

The Therapeutic Effects of Curcumin on Oral Disease: A Systematic Review

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Introduction: Curcumin is an extract from herbal plants that has been implicated in the treatment of any disease, including oral disease. There are various types of curcumin formulation as the option of the therapy. The aim of this review is to describe the curcumin mechanism in reducing the severity, pain score, and oral lesion size as the therapeutic effects.

Methods: This systematic review used the Preferred Reporting Items for Systematic Review and Meta Analysis (PRISMA) guidelines. Databases used for articles include PubMed, Science Direct, and Scopus with inclusion criteria published from 2014 to 2024, full text, in English, and randomized controlled trial (RCT).

Results: The present study included 21 RCTs with a total of 1244 individuals. In this study, curcumin was most commonly used for oral submucous fibrosis, with 9 studies demonstrating that curcumin has anti-inflammatory properties and inhibits collagenase. All studies demonstrate that curcumin produces significant results in the management of oral disease. The remain studies showed curcumin has antioxidant, inhibit collagenase, antifungal, and wound healing properties for oral leukoplakia, recurrent aphthous stomatitis (RAS), oral lichen planus (OLP), and denture stomatitis.

Conclusion: Curcumin has anti inflammatory, antioxidant, inhibit collagenase, antifungal, and wound healing properties for reducing the severity of lesion, pain score and oral lesion size as the therapeutic effects in the patients with oral disease including OSMF, mucositis, leukoplakia, RAS, OLP, and denture stomatitis.

Keywords: curcumin, oral disease, therapeutic effect

Introduction

Turmeric is the most food ingredient used in India, and is commonly known as Indian Saffron. One of its compositions is curcumin, which comes from the root of turmeric.¹ Turmeric is a rhizome plant that comes from the ginger family. Turmeric's ability to treat disease was found in curcumin, a natural polyphenol. Polyphenols have roles in body metabolism, chronic diseases, and cell proliferation.² The use of oral drugs to treat various oral diseases often leads to several side effects, emphasizing the need for safer and more effective treatment options.³ 80% of people in developing countries use traditional plants as therapy. Inaccurate therapy leading to pathogen resistance and increased side effects has been the cause. Therefore, research was conducted on natural phytochemicals from plants that are used as alternatives, one of which is curcumin.⁴

Turmeric was used as an alternative medicine more than 4000 years ago in India. The Latin name of turmeric is *Curcuma longa*. There are several chemical compositions in turmeric, there are 3% curcumin, 1.4% detoxycurcumin, and 1.2%. The combination of these three components is called curcuminoids.⁵ Several studies have shown that in medicine, curcumin has therapeutic effects in medicine.⁶ In dentistry, curcumin plays a significant role in maintaining oral health, including the treatment of RAS, leukoplakia, candidiasis, gingivitis, and other conditions. Advancements in drug delivery systems are crucial for enhancing the effectiveness of curcumin therapy within the oral cavity. Various forms of curcumin preparations are utilized in medical treatments.⁷ Several studies indicates that curcumin is effective in reducing the severity of oral mucositis, promoting faster healing, and alleviating symptoms such as pain and difficulty swallowing. It

also helps manage symptoms and slow the progression of oral potentially malignant disorders. Moreover, curcumin offers anti-inflammatory and antibacterial benefits for periodontitis and holds potential as an adjunct therapy in oral cancer due to its anticancer and immune-modulating effects.⁸

In 2024, Inchingolo et al reviewed 17 studies on the therapeutic effects of curcumin on oral health. They concluded that curcumin is a promising treatment for oral cancer, mucositis, periodontal disease, and potentially malignant illnesses.⁸ However, the study did not specify which oral diseases are most effectively treated with curcumin. In contrast, this systematic review includes 21 studies on 6 oral mucosal diseases, with significance values and the best curcumin preparations for treatment. Curcumin has a limitation due to its low bioavailability, which makes it difficult to reach therapeutic levels in the blood. This is influenced by its poor solubility in water, limited distribution, and inefficient absorption in the intestines.⁹ Based on the search results, this systematic review can aid in choosing therapies for oral diseases.

Materials and Methods

This systematic review adhered to the guidelines of literature writing as outlined by the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). The research questions were structured using the PICO (Population, Intervention, Comparison, and Outcome) framework. The population studied comprised patients diagnosed with oral diseases, the intervention involved curcumin, the comparison was made with a control group, and the outcome focused on assessing the effects of the intervention in the treatment group.

