Check for updates

OPEN ACCESS

EDITED BY Eric Gumpricht, Independent Researcher, Gilbert, AZ, United States

REVIEWED BY Seyed Ali Arab, Guilan University of Medical Sciences, Iran Minati Choudhury, International Medical University, Malaysia

*CORRESPONDENCE

Ana Maria Soares Pereira, ⊠ apereira@unaerp.br

⁺These authors have contributed equally to this work

RECEIVED 14 January 2025 ACCEPTED 24 March 2025 PUBLISHED 02 April 2025

CITATION

Amatto PdPG, Chaves L, França SdC, Carvalho JCT, Carmona F and Pereira AMS (2025) Efficacy of different pharmaceutical forms of *Curcuma longa* or curcumin in reducing oral mucositis severity and incidence in cancer patients: a systematic review and meta-analysis. *Front. Pharmacol.* 16:1560729. doi: 10.3389/fphar.2025.1560729

COPYRIGHT

© 2025 Amatto, Chaves, França, Carvalho, Carmona and Pereira. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms. Efficacy of different pharmaceutical forms of *Curcuma longa* or curcumin in reducing oral mucositis severity and incidence in cancer patients: a systematic review and meta-analysis

Pedro de Padua G. Amatto ⁽¹⁾, Lucas Chaves ⁽²⁾², Suzelei de Castro França ⁽²⁾¹, José Carlos Tavares Carvalho ⁽³⁾, Fabio Carmona ⁽²⁾^{2†} and Ana Maria Soares Pereira ⁽³⁾^{1,4}*[‡]

¹Department of Biotechnology in Medicinal Plants, University of Ribeirão Preto, Ribeirão Preto, São Paulo, Brazil, ²Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, São Paulo, Brazil, ³Department of Biological and Health Sciences, Federal University of Amapá, Macapá, Amapá, Brazil, ⁴Botanical Garden of Medicinal Plants Ordem e Progresso, Jardinópolis, Brazil

Background: *Curcuma longa* L. (turmeric, Zingiberaceae) has been traditionally used for its anti-inflammatory, wound-healing, and antimicrobial properties. These characteristics have made it a key component in managing inflammatory and ulcerative conditions like oral mucositis (OM). This study aimed to evaluate the effectiveness of various pharmaceutical formulations of *C. longa* or curcumin in reducing the OM severity, incidence and associated pain in patients undergoing chemotherapy and/or radiotherapy for cancer.

Methods: This systematic review and meta-analysis of randomized clinical trials was conducted according to PRISMA guidelines, registered in PROSPERO (#CRD42024504111). Searches were performed in PubMed, Embase, and Cochrane databases. Studies comparing *C. longa* or curcumin with placebo in cancer patients experiencing oral mucositis, reporting outcomes such as the World Health Organization Oral Mucositis Grading Scale, pain scores (visual analogue scale), or OM incidence were included. Risk ratios and weighted mean differences with 95% confidence intervals were calculated using fixed-or random-effects models.

Results: Six studies with 159 patients (mean age ~50 years, 40% women) were included. *C. longa* extracts, curcumin, or nanocurcumin were administered in capsules, mouthwash, or gel formulations. The pooled analysis showed significant reductions in WHO scores and oral pain compared to placebo. OM incidence decreased by 6% overall, with a notable 37%-reduction observed in patients using curcumin-containing mouthwash during radiotherapy alone. Subgroup analyses revealed consistent benefits across all oncological treatments.

Conclusion: *C. longa*, curcumin, or nanocurcumin in various formulations, effectively reduce OM severity and pain while curcumin-containing mouthwash reduced OM incidence in cancer patients undergoing treatment.

Systematic Review Registration: identifier CRD 42024504111.

KEYWORDS

turmeric, anti-inflammatory agents, chemotherapy-induced mucositis, radiotherapy side effects, herbal medicine

Highlights

- *Curcuma longa* L. (turmeric) is used to treat skin and mucosal ailments.
- *C. longa* extracts decreased oral mucositis severity and pain in cancer patients.
- Mouthwash with curcumin decreased oral mucositis incidence of during radiotherapy.
- Benefits observed across chemotherapy, radiotherapy, and combined treatment modalities.
- Anti-inflammatory and wound-healing properties of *C. longa* contribute to its efficacy.

1 Introduction

Chemotherapy (CHT) and radiotherapy (RT) for cancer are frequently associated with significant adverse toxic effects. Among these, oral mucositis (OM) is one of the most prevalent and debilitating, affecting approximately 90% of patients undergoing such treatments (Sroussi et al., 2017; Villa and Sonis, 2016). OM is an acute inflammatory response characterized by ulceration of the mucosal and submucosal layers of the oral epithelium, leading to symptoms that range from localized pain to systemic complications such as anorexia, dehydration, and dysphagia (Lalla et al., 2019). The inflammatory and ulcerative nature of OM impacts the quality of life and increases the risk of secondary infections such as bacteremia (Facchini et al., 2012; Gamis et al., 2000; Kim et al., 2012; Lee and Galloway, 2022).

While multiple management strategies have been proposed, the burden of OM underscores the urgent need for effective interventions to prevent and treat it. Current treatments for OM, such as cryotherapy, benzydamine mouthwash, and palifermin, show varying degrees of efficacy but are associated with side effects or high costs. *Curcuma longa* (turmeric), a member of the Zingiberaceae family, provides a promising alternative due to its well-documented antiinflammatory and wound-healing properties, as well as its favorable safety profile. Several studies suggest that its bioactive compounds can modulate inflammatory cytokines and accelerate mucosal regeneration, making it a viable complementary approach for OM management (Arun et al., 2020; Khafif et al., 2009; van't Land et al., 2004; Zlotogorski et al., 2013).

In fact, systematic reviews and meta-analyses have shown that *C*. *longa* and/or curcumin decrease OM incidence and severity,

(Dipalma et al., 2024; Wu et al., 2024; Zhang et al., 2021), but the routes, pharmaceutical forms, and dosages varied considerably. Understanding the effects of various pharmaceutical forms of *C. longa* and curcumin on the incidence and progression of OM is critical.

