 weeks after the completion of therapy.							At the end of the fourth week, the mean OM score of the control group was statistically higher than the intervention group (P=0.01).
		Placebo group n=25								
Thomas et al. [33]	RCT	HNC n=44	OHAT	Oral health status	Oral dysfunction	Rinsing the mouth with 10 ml solution 6 times a day during the therapy period	Turmeric	Benzydamine	Radiation dose 60 to 70 Gy for 6 to 7 weeks	The baseline OHAT scores between the two groups differed significantly (p>0.05).
		Turmeric group N=21	WHO OTS	OM grade						There were found differences significantly between the intervention and control groups in regard to the onset and severity of OM (p=0.001), oral health status (p=0.001) and oral dysfunctions (P=0.001).
		Benzydamine group n=23	Oral Mucositis Symptom (PROMS) scale							
			Xerostomia Short Form Inventory							
			Patients were assessed before treatment started and weekly up until the end of treatment.							

CT=chemotherapy, EORTC QLQ= European Organisation for Research and Treatment of Cancer Quality of Life Scale, Gy=gray, H&N=head and neck, HNC=head and neck cancer, LLLT= low-level laser therapy, NCI-CTCAE= National Cancer Institute's Common Terminology Criteria for Adverse Events, OHAT= Oral Health Assessment Tool, OM=oral mucositis, OMAS=Oral Mucositis Assessment Scale, OP=oral pain, PROMS= International Prospective Register of Systematic Reviews, RCT=randomized controlles trial, RT=radiotherapy, RTOG=Radiation Therapy Oncology Group, SW=saline water,VAS= Visual Analogue Scale, WHO OTS= World Health Organization Oral Toxicity Scale

OM was statistically significantly more frequent in the benzydamine group, while sumac-rose water significantly delayed the onset of OM and improved quality of life (P<0.05) [26]. An older trial from Thailand (2018) evaluated the use of benzydamine 0.15% mouthwash compared to sodium bicarbonate solution in 60 chemoradiotherapy patients. Benzydamine was found to be effective in reducing OM severity and decreasing the need for antifungal medication (P<0.01) [27]. Benzydamine 0.15%, in comparison to a mask scheme (povidone-iodine 0.1%, four times daily), was applied in another research done in Thailand (2023) with 71 HNC patients and RT. In addition, the povidone-iodine group was more effective in preventing severe OM (grade III-IV) (P<0.05) [28].

A study conducted in Egypt (2022) assessed the comparative effectiveness of benzydamine mouthwash (administered 4-8 times daily) and LLLT (administered three times weekly) in 90 patients undergoing RT, with or without CT. The findings indicated that LLLT provided superior efficacy in reducing OM severity and pain levels (P<0.001) [29]. Another study from India (2017) included 120 patients receiving ≥60 Gy RT, randomized to either benzydamine plus saline or saline alone, administered 4-6 times daily. The results showed that benzydamine significantly reduced the incidence of grade III OM (P<0.05) [30]. In a trial conducted in Iran (2015), 26 HNC patients receiving RT were randomized to receive either benzydamine 0.15% or aloe vera mouthwash, used three times daily. The results indicated no significant difference in OM severity between the two groups (P>0.05) [31].

An Indian study (2020) compared benzydamine 0.15% with curcumin mouthwash administered three times daily in 68 patients on RT. The results showed that curcumin is more potent in delaying the onset of OM and for reducing severity (P<0.001) [32]. Another RCT was published by Prasad *et al*. [17] (2015) in India and looked at benzydamine 0.15% versus placebo mouthwash in 51 patients receiving RT. Result: Significant delay to the onset of severe OM with benzydamine use (P=0.01) [17]. Finally, one study from India (2023) compared benzydamine 0.15% vs. turmeric mouthwash in 44 patients receiving RT. Results suggested that turmeric showed more efficacy as compared to placebo

Article	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the autcome	Bias in selection of the reported result	Overall risk of bias
Ameri et al. 2023	?	?	?	+	+	?
Chitapanarux et al.2018	+	−	+	+	+	+
Kannarunimit et al. 2023	+	−	+	+	+	+
Mohamed et al. 2022	+	?	+	+	+	+
Rastogi et al. 2017	+	?	+	+	+	+
Sahebjamee et al. 2015	+	?	+	+	+	+
Shah et al. 2021	+	−	−	+	+	?
Sheibani et al. 2015	+	?	?	−	+	?
Thomas et al. 2023	+	?	+	+	+	+

Judgement: + : Low, ? : Some concerns, − : High

Fig. 2. Results from RoB 2 bias analysis of RCTs.

in decreasing the overall severity of OM and improving oral health in patients (P=0.001) [33].