Data Search

The electronic media used in the literature search were PubMed, Science Direct, and Scopus with combined keywords to search the article: ((oral disease) OR (oral disease)) AND ((curcumin) OR (turmeric)), (oral mucosal lesion) AND (curcumin), (oral disease) AND (curcumin), (oral disease) AND (curcumin) AND (therapeutic effects).

Inclusion and Exclusion Criteria

To evaluate the effectiveness of curcumin in treating oral diseases, the following inclusion criteria were applied: international journals that discuss the therapeutic effects of curcumin on oral diseases, published between 2014 and 2024, with full text available, randomized controlled trials (RCTs), written in English, and using curcumin formulations such as gel, tablets, capsules, patches, and solutions for intervention. Articles were excluded if they were irrelevant to the topic, duplicates, or did not follow an RCT design. The research is taken from the last 10 years to ensure that the information used is relevant and aligns with technological developments, thus accurately reflecting the current conditions.

Risk of Bias

The Jadad scale was employed to evaluate the risk of bias and quality of the chosen articles. This scale, developed by Oxford, is a system for assessing the methodological quality of the selected studies based on objective criteria. The total score from the five questions indicates the article's risk of bias and quality, as illustrated in Table 1.

Table 1 Risk of Bias

No	Reference	Question No.					Total Score	Result
		1	2	3	4	5		
1	Rao et al, 2014 ¹⁰	1	1	0	-1	1	3	High Range of Quality
2	Yadav et al, 2014 ¹¹	1	1	0	-1	0	1	Low Range of Quality
3	Kuriakose et al, 2016 ¹²	1	1	1	1	1	5	High Range of Quality
4	Pipalia et al, 2016 ¹³	1	1	1	1	0	4	High Range of Quality
5	Piyush et al, 2018 ¹⁴	1	1	0	-1	0	1	Low Range of Quality

(Continued)

Table 1 (Continued).

No	Reference	Question No.					Total Score	Result
		1	2	3	4	5		
6	Saran et al, 2018 ¹⁵	1	1	0	-1	0	1	Low Range of Quality
7	Delavarian et al, 2019 ¹⁶	1	1	1	1	1	5	High Range of Quality
8	Mustafa et al, 2019 ¹⁷	1	1	0	-1	0	1	Low Range of Quality
9	Bhowate et al, 2020 ¹⁸	1	1	0	-1	0	1	Low Range of Quality
10	Kia et al, 2020 ¹⁹	1	1	1	1	0	4	High Range of Quality
11	Kia et al, 2020 ²⁰	1	1	1	1	0	4	High Range of Quality
12	Shah et al, 2020 ²¹	1	1	1	1	1	5	High Range of Quality
13	Bohra et al, 2021 ²²	1	1	0	-1	0	1	Low Range of Quality
14	Chandrashekar et al, 2021 ²³	1	1	0	-1	1	3	High Range of Quality
15	Kia et al, 2021 ²⁴	1	1	1	1	0	4	High Range of Quality
16	Nerkar Rajbhoj et al, 2021 ²⁵	1	1	0	-1	0	2	Low Range of Quality
17	Adhikari et al, 2022 ²⁶	1	1	1	1	0	4	High Range of Quality
18	Bakhshi et al, 2022 ²⁷	1	1	1	1	0	4	High Range of Quality
19	Fardad et al, 2022 ²⁸	1	1	1	1	1	5	High Range of Quality
20	Fathima et al, 2022 ²⁹	1	1	0	-1	0	1	Low Range of Quality
21	Ramezani et al, 2023 ³⁰	1	1	0	-1	1	3	High Range of Quality

Results

The systematic review described the process of searching articles through PRISMA with different keywords in each digital sources. Twenty-one articles were screened by setting inclusion and exclusion criteria. Risk of bias (Table 1) and the quality assessment JADAD scale were used to assessed the eligibility of the article. The flowchart of the article selection process is shown in the Figure 1. A general summary from selected articles is presented in Table 2 which describes the title, aim of the article, type of oral disease, intervention, outcome parameter, and result. The results showed from 21 articles there were two with oral lesions most discussed, 9 OSMF lesions and 6 oral mucositis. Five OSMF articles showed the visual analogue scale (VAS) improved in systemic curcumin than systemic steroid. Six studies on oral mucositis indicated that curcumin has therapeutic effects in inhibiting and reducing lesions. All the studies showed that curcumin is effective in treating oral diseases across different formulations.