To address this gap, we conducted a systematic review and meta-analysis to compare the efficacy of different pharmaceutical forms of *C. longa* or curcumin in reducing the incidence and severity of OM in patients undergoing cancer treatment.

2 Methods

This article was based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines (Page et al., 2021). A protocol was registered on the PROSPERO platform (CRD 42024504111).

2.1 Inclusion and exclusion criteria

This systematic review included only randomized clinical trials (RCTs) comparing C. longa with placebo in patients with OM during CHT or RT and which reported: at least one among these outcomes: (a) the World Health Organization (WHO) Oral Mucositis Grading Scale (Sonis et al., 1999), (b) a pain score (visual analogue scale), or (c) the incidence of OM; and well-defined C. longa- or curcumin-containing systemic or topical pharmaceutical forms (solutions, mouthwashes, tinctures, capsules, gels, creams and others). These formulations may differ in bioavailability, application convenience, and effectiveness in reducing OM severity and pain. Studies without a control group, which studied mixtures of medicinal plants, which did not report the outcomes of interest, and which studied patients without cancer, were excluded. Preclinical studies, case reports, observational studies, and articles not written in English were also excluded.

2.2 Source of information and search strategy

Only articles published before 19 December 2023, were searched in the following databases: PubMed, Embase, and Cochrane. The initial publication date was not limited. The query search used in this study was constructed using the PICOTS (population, intervention, comparison, outcome, time, and study type) method and is presented in Box 1.

BOX 1 | Simplified search query used in PubMed, Embase and Scopus databases. I("mucositis" OR "cancer" OR "stomatitis" OR "chemotherapy" OR

"radiotherapy") AND ("curcumin" OR "curcuminoids" OR "curcum longa" OR "turmeric" OR "curcumin" OR "curcuminoids") AND ("placebo")].

2.3 Article selection

Two independent and initially blind reviewers (PA and LC) conducted the screening of articles by reading titles and abstracts. The PICOTS acronym guided this step: Patients receiving CHT or RT with OM (P), who used *C. longa* or curcumin (I), compared with placebo (C), for at least 3 weeks of treatment (T), with assessments of the WHO scale, pain, or incidence (O), in RCTs (S). The entire process used the Rayyan software (Ouzzani et al., 2016). Then, the blinding was revealed, and the reviewers resolved any disagreements.

2.4 Data collection

The articles selected to be read in full were randomly assigned to either of the two reviewers (PG and LC). The retrieved data were recorded in a Google Sheets spreadsheet (Alphabet Inc., Mountain View, CA, United States).

2.5 Quality assessment

This stage was conducted by FC, who assessed the risk of bias and quality of each study using the Cochrane Risk of Bias 2 tool (RoB 2, The Cochrane Collaboration, Copenhagen, Denmark).

2.6 Statistical analysis

Binary endpoints were summarized using the Mantel-Haenszel (MH) fixed-effects model, reporting risk ratios (RR) and 95% confidence intervals (CI). Treatment effects for continuous outcomes were summarized using mean differences (MD) and standard deviations (SD) retrieved from all trials. When not reported, they were estimated. MDs were calculated by subtracting the post-treatment mean from the baseline mean. SDs were estimated as follows: (a) from SE by the formula SD = SE × \sqrt{n} , where n is the number of patients; (b) from CI, calculating the range between the lower and upper limits, then dividing it by (SD = (95% CI_{upper} – 95% CI_{lower}) ÷ 3.92); or (c) from p-values, obtaining corresponding t values from a t distribution table, then calculating SE by dividing MD by the t value (SE = MD ÷ t), then proceeding as above. The tool by Amy Drahota and Elaine Bellor, based on the calculations provided

in the Cochrane Handbook, was used to aid the process (Higgins et al., 2022). GraphPad Prism version 8.0.0 statistical software (GraphPad, LaJolla, CA, United States) was used to calculate MD and SE in cases where only weekly patient data were provided. Standardized mean differences (SMD) were used to analyze outcomes reported in different units. Review Manager 5.4 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis. Heterogeneity was assessed with the Cochran Q test and I² statistics; p-values < 0.10 and I² > 50% were considered significant for heterogeneity. Fixed-effects models were used for endpoints with I² \leq 50% (low heterogeneity), while random-effects models were used for outcomes with I² > 50% (high heterogeneity). A sensitivity analysis was done for each outcome, seeking to assess the impact of individual studies on the overall result of each endpoint.