Measurement Tools Used and Effectiveness of the Application

The included studies of this systematic review used a variety of standardized assessment tools to assess OM severity, pain, and quality of life. Of the instruments used to assess grading, WHO OTS was employed in five studies [17, 26-28, 30] and NCI-CTCAE versions 4.0 & 5.0 were used in four studies [28, 29, 31, 32]. Two studies utilized the Oral Mucositis Assessment Scale (OMAS) [29, 31] and one study used the Radiation Therapy Oncology Group (RTOG) Scale [33]. Moreover, two studies contained the Visual Analogue Scale (VAS) for pain [27, 32] and one paper contained the European Organisation for Research and Treatment of Cancer Quality of Life Scale (EORTC QLQ-H&N35) [29]. One study performed an assessment using the Oral Health Assessment Tool (OHAT) [33]. The diversity in measurement tools underscores variations in study methodology, which may account for differences in reported outcomes.

Effectiveness of Benzydamine

Benzydamine had variable efficacy on OM in different studies. In two studies, the authors showed that benzydamine was effective for OM, reducing OM severity and delaying the onset of severe OM [17, 27]. However, five of them found that benzydamine did not have statistically significant advantages over different drugs, including sumac-rose water, povidone-iodine, LLLT, turmeric, or curcumin [26, 28, 29, 32, 32]. Benzydamine was as effective as other interventions, including aloe vera and saline mouthwash, in two further studies with no difference in outcomes [30, 31]. These observations imply that whilst benzydamine underlines some potential advantages, its efficacy remains heterogeneous and is likely influenced by treatment regimen, patient demographics, and assessment criteria.

Risk of Bias in Included Studies

We used the RoB 2 tool to evaluate the risk of bias among the nine included studies (Fig. 2). When bias across studies was assessed, six studies were judged to have a low risk of bias [27-31, 33] and three with a moderate risk of bias [17, 26, 32]. The randomization process was appropriate in eight studies, and the risk of bias was low. In one study, the lack of stratified randomization was identified as a potential effect modifier of the study outcome [26]. These include bias in most of the studies due to methodological issues that were experienced in the course of conducting the studies themselves [17, 26, 29-31, 33]. Three studies tested other interventions with a potential impact on the development of OM, which increases the risk of deviation from the interventions received as planned [27, 28, 32]. One study was judged to have a high risk of bias concerning missing outcome data because of lost to follow-up or exclusion from the planned analysis [32]. One additional study did not provide information on the validity and reliability of the OM rating scale applied, which raises concerns regarding measurement bias [17]. In contrast, the overall risk of bias due to selective reporting was low for all included studies, suggesting that the outcome measures reported were in accordance with study protocols.

DISCUSSION

This systematic review includes data from several studies assessing the potential efficacy of benzydamine in the management of OM caused by RT or CT during HNC therapy. In related studies, benzydamine was compared with different substances such as sumac-rose water, curcumin, turmeric, aloe vera, sodium bicarbonate solution, povidone-iodine, and LLLT, and its effects on the OM severity, pain, quality of life, and other associated factors were analyzed. Sumac-rose mixture use was associated with lower grade OM and better quality of life than benzydamine [26]. Curcumin reduced the risk of OM onset and delayed it compared to benzydamine [32]. Compared with benzydamine, turmeric mouthwash is more effective in decreasing OM severity [33]. Aloe vera mouthwash and benzydamine mouthwash were found to have similar effects in OM management [31]. This may suggest that natural mixtures may be effective in OM management beyond benzydamine. The findings suggest that while benzydamine is a relatively effective agent in the management of OM, some alternative interventions may also achieve similar or marked results. Although benzydamine is recognized as a standard, alternative methods can be used when the

individual circumstances and preferences of patients are taken into account.

Recent systematic reviews and meta-analyses have also evaluated the role of benzydamine in managing OM. A 2021 systematic review by Nicolatou-Galitis *et al*. found that benzydamine is effective in reducing the severity and delaying the onset of OM, particularly in patients receiving moderate-dose RT [15]. Another meta-analysis by Peng *et al*. (2022) comparing various OM interventions identified LLLT and benzydamine as two of the most effective options in OM prevention and treatment [8]. However, discrepancies among individual studies have raised concerns about the consistency of benzydamine's efficacy, particularly in combination treatment protocols.

LLLT has been demonstrated to be effective in reducing OM severity compared with benzydamine [29]. This shows that the alternative therapy method may be effective in achieving better results than benzydamine. Povidone-iodine was associated with less radiation therapy-induced OM compared to benzydamine, and povidone-iodine was generally more effective in the last week of CT therapy [28]. When compared with benzydamine sodium bicarbonate solution, benzydamine was reported to be more effective in decreasing the OM severity and also reduced the need for oral antifungal medication [27]. These findings align with previous meta-analyses that suggest benzydamine may be beneficial as part of a broader OM management strategy, but its standalone efficacy remains variable [15, 16].