Discussion

Curcumin is one of the ingredients derived from turmeric which is widely used in Asia. This systematic review discussed therapeutic effects of curcumin on oral disease. A general summary of the articles is described in Table 2. Twenty-one articles have been analysed and OSMF was the highest prevalence. There were 9 articles showed therapeutic effect of curcumin for OSMF. OSMF is a long-term condition characterized by fibroelastic alterations in the lamina propria near the epithelial layer. The component of areca nut increased cytokines and growth factors, which activate pro-collagen genes lead to excessive collagen and decrease matrix degradation. Furthermore, flavonoids prevent collagen breakdown by inhibiting collagenase. As a result, unbalanced collagen leads to fibrosis.³¹ The proliferation of fibroblasts and myofibroblasts was inhibited by curcumin. The cell cycle was disrupted, leading to apoptosis and decreased production of collagen types I and III in myofibroblasts.³²

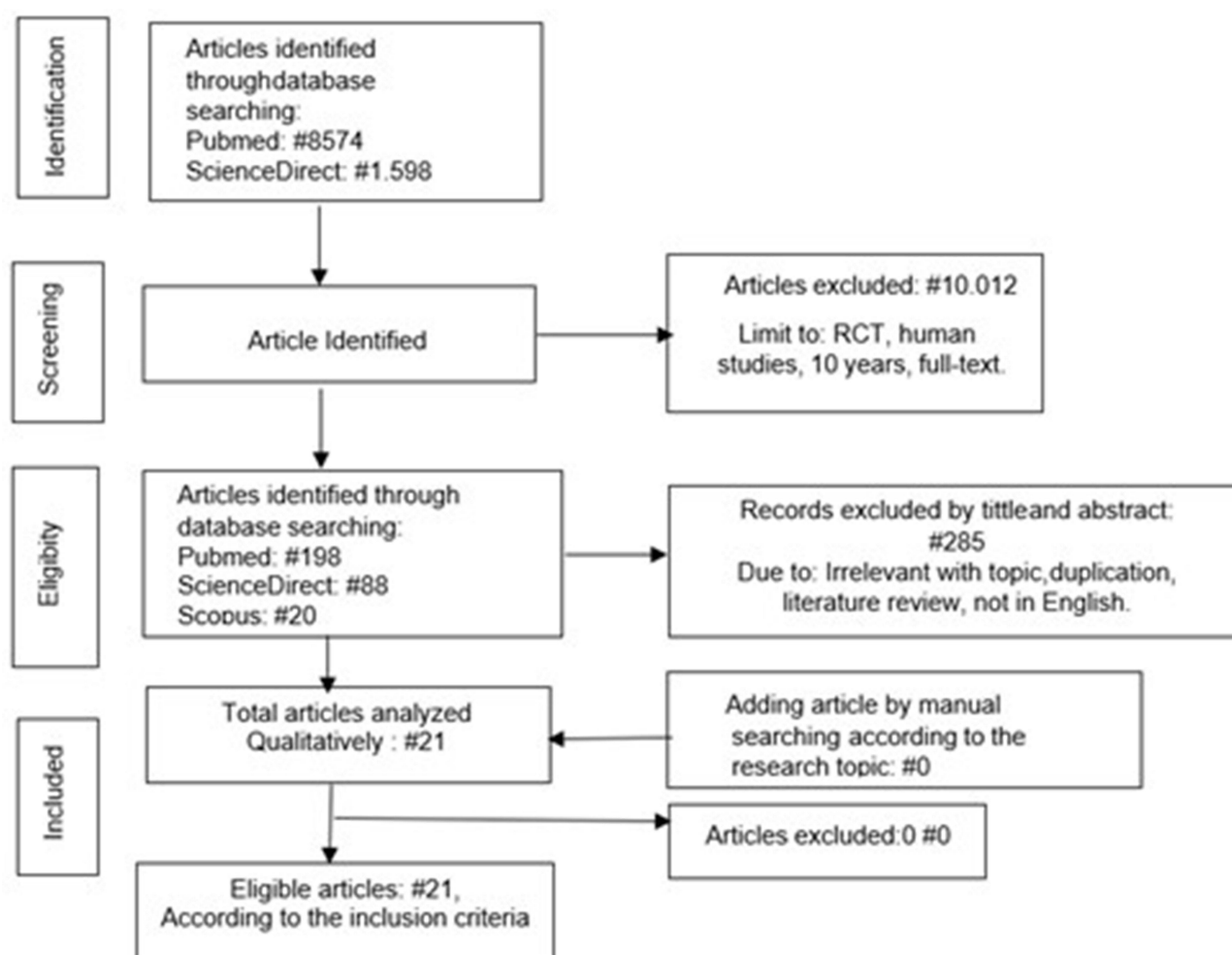


Figure 1 The PRISMA flow diagram of the article search and selection process.