3 Results

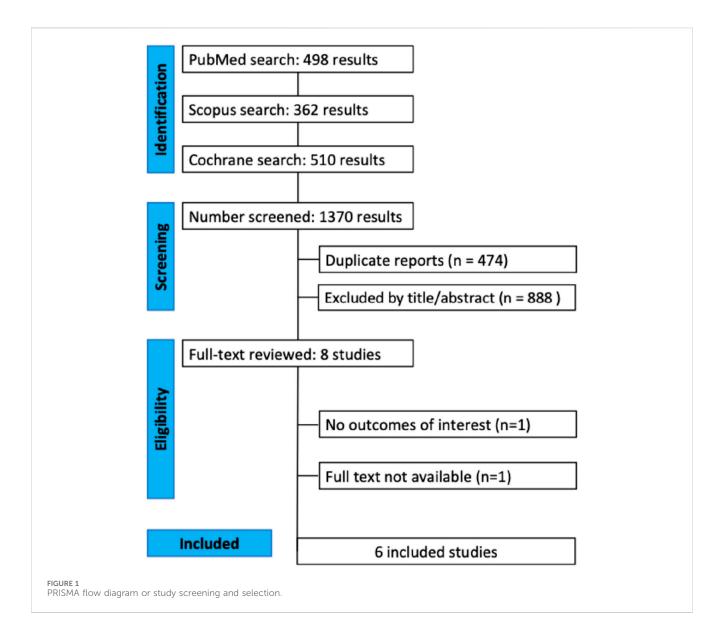
3.1 Study selection and characteristics

The initial search yielded 1,370 articles. After removing duplicates and articles that were not of interest, eight (0.58% of the total) articles remained for full reading (Figure 1). One was excluded because the full text could not be obtained. Finally, six studies were included in the meta-analysis. All included studies had a 3- to 8-week follow-up time. C. longa or curcumin were used in four different pharmaceutical forms: (a) capsules containing SinaCurcumin® (nano-micelles containing curcumin with the ability to disperse and dissolve in water) 40 or 80 mg/day (orally), (b) capsules containing BCM-95[®] (purified extract containing 95% curcuminoids plus the essential oil, DER 25:1) 1.0 or 1.5 g/day (orally), (c) a mouthwash containing 0.1% (w/v) curcumin (topically), and (d) a gel containing 0.5% crude dried hydroethanolic extract of C. longa roots (topically). Most patients had head and neck cancer (mainly oral cancer), while some others had rectal cancer and other types. The included articles had 159 patients, of which 60 (40%) were women. Their mean age was around 50 years. The lowest radiation dose absorbed was 50 Gy, and the CHT scheme used was cisplatin alone or associated with 5-fluorouracil. Most studies had a two-arm study design, and all were placebo-controlled (Table 1).

3.2 Pooled analysis of all studies

3.2.1 WHO scale

Five studies compared 136 participants who received intervention with 136 who received placebo. The pooled result indicated that the WHO scale was significantly lower in patients receiving the interventions (WMD: -0.60%, 95% CI: -0.74, -0.45, p < 0.00001, Figure 2). All three formulations reduced the outcome (Delavarian et al., 2019, Soni et al., 2021, Kia et al., 2021, Ramezani et al., 2023, Arun et al., 2020). There was no significant heterogeneity (p = 0.28, I² = 20%). Although the effect size for the mouthwash appears to be stronger, the subgroups did not differ significantly. Subgroup analysis according to the cancer treatment demonstrated that the intervention was equally effective in all three subgroups (WMD: -0.63, 95% CI: -0.76, -0.49, p < 0.00001, Figure 3), and there was no significant heterogeneity (p = 0.21, I² = 27%).



3.2.2 Pain

Oral pain was assessed in five studies (90 participants who received *C. longa* or curcumin and 89 participants who used placebo) and was significantly lower in patients receiving the interventions (WMD: -0.81, 95% CI: -1.17, -0.45, p < 0.00001, Figure 4), and the three formulations equally decreased the outcome. There was no significant heterogeneity (p = 0.99, I² = 0%). Subgroup analysis according to the cancer treatment demonstrated that the intervention was effective in all three subgroups (WMD: -0.96, 95% CI: -1.35, -0.58, p < 0.00001, Figure 5), but the effect was more prominent in the subgroup of patients undergoing CHT who received the SinaCurcumin[®] (WMD: -1.93, 95% CI: -2.73, -1.14, p < 0.00001). There was no significant heterogeneity (p = 0.21, I² = 31%).

3.2.3 Incidence

The incidence of OM was compared in 155 individuals who received *C. longa* or curcumin with 154 who received a placebo. The pooled analysis showed a 6%-reduction in OM incidence (RR

0.94, 95% CI: 0.90, 0.99, p = 0.03, Figure 6). The heterogeneity was not significant (p = 0.13, $I^2 = 37\%$), but the pooled result was driven mainly by one study, where the mouthwash containing curcumin led to a 37%-reduction in OM incidence (RR 0.63, 95% CI: 0.41, 0.98, p = 0.04) when compared to placebo, while the others were not statistically significant. In the subgroup analysis by cancer treatment, only patients undergoing RT and who received the mouthwash containing curcumin experienced an 37%-reduction in OM incidence compared to the placebo (RR 0.63, 95% CI: 0.41, 0.98, Figure 7), and this drove the pooled analysis, despite the low heterogeneity (p = 0.25, $I^2 = 22\%$).

3.3 Sensitivity analysis

For the WHO scale and pain outcomes, removing individual studies did not change the results. However, the positive result with the OM incidence outcome was driven mainly by the study by Ramezani et al., 2023, especially the group using mouthwash

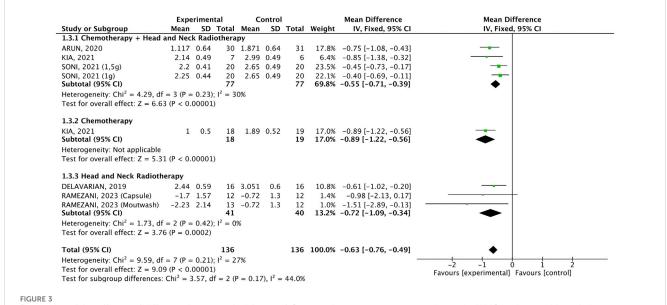
TABLE 1 Baseline characteristics of included studies.

Study	Design	Intervention	Follow- up	Patients IN/CON	Females	Mean age (years)	Treatment	Inclusion criteria	Outcomes	Main finding
Mansourian et al. (2015)	Double- arm RCT	Gel containing 0.5% crude dried hydroethanolic extract of <i>C. longa</i> roots	8 weeks	19/18	15/16	47/55	RT (minimum radiation dose of 50 Gy)	Adults with HNC, minimally 50% of patient's oral cavity in radiation field	WHO scale, pain, and incidence	Reduced OM severity and size o oral lesions
		Route: topical								
	Double- arm RCT	Curcumin (nanocurcumin) 80 mg/day	6 weeks	15/14	7/6	62/56	RT (minimum radiation dose of 50 Gy)	Adults with HNC, minimally 50% of patient's oral cavity in radiation field	WHO scale, and incidence	Reduced OM incidence and severity
		Route: oral								
	Double- arm RCT	<i>C. longa</i> extract (BCM-95 [*] , 95% curcuminoids, DER 25: 1) 1.5 g/day	8 weeks	30/31	15/18	n/r (30–80)) Post-operative RT or CHT+RT, or concurrent CHT [RT: Cobalt 60 (66 Gy); CHT: cisplatin (50 mg/m ²)]	Adults with advanced HNC (only squamous cell carcinoma)	WHO scale, and incidence	Reduced OM incidence and severity
		Route: oral	-							
Kia (2021)	Double- arm RCT	Curcumin (nanocurcumin) 80 mg/day	7 weeks	25/25	10/12	n/r (~56)	RT+CHT or CHT [RT: 60–70 Gy; CHT: cisplatin 30–50 mg plus 5-fluorouracil 640–750 mg]	Adults with HNC before starting CHT+RT or with other cancer types before starting CHT alone.	WHO scale, pain, and incidence	Reduced OM incidence and severity
		Route: oral								
Soni (2021)	Triple- arm RCT	<i>C. longa</i> extract (BCM-95 [*] , 95% curcuminoids, DER 25: 1) 1.0 or 1.5 g/day	6 weeks	20/20/20	1/2/2	40/46/45	RT+CHT [RT: 60 Gy; CHT: cisplatin 40 mg/m ²]	Adults after radical surgery for oral carcinoma from any primary site, with no prior history of RT to the head-neck Region	WHO scale, pain, and incidence	Reduced OM incidence and severity
		Route: oral								
Ramezani et al. (2023)	Triple- arm RCT	1) Mouthwash containing 0.1% w/v curcumin	3 weeks	13/12/12	5/5/4	52/56/52	RT [RT: minimum 60 Gy)	Adults with mild to moderate radiation-induced OM (grade 1–3)	WHO scale, pain, and incidence	Reduced OM incidence and severity with the two treatments
		Route: topical								
		2) Curcumin (nanocurcumin) 40 mg/day								
		Route: oral								