In the included studies, it may be difficult to make a direct generalization about the duration of benzydamine application. Because each study seems to have used different protocols and application periods. Comparing the results between these different application periods will be important in determining which method is more effective. The period of benzydamine application was continued throughout cancer treatment in six studies, while in three studies it started before cancer treatment and continued for some time after therapy ended. Benzydamine has been found to be effective in the mouthwash protocol applied starting before cancer treatment and continuing for a while after therapy [17, 27]. However, further research is needed to determine the optimal timing and duration of benzydamine administration. In addition, meta-analyses recommend at least 3 to 8 rinses per day, but the effect of frequency on efficacy remains unclear [15]. In the included studies, it can be stated that the number of daily applications was not considered as a determining factor in benzydamine efficacy. For example, one of the two studies in which benzidamine was administered 4-8 times a day showed the positive effect of benzidamine on OM [17], while the other failed to show the effectiveness of benzidamine [26]. However, further research is needed to set a definitive standard in this regard. In addition, the individual condition and tolerance of patients may also influence differences in the period of application. In general, studies show that regular use of benzydamine over a period of time is relatively efficient in reducing OM severity.

In the included studies, the measurements used to assess the efficacy of benzydamine were performed through a variety of scales and assessment tools. These measurement tools include scales such as RTOG, numerical pain assessment scale, EORTC QLQ All-H&N 35, OMAS, OP score, NCI-CTCAE Version 4.0 and 5.0, WHO OTS, OHAT, and VAS. These measurement tools allow assessment in different areas such as OM severity, OP, quality of life, and oral health. The use of these measurement tools plays an important role in the interpretation of the results. However, the use of different measurement tools in studies and inconsistency in reaching similar results may make it difficult to reach a definite conclusion about the effectiveness of benzydamine. When the results of the studies were analyzed, it was reported that benzydamine was effective in two studies, it was not effective in five studies, and there was no significant difference in two studies. This difference may be due to the measurement tools used. In addition, factors such as sensitivity and reliability in the measurement tools used may also cause differences in results. In two included studies, OMAS was used to assess the efficacy of benzydamine. However, there are conflicting findings regarding OMAS results among studies. For example, one study reported a positive effect of benzidamine on OMAS scores [27], while the other failed to demonstrate the effectiveness of benzidamine [28]. In conclusion, it was noted that there is diversity among studies assessing the efficacy of benzydamine in terms of the measurement tools used, population characteristics, and therapy protocols. This diversity should be taken into account to understand and compare the results on the efficacy of benzydamine. Researchers may

endeavor to obtain more precise results by using standardized measurement tools in future studies.

The risk of bias was analyzed in nine included studies. According to the findings, the risk of bias due to the randomisation process was found to be low in most of the assessed studies, indicating that the groups in the studies were balanced at baseline. In particular, it is important to note that three studies were considered at high risk of deviating from the intended interventions due to the inclusion of additional interventions. This means that the results of the study may be influenced by other factors and that there may be difficulties in fully assessing the efficacy of benzydamine. One study found an increased risk of missing outcome data due to patients being lost to follow-up and excluded from the analysis. This may affect the results of the studies and reduce the generalizability of the results. In one study, the validity and reliability of the OM rating scale were not reported, and therefore the bias risk in the measurement of the outcome was considered high. This may call into doubt the reliability of the results obtained.

CONCLUSION

This systematic review evaluated the effectiveness of benzydamine in managing OM induced by cancer treatment, particularly RT and CT. The findings from nine RCTs demonstrated inconsistent results regarding its efficacy. While some studies reported that benzydamine could reduce the severity of OM and delay its onset, others found no statistically significant advantage over alternative interventions such as povidone-iodine, sumac-rose water, LLLT, turmeric, and curcumin-based mouthwashes.

The variability in study methodologies, intervention protocols, and outcome assessment tools likely contributed to these inconsistent findings. Some studies initiated benzydamine prophylactically before cancer treatment, while others applied it only during therapy. Furthermore, the frequency of mouth rinses per day and duration of treatment differed across studies, influencing the reported outcomes. The measurement tools used to assess OM severity and pain levels also varied, leading to potential differences in reported efficacy.

Despite these discrepancies, benzydamine remains a widely used and recommended agent, particularly for patients undergoing moderate-dose RT without concurrent CT. However, the findings suggest that alternative treatments may offer similar or superior benefits in certain clinical settings. Future large-scale, well-designed RCTs with standardized treatment protocols and uniform assessment tools are needed to establish the definitive role of benzydamine in OM management.

Ethical Statement

This systematic review was focused on previously published papers and did not involve any direct human or animal participants. Thus, ethical approval was not required.

Authors' Contribution

Study Conception: DG, ZY, FT; Study Design: DG, ZY; Supervision: FT; Funding: N/A; Materials: DG; Data Collection and/or Processing: DG, ZY; Statistical Analysis and/or Data Interpretation: DG, ZY; Literature Review: DG, ZY; Manuscript Preparation: DG, ZY, FT and Critical Review: DG, ZY, FT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Editor's note

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