Nine studies featured in the systematic review emphasized the efficacy of curcumin for patients with oral submucous fibrosis (OSMF). Five articles authored by Yadav et al (2014), Pipalia et al (2016), Piyush et al (2019), Saran et al (2018), and Adhikari et al (2022) examined systemic curcumin, while four studies by Bhowate et al (2020), Bohra et al (2021), Chandrashekar et al (2021), and Nerkar Rajbhoj et al (2021) focused on topical curcumin. The visual analogue scale (VAS) score showed improvement with systemic curcumin compared to systemic steroids ($p < 0.01$), although topical steroids were more effective in alleviating burning sensations. Research by Nerkar Rajbhoj et al (2021) indicated that aloe vera yielded better results than curcumin in reducing burning sensations and improving mouth opening ($p < 0.01$), despite both treatments demonstrating significant benefits. Both curcumin and lycopene showed statistical significance in all measured parameters; however, there was no notable difference between the two treatments. The curcumin patch proved to be more effective than the gel in alleviating burning sensations and improving mouth opening, leading to significant results in both groups ($p < 0.001$). Moreover, the combination of curcumin with black pepper amplified the therapeutic effects of curcumin.^{11,13–15,18,22,23,25,26}

In several articles that have been assessed, there are 6 studies showing a relationship between curcumin and oral mucositis. The pathogenesis of mucositis consists of a cascade of events divided into initiation, upregulation, signalling, amplification, ulceration and inflammation and healing. The initiation phase produces reactive oxygen species (ROS) that cannot be controlled by the body, causing various cytokines to be released lead to epithelial changes and the abundance of transcription factor (nuclear factor- κ B) causes apoptosis and tissue damage. The ulceration phase is accompanied by bacterial colonization that activates macrophages and triggers cytokines. Healing phase occurred when there are

Table 2 General Summary of The Therapeutic Effects of Curcumin on Oral Disease

No	Reference	Title	Aim	Oral disease	Intervention	Outcome	Result
1	Rao et al, 2014 ¹⁰	The Indian Spice Turmeric Delays and Mitigates Radiation-Induced Oral Mucositis in Patients Undergoing Treatment for Head and Neck Cancer: An Investigational Study	To evaluate the efficacy of turmeric in preventing radiation-induced mucositis	Oral mucositis	Group A: povidone iodine mouthwash Group B: turmeric mouthwash (400 mg)	1. Fourteen of 39 patients developed intolerable mucositis in group B and 34 of the 40 patients developed intolerable mucositis in group A 2. Weight loss less in group B	Gargling with turmeric provided significant benefit by delaying and reducing the severity of mucositis
2	Yadav et al, 2014 ¹¹	Comparison of curcumin with intralesional steroid injections in Oral Submucous Fibrosis: A randomized, open-label interventional study	To establish the efficacy of curcumin in OSMF patients.	OSMF	Group I: 4 mg dexamethasone intralesion and 1500 IU hyaluronidase Group II: curcumin tablets (300 mg Turmix)	1. Burning sensation had improved completely and rapidly in group 2 compared with group I 2. IID improved in both groups 3. Tongue protrusion greater recovery in group I	Turmix is beneficial and effective in reducing burning sensation in early OSMF patients
3	Kuriakose et al 2016 ¹²	A Randomized Double-Blind Placebo-Controlled Phase IIB Trial of Curcumin in Oral Leukoplakia	Investigated the effectiveness of curcumin, a potent inhibitor of NF- κ B/COX-2, molecules perturbed in oral carcinogenesis, to treat leukoplakia	Oral leukoplakia	Group A: curcumin capsules Group B: placebo	1. Clinical response rate between the curcumin and the placebo arms was statistically significant ($P = 0.02$). 2. Histologic response rates between curcumin arm and the placebo arm was not statistically significant ($P = 0.714$) 3. Durability response and safety result: not significant	Curcumin (3.6 g/day for six months) showed significant and durable clinical response in treating oral leukoplakia
4	Pipalia et al, 2016 ¹³	Clinicobiochemical evaluation of turmeric with black pepper and nigella sativa in management of oral submucous fibrosis-a double-blind, randomized preliminary study	To investigate the effectiveness of turmeric with black pepper and <i>Nigella sativa</i> in oral submucous fibrosis (OSMF)	OSMF	Group A: turmeric 400 mg with black pepper 100 mg Group B: <i>Nigella sativa</i>	Group A and group B: 1. Mouth opening > group A 2. VAS score reduction better in group A	Turmeric with black pepper and <i>Nigella sativa</i> improved mouth opening, burning sensation and SOD levels in the present OSMF
5	Piyush et al, 2018 ¹⁴	Comparison of therapeutic response of lycopene and curcumin in oral submucous fibrosis: A randomized controlled trial	To evaluate and compare the therapeutic response of Lycopene and Curcumin with placebo in patients suffering from oral submucous fibrosis (OSMF) and to correlate the habit variables of smoked and smokeless tobacco products in OSMF	OSMF	Group A: lycopene capsules Group B: curcumin tablet	1. Complete cessation of burning sensation in both the groups and was statically no significant 2. Lycopene produced better improvement in mouth opening	Lycopene showed better results than curcumin in improving mouth opening; both the drugs were equally effective in decreasing burning sensation in OSMF patients.
6	Saran et al, 2018 ¹⁵	A comparative study to evaluate the efficacy of lycopene and curcumin in oral submucous fibrosis patients: A randomized clinical trial	To compare and evaluate the efficacy of lycopene and curcumin given orally in clinically diagnosed OSMF patients	OSMF	Group A: lycopene capsules Group B: curcumin tablet	1. Burning sensation between two group statistically nonsignificant 2. Lycopene showed better result in mouth opening	Lycopene showed better results than curcumin in improving mouth opening; both the drugs were equally effective in decreasing burning sensation in OSMF patients.