	Expe	rimen	tal	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.5.1 SinaCurcumin®									
DELAVARIAN, 2019 (80mg/day)	2.44	0.59	16	3.051	0.6	16	11.8%	-0.61 [-1.02, -0.20]	
KIA, 2021 (160mg/day)	1.36	0.63	25	2.187	0.64	25	16.2%	-0.83 [-1.18, -0.47]	
RAMEZANI, 2023 (40mg/day)	-1.7	1.57	12	-0.72	1.3	12	1.5%	-0.98 [-2.13, 0.17]	
Subtotal (95% CI)			53			53	29.6%	-0.75 [-1.01, -0.49]	•
Heterogeneity: $Chi^2 = 0.77$, df =	2 (P = 0)	.68); 14	= 0%						
Test for overall effect: Z = 5.62 (I									
1.5.2 Turmeric extract									
ARUN. 2020	1.117	0.64	20	1.871	0.64	31	10 5%	-0.75 [-1.08, -0.43]	_
		0.64		2.65					
SONI, 2021 (1,5g)						20		-0.45 [-0.73, -0.17]	
SONI, 2021 (1g) Subtotal (95% CI)	2.25	0.44	20 70	2.65	0.49	20 71		-0.40 [-0.69, -0.11] -0.52 [-0.69, -0.35]	
						/1	09.5%	-0.52 [-0.69, -0.55]	•
Heterogeneity: $Chi^2 = 2.94$, df =			= 32%						
Test for overall effect: $Z = 5.96$ (I	P < 0.00	001)							
1.5.3 Mouthwash									
RAMEZANI, 2023 (Moutwash)	-2.23	2.14	13	-0.72	1.3	12	1.1%	-1.51 [-2.89, -0.13]	
Subtotal (95% CI)			13			12	1.1%	-1.51 [-2.89, -0.13]	
Heterogeneity: Not applicable									
Test for overall effect: $Z = 2.15$ (I	P = 0.03)							
Total (95% CI)			136			136	100.0%	-0.60 [-0.74, -0.45]	•
Heterogeneity: $Chi^2 = 7.52$, df =	6(P = 0)	28) 1	= 20%						
Test for overall effect: $Z = 8.24$ (I			20/0						-2 -1 0 1 2 Favours [experimental] Favours [control]

FIGURE 2

Forest plot of the efficacy of different pharmaceutical forms of *Curcuma longa* extract or curcumin on the WHO oral mucositis scale in cancer patients undergoing chemotherapy or radiotherapy, by pharmaceutical form.



Forest plot of the efficacy of different pharmaceutical forms of *Curcuma longa* extract or curcumin on the WHO oral mucositis scale in cancer patients undergoing chemotherapy or radiotherapy, by cancer treatment.

containing curcumin. Removing this study changes the pooled analysis to a negative result.

bias (Figure 8). By analyzing the funnel plots, we did not find evidence of publication bias (Supplementary Figures).

3.4 Quality assessment

Of the six studies included in the meta-analysis, the study by (Arun et al., 2020) brought greater concern because it was at high risk of selection, performance, and detection biases. The study by (Ramezani et al., 2023) was at high risk of selection and attrition bias (>10% dropout rate), while the study by (Delavarian et al., 2019) was at high risk of detection bias. The other studies were at low risk of

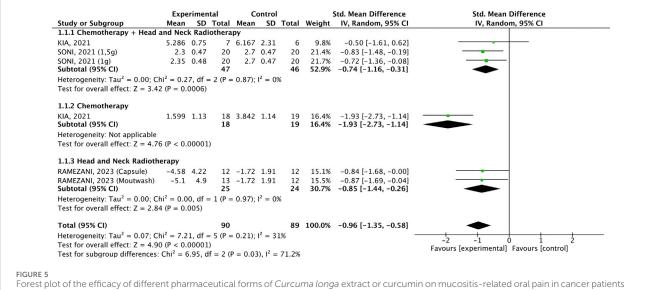
4 Discussion

This systematic review and meta-analysis of six studies involving over 300 patients with cancer demonstrated that *C. longa* extracts and curcumin, in different routes and pharmaceutical forms, significantly reduced OM severity, as measured by WHO scores, and oral pain, in a similar way. These benefits were seen in all oncological therapeutic modalities (CHT, RT, or CHT+RT), with slightly better outcomes in the

	Expe	rimen	tal	С	ontrol			Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
1.4.1 SinaCurcumin®										
KIA, 2021 (160mg/day)	1.96	2.3	25	3.52	2.1	25		Not estimable		
RAMEZANI, 2023 (40mg/day)	-4.58	4.22		-1.72	1.91					
Subtotal (95% CI)			12			12	18.4%	-0.84 [-1.68, -0.00]		
Heterogeneity: Not applicable										
Test for overall effect: $Z = 1.96$	6 (P = 0.	05)								
1.4.2 Turmeric extract										
SONI, 2021 (1,5g)	2.3	0.47	20	2.7	0.47	20	30.9%	-0.83 [-1.48, -0.19]		
SONI, 2021 (1g)	2.35	0.48	20	2.7	0.47	20	31.6%	-0.72 [-1.36, -0.08]		
Subtotal (95% CI)			40			40	62.6%	-0.78 [-1.23, -0.32]	•	
Heterogeneity: $Chi^2 = 0.06$, df	= 1 (P =	0.81)	$ I^2 = 0$	%						
Test for overall effect: $Z = 3.34$	P = 0.	0008)								
1.4.3 Mouthwash										
RAMEZANI, 2023 (Moutwash)	-5.1	4.9	13	-1.72	1.91	12	19.0%	-0.87 [-1.69, -0.04]		
Subtotal (95% CI)			13			12	19.0%	-0.87 [-1.69, -0.04]		
Heterogeneity: Not applicable										
Test for overall effect: $Z = 2.05$	P = 0.	04)								
Total (95% CI)			65			64	100.0%	-0.81 [-1.17, -0.45]		
Heterogeneity: $Chi^2 = 0.10$, df	= 3 (P =	0.99)	$1^2 = 0$	%						
Test for overall effect: $Z = 4.38$									-2 -1 0 1 Favours [experimental] Favours [control]	2

FIGURE 4

Forest plot of the efficacy of different pharmaceutical forms of *Curcuma longa* extract or curcumin on mucositis-related oral pain in cancer patients undergoing chemotherapy or radiotherapy, by pharmaceutical form.



Forest plot of the efficacy of different pharmaceutical forms of *Curcuma longa* extract or curcumin on mucositis-related oral pain in cancer patier undergoing chemotherapy or radiotherapy, by cancer treatment.

CHT subgroup. Notably, mouthwash containing curcumin was the only formulation that decreased the incidence of OM in patients undergoing RT alone. In contrast, nanomicellar curcumin capsules demonstrated superior pain reduction in CHT-treated patients, likely due to improved systemic absorption. While all formulations were beneficial, the route of administration influenced the extent of the observed effects.

This is the first meta-analysis to systematically compare different pharmaceutical forms of *C. longa* and curcumin and assess their effectiveness across various cancer treatment modalities. Our findings align with previous meta-analyses (Zhang et al., 2021), which suggested a reduction in OM severity with *C. longa*, but extend this knowledge by addressing specific formulations and treatment subgroups.

Each formulation has distinct pharmacokinetic properties, limitations. Oral curcumin advantages. and capsules (nanomicellar or standard) deliver precise dosing and exert systemic anti-inflammatory and antioxidant effects, potentially benefiting mucosal healing beyond the oral cavity, but have a delayed onset of action due to the time required for absorption and systemic distribution, and limited direct contact with oral mucosa, potentially reducing its localized therapeutic effect. Curcumin-containing mouthwashes have a rapid onset of action because it is directly applied to the oral cavity, maximizing local prophylactic and therapeutic effects, but may require multiple daily applications for sustained effects, which may reduce patient adherence, may have poor palatability and cause patient

	Experim		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M–H, Fixed, 95% Cl
1.6.1 SinaCurcumin®							
DELAVARIAN, 2019 (80mg/day)	16	16	16	16	10.4%	1.00 [0.89, 1.12]	
KIA, 2021 (160mg/day)	25	25		25	16.1%	1.00 [0.93, 1.08]	+
RAMEZANI, 2023 (40mg/day) Subtotal (95% CI)	10	12 53	12	12 53	7.9% 34.4%	0.84 [0.63, 1.12] 0.96 [0.89, 1.04]	•
Total events	51		53				
Heterogeneity: $Chi^2 = 2.20$, df = Test for overall effect: Z = 0.92 (3); I ² =	9%				
1.6.2 Turmeric extract							
ARUN, 2020	28	30		31		0.93 [0.83, 1.05]	
SONI, 2021 (1,5g)	20	20	20	20	12.9%	1.00 [0.91, 1.10]	+
SONI, 2021 (1g)	20	20		20		1.00 [0.91, 1.10]	+
Subtotal (95% CI)		70		71	45.4%	0.97 [0.91, 1.03]	•
Total events Heterogeneity: $Chi^2 = 1.19$, $df =$ Test for overall effect: Z = 0.92 (5); I ² =	71 0%				
1.6.3 Topical gel							
MANSOURIAN, 2015 Subtotal (95% CI)	19	19 19		18 18	12.0% 12.0%	1.00 [0.90, 1.11] 1.00 [0.90, 1.11]	★
Total events Heterogeneity: Not applicable Test for overall effect: Z = 0.00 (19 P = 1.00)		18				
1.6.4 Mouthwash							
RAMEZANI, 2023 (Moutwash) Subtotal (95% CI)	8	13 13		12 12	8.2% 8.2%	0.63 [0.41, 0.98] 0.63 [0.41, 0.98]	
Total events	8		12				
Heterogeneity: Not applicable Test for overall effect: Z = 2.07 (P = 0.04)						
Total (95% CI)		155		154	100.0%	0.94 [0.90, 0.99]	◆
Total events	146		154				
Heterogeneity: $Chi^2 = 11.10$, df = Test for overall effect: Z = 2.21 (Test for subgroup differences: C	P = 0.03)			5), l ² =	27.1%	-	0.5 0.7 1 1.5 2 Favours [experimental] Favours [control]

discomfort due to taste or texture. Besides, the bioavailability of curcumin remains limited to the oral mucosa, with minimal systemic effects.

Topical curcumin gels provide prolonged mucosal contact, allowing sustained curcumin absorption at the site of inflammation, thus enhancing wound healing through direct anti-inflammatory and antimicrobial actions, besides easy application to localized lesions, but requires patient compliance and may be difficult in severe OM cases with widespread ulcerations. Curcumin release and absorption may vary, and systemic anti-inflammatory effects are lower than with oral administration.