(Continued)

Table 2 (Continued).

No	Reference	Title	Aim	Oral disease	Intervention	Outcome	Result
7	Delavarian et al, 2019 ¹⁶	Oral administration of nanomicelle curcumin in the prevention of radiotherapy-induced mucositis in head and neck cancers	To evaluate the effect of curcumin in the form of nanomicelle on OM in HNC patients receiving radiotherapy	Oral mucositis	Group study: nanocurcumin capsule 80 mg Group control: placebo tablet	1. Delayed in onset of OM in study group > control group 2. The grade of mucositis was lower in the study group	Nanomicelle curcumin is an effective agent in the prevention of OM or reducing its severity
8	Mustafa et al, 2019 ¹⁷	Effectiveness of an Alcohol-Free Chitosan-Curcuminoid Mouthwash Compared with Chlorhexidine Mouthwash in Denture Stomatitis Treatment: A Randomized Trial	Efficacy and safety in management of denture stomatitis (DS) in comparison of curcumin and chlorhexidine (CHX) mouthwash	Denture stomatitis	Group 1: chitosan-curcuminoid (CHI-CUR) mouthwash Group 2: CHX mouthwash Group 3: chitosan and PEG 400.	1. Site activity score group 1 significantly lower than group 2 and group 3 2. No serious side with CHI-CUR mouthwash. One of 10 patients CHX mouthwash had staining on the tongue and 2 of 10 had a burning sensation on the tongue 3. The number of candida significantly decreased, no differences in three interventions	CHI-CUR mouthwash may serve as safe and potential therapeutic alternative in treating DS
9	Bhowate et al, 2020 ¹⁸	Comparison of efficacy of topical curcumin gel with triamcinolone-hyaluronidase gel individually and in combination in the treatment of oral submucous fibrosis	To study the efficacy of topical curcumin mucoadhesive semisolid gel, triamcinolone acetanide/hyaluronidase mucoadhesive semisolid gel, and a combination of both in the treatment of oral submucous fibrosis (OSMF)	OSMF	Group I: 1% curcumin gel Group II: 1% hyaluronidase and 1% triamcinolone gel Group III: 1% curcumin gel 1% hyaluronidase and 1% triamcinolone gel	1. Mouth opening better in group III 2. VAS better result in group II 3. Mucosa color better result in group III	Curcumin has a therapeutic effect on patients diagnosed with OSMF
10	Kia et al, 2020 ¹⁹	Comparison of oral Nano-Curcumin with oral prednisolone on oral lichen planus: a randomized double-blinded clinical trial	Comparison of oral Nano-Curcumin with oral prednisolone on oral lichen planus	OLP	Group Study: nanocurcumin capsule 80 mg Group control: prednisolone 10 mg tablet	1. VAS no significant difference at both group 2. Lesion size significantly reduce in both group, but no significant compared in between	The level of pain, burning sensation, and OLP lesion decreased in both groups and no significant difference between them
11	Kia et al, 2020 ²⁰	New concentration of curcumin orabase in recurrent aphthous