The reduction in OM severity appears to be driven by *C. longa*'s anti-inflammatory, antioxidant, and analgesic properties. Its effects are likely mediated through inhibition of cyclooxygenase 2 and lipoxygenase enzymes, inhibition of the nuclear transcription factor kappa B (NF- κ B), and suppression of inflammatory cytokines such as TNF- α , IL-1, IL-6, and IL-8 (Khafif et al., 2009; Zlotogorski et al., 2013). Additionally, *C. longa* promotes wound healing through re-epithelialization, macrophage migration, neovascularization, and antibacterial activity (Arun et al., 2020; van't Land et al., 2004).

Interestingly, the benefit of the curcumin mouthwash in reducing OM incidence was investigated only in patients undergoing RT. This finding resonates with preclinical studies where curcumin reduced radiation-induced dermatitis in mice by modulating TGF- β pathways (Jagetia and Rajanikant, 2012) and a *C. longa* extract protected against 5-fluorouracil-induced oral mucositis in hamsters (Araújo et al., 2022). In a pilot study, this same mouthwash delayed the onset of OM in patients with head and neck cancer, similarly to a 0.15% benzydamine mouthwash (Shah et al., 2020).

Currently, there is a trend to use nanomicelles of natural substances to increase the availability in the body or site of action. The bioavailability of curcumin in the bloodstream is remarkably low after oral administration, which compromises its therapeutic efficacy. This limitation is attributed to low absorption, chemical instability, and rapid systemic elimination. Oral administration of curcumin fails to achieve adequate therapeutic results due to these challenges, resulting in minimal blood concentrations (Anand et al., 2007). An *in vivo* study demonstrated that low-dose nanocurcumin (20 mg/kg) exhibits comparable therapeutic effects to high-dose pure curcumin (400 mg/kg) (Szymusiak et al., 2016).

Other technologies can enhance curcumin's bioavailability by up to 100-fold (Jamwal, 2018). Simpler strategies have also been employed, such as the association with piperine, which increases curcumin absorption up to 20-fold (Shoba et al., 1998), and the association of curcumin with *C. longa* essential oils, which increases curcumin absorption to 96% (Kiefer, 2007). The oral administration of a *C. longa* fresh root extract (rich in curcuminoids) to Wistar rats yielded higher plasma curcumin levels than an equivalent dose of purified

	Experim		Contro			Risk Ratio	Risk Ratio
study or Subgroup				Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
L.2.1 Chemotherapy + Head a			erapy				
ARUN, 2020	28	30	31	31	19.5%	0.93 [0.83, 1.05]	
KIA, 2021	7	7	6	6	4.4%	1.00 [0.76, 1.31]	
SONI, 2021 (1,5g)	20	20	20	20	12.9%	1.00 [0.91, 1.10]	+
SONI, 2021 (1g)	20	20	20	20	12.9%	1.00 [0.91, 1.10]	-
Subtotal (95% CI)		77		77	49.7%	0.97 [0.92, 1.04]	•
Total events	75		77				
Heterogeneity: $Chi^2 = 1.16$, df	= 3 (P = 0)	.76); I ²	= 0%				
Test for overall effect: $Z = 0.85$	5 (P = 0.40))					
1.2.2 Chemotherapy							
KIA, 2021	18	18	19	19	12.0%	1.00 [0.90, 1.11]	
Subtotal (95% CI)		18		19	12.0%	1.00 [0.90, 1.11]	★
Total events	18		19				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 0.00$	O(P = 1.00))					
1.2.3 Head and Neck Radioth	erapy						
DELAVARIAN, 2019	16	16	16	16	10.4%	1.00 [0.89, 1.12]	
MANSOURIAN, 2015	19	19	18	18	11.9%	1.00 [0.90, 1.11]	
RAMEZANI, 2023 (Capsule)	10	12	12	12	7.9%	0.84 [0.63, 1.12]	
RAMEZANI, 2023 (Moutwash)	8	13	12	12	8.2%	0.63 [0.41, 0.98]	
Subtotal (95% CI)		60		58	38.4%	0.89 [0.80, 0.99]	•
Total events	53		58				
Heterogeneity: Chi ² = 11.56, d	f = 3 (P =	0.009);	$I^2 = 74\%$				
Test for overall effect: $Z = 2.14$	4 (P = 0.03))					
Total (95% CI)		155		154	100.0%	0.94 [0.90, 0.99]	•
Total events	146		154				
Heterogeneity: Chi ² = 10.28, d	f = 8 (P =	0.25); 1	$^{2} = 22\%$			-	0.5 0.7 1 1.5 2
Test for overall effect: $Z = 2.15$							Favours [experimental] Favours [control]
Test for subgroup differences:	$Chi^2 = 2.7$	'9, df =	2 (P = 0.	25), I ²	= 28.3%		ravours [experimental] ravours [control]

(95.1%) curcuminoids extracted from dry *C. longa* roots, which failed to produce detectable curcumin in plasma. In humans, the absorption of total curcuminoids from the same extract was 46 times higher than equivalent doses of purified curcuminoids (Krishnakumar et al., 2015).

The cultivation of *C. longa* for extract production is wellestablished, and obtaining curcumin is an easy and costeffective process. This makes the production of medicines from this medicinal plant feasible not only for developed countries but also for economically underdeveloped nations. The most used technologies (e.g., nano-micelles) are relatively simple and inexpensive, but even when these technologies are unavailable, a crude extract or even the powdered plant material can be used.

Although our results corroborate the findings by Zhang et al., 2021, these authors reported that *C. longa* only decreased the incidence of severe OM. Another recent meta-analysis reported the benefits of *C. longa* use in patients with head and neck cancer only in the fourth treatment week and not before or after (Wu et al., 2024). Although our study did not address the specific timing of effect onset, the mouthwash containing curcumin was effective as early as after 3 weeks.

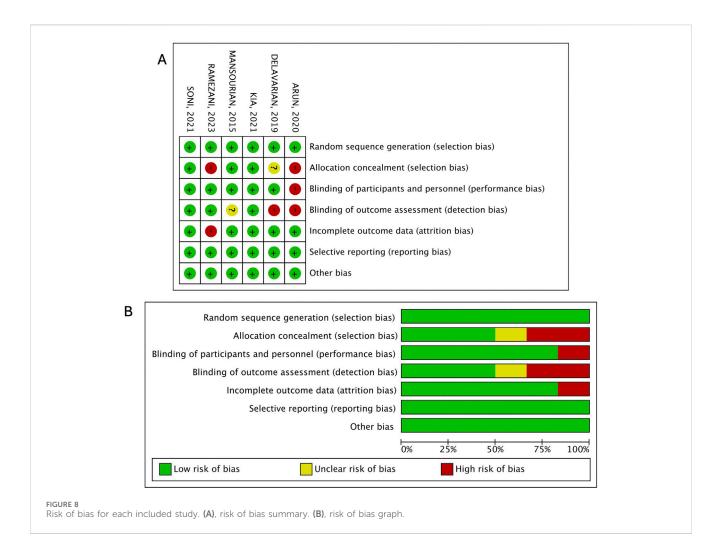
These findings suggest that *C. longa* offers a promising therapeutic option for managing OM in cancer patients, with implications for prevention and treatment. Beyond its direct effects on OM, *C. longa* may also provide additional benefits such as enhanced wound healing and reduced systemic

inflammation, potentially improving overall patient quality of life during cancer treatment (Kalluru et al., 2020). Given the ease of administration, especially with mouthwash formulations, *C. longa* could be incorporated into standard care protocols to mitigate OM in cancer patients.

Despite these promising results, our study has limitations. The evidence presented was restricted to the oral cavity, and the effectiveness of *C. longa* in preventing or managing mucositis beyond this region remains unclear. Additionally, the included studies varied in sample size, pharmaceutical forms, and dosage, which may limit the generalizability of our findings. Future research should address these gaps by standardizing formulations and exploring the effects of *C. longa* in larger, more diverse populations, including pediatric patients. Future studies should investigate the long-term effects of *C. longa* on chronic mucositis outcomes and its potential role in systemic inflammation management. Further exploration of specific formulations, such as mouthwashes, could provide insights into optimal dosing and administration frequency.

5 Conclusion

In conclusion, this meta-analysis demonstrates that *C. longa* extracts and curcumin, in different pharmaceutical forms, particularly curcumin-containing mouthwashes, significantly



reduces OM severity and oral pain in cancer patients undergoing oncological treatment. These findings support its incorporation into clinical practice as a complementary therapy. Future research should focus on standardizing curcumin formulations, optimizing dosages, and expanding investigations to a broader oncological population to further validate these findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

PA: Data curation, Formal Analysis, Investigation, Software, Visualization, Writing – original draft. LC: Data curation, Formal Analysis, Investigation, Software, Visualization, Writing – original draft. SF: Methodology, Writing – review and editing. JC: Funding acquisition, Supervision, Writing – review and editing. FC: Data curation, Formal Analysis, Supervision, Validation, Writing – original draft, Writing – review and editing. AP: Conceptualization, Formal Analysis, Methodology, Supervision, Writing – original draft, Writing – review and editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that Generative AI was used in the creation of this manuscript. Generative AI was used for the

creation of this manuscript. Authors used ChatGPT 4.0 to perform statistical analyses.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that

References

Anand, P., Kunnumakkara, A. B., Newman, R. A., and Aggarwal, B. B. (2007). Bioavailability of curcumin: problems and promises. *Mol. Pharm.* 4, 807–818. doi:10. 1021/mp700113r

Araújo, A.A. de, Silva, E. M., Mafra, C. A., da, C. C., Costa, Í. do C. C., Barbalho, A. L. A., et al. (2022). Curcuma longa extract protects against 5-fluorouracil-induced oral mucositis in hamsters. *Braz. J. Pharm. Sci.* 58. doi:10.1590/s2175-97902022000xe20114

Arun, P., Sagayaraj, A., Azeem Mohiyuddin, S. M., and Santosh, D. (2020). Role of turmeric extract in minimising mucositis in patients receiving radiotherapy for head and neck squamous cell cancer: a randomised, placebo-controlled trial. *J. Laryngol. Otol.* 134, 159–164. doi:10.1017/S0022215120000316

Delavarian, Z., Pakfetrat, A., Ghazi, A., Jaafari, M. R., Homaei Shandiz, F., Dalirsani, Z., et al. (2019). Oral administration of nanomicelle curcumin in the prevention of radiotherapy-induced mucositis in head and neck cancers. *Special Care Dent.* 39, 166–172. doi:10.1111/scd.12358

Dipalma, G., Inchingolo, A. M., Latini, G., Ferrante, L., Nardelli, P., Malcangi, G., et al. (2024). The effectiveness of curcumin in treating oral mucositis related to radiation and chemotherapy: a systematic review. *Antioxidants* 13, 1160. doi:10.3390/antiox13101160

Facchini, L., Martino, R., Ferrari, A., Piñana, J. L., Valcárcel, D., Barba, P., et al. (2012). Degree of mucositis and duration of neutropenia are the major risk factors for early post-transplant febrile neutropenia and severe bacterial infections after reduced-intensity conditioning. *Eur. J. Haematol.* 88, 46–51. doi:10.1111/j.1600-0609.2011.01724.x

Gamis, A. S., Howells, W. B., DeSwarte-Wallace, J., Feusner, J. H., Buckley, J. D., and Woods, W. G. (2000). Alpha hemolytic streptococcal infection during intensive treatment for acute myeloid leukemia: a report from the children's cancer group study CCG-2891. J. Clin. Oncol. 18, 1845–1855. doi:10.1200/JCO.2000.18.9.1845

Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., et al. (2022). *Cochrane Handbook for systematic reviews of interventions, version* 6.5. Cochrane. Available online at: www.training.cochrane.org/handbook (Accessed August 2024).

Jagetia, G. C., and Rajanikant, G. K. (2012). Acceleration of wound repair by curcumin in the excision wound of mice exposed to different doses of fractionated *y* radiation. *Int. Wound J.* 9, 76–92. doi:10.1111/j.1742-481X.2011.00848.x

Jamwal, R. (2018). Bioavailable curcumin formulations: a review of pharmacokinetic studies in healthy volunteers. *J. Integr. Med.* 16, 367–374. doi:10.1016/j.joim.2018. 07.001

Kalluru, H., Kondaveeti, S. S., Telapolu, S., and Kalachaveedu, M. (2020). Turmeric supplementation improves the quality of life and hematological parameters in breast cancer patients on paclitaxel chemotherapy: a case series. *Complement. Ther. Clin. Pract.* 41, 101247. doi:10.1016/j.ctcp.2020.101247

Khafif, A., Lev-Ari, S., Vexler, A., Barnea, I., Starr, A., Karaush, V., et al. (2009). Curcumin: a potential radio-enhancer in head and neck cancer. *Laryngoscope* 119, 2019–2026. doi:10.1002/lary.20582

Kiefer, D. (2007). Novel turmeric compound delivers much more curcumin to the blood. *Life Ext. Mag.* Available online at: http://www.lef.org/magazine/2007/10/report_curcumin/Page-01.

Kim, J. W., Cha, Y., Kim, S.-J., Han, S.-W., Oh, D.-Y., Lee, S.-H., et al. (2012). Association of oral mucositis with quality of life and symptom clusters in patients with solid tumors receiving chemotherapy. *Support. Care Cancer* 20, 395–403. doi:10.1007/s00520-011-1126-8

Krishnakumar, I. M., Kumar, D., Ninan, E., Kuttan, R., and Maliakel, B. (2015). Enhanced absorption and pharmacokinetics of fresh turmeric (Curcuma Longa L) derived curcuminoids in comparison with the standard curcumin from dried rhizomes. *J. Funct. Foods* 17, 55–65. doi:10.1016/j.jff.2015.04.026

Lalla, R. V., Brennan, M. T., Gordon, S. M., Sonis, S. T., Rosenthal, D. I., and Keefe, D. M. (2019). Oral mucositis due to high-dose chemotherapy and/or head and neck radiation therapy. *J. Natl. Cancer Inst. Monogr.* 2019, lgz011. doi:10.1093/jncimonographs/lgz011

may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1560729/ full#supplementary-material

Lee, C. T., and Galloway, T. J. (2022). Pathogenesis and amelioration of radiationinduced oral mucositis. *Curr. Treat. Options Oncol.* 23, 311–324. doi:10.1007/s11864-022-00959-z

Mansourian, A., Amanlou, M., Shirazian, S., Moosavian Jahromi, Z., and Amirian, A. (2015). The effect of "Curcuma Longa" topical gel on radiation-induced oral mucositis in patients with head and neck cancer. *Int. J. Radiat. Res.* 13, 269–274. doi:10.7508/ijrr. 2015.03.011

Ouzzani, M., Hammady, H., Fedorowicz, Z., and Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Syst. Rev.* 5, 210–10. doi:10.1186/s13643-016-0384-4

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372, n71. doi:10.1136/BMJ.N71

Ramezani, V., Ghadirian, S., Shabani, M., Boroumand, M. A., Daneshvar, R., and Saghafi, F. (2023). Efficacy of curcumin for amelioration of radiotherapy-induced oral mucositis: a preliminary randomized controlled clinical trial. *BMC Cancer* 23, 354. doi:10.1186/s12885-023-10730-8

Shah, S., Rath, H., Sharma, G., Senapati, S., and Mishra, E. (2020). Effectiveness of curcumin mouthwash on radiation-induced oral mucositis among head and neck cancer patients: a triple-blind, pilot randomised controlled trial. *Indian J. Dent. Res.* 31, 718–727. doi:10.4103/ijdr.IJDR_822_18

Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R., and Srinivas, P. (1998). Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med.* 64, 353–356. doi:10.1055/s-2006-957450

Sonis, S. T., Eilers, J. P., Epstein, J. B., LeVeque, F. G., Liggett, W. H., Mulagha, M. T., et al. (1999). Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. *Cancer* 85, 2103–2113. doi:10.1002/(SICI)1097-0142(19990515)85:10<2103:: AID-CNCR2>3.0.CO;2-0

Sroussi, H. Y., Epstein, J. B., Bensadoun, R., Saunders, D. P., Lalla, R. V., Migliorati, C. A., et al. (2017). Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. *Cancer Med.* 6, 2918–2931. doi:10.1002/cam4.1221

Szymusiak, M., Hu, X., Leon Plata, P. A., Ciupinski, P., Wang, Z. J., and Liu, Y. (2016). Bioavailability of curcumin and curcumin glucuronide in the central nervous system of mice after oral delivery of nano-curcumin. *Int. J. Pharm.* 511, 415–423. doi:10.1016/j. ijpharm.2016.07.027

van't Land, B., Blijlevens, N. M. A., Marteijn, J., Timal, S., Donnelly, J. P., de Witte, T. J. M., et al. (2004). Role of curcumin and the inhibition of NF-kappaB in the onset of chemotherapy-induced mucosal barrier injury. *Leukemia* 18, 276–284. doi:10.1038/sj. leu.2403233

Villa, A., and Sonis, S. T. (2016). Pharmacotherapy for the management of cancer regimen-related oral mucositis. *Expert Opin. Pharmacother.* 17, 1801–1807. doi:10. 1080/14656566.2016.1217993

Wu, C.-F., Wu, H.-J., Shih, C.-L., Yeh, T.-P., and Ma, W.-F. (2024). Efficacy of turmeric in the treatment of oral mucositis in patients with head and neck cancer after radiotherapy or chemoradiotherapy: a systematic review and meta-analysis. *Front. Pharmacol.* 15, 1363202. doi:10.3389/fphar.2024.1363202

Zhang, L., Tang, G., and Wei, Z. (2021). Prophylactic and therapeutic effects of curcumin on treatment-induced oral mucositis in patients with head and neck cancer: a meta-analysis of randomized controlled trials. *Nutr. Cancer* 73, 740–749. doi:10.1080/01635581.2020.1776884

Zlotogorski, A., Dayan, A., Dayan, D., Chaushu, G., Salo, T., and Vered, M. (2013). Nutraceuticals as new treatment approaches for oral cancer – I: curcumin. *Oral Oncol.* 49, 187–191. doi:10.1016/j.oraloncology.2012.09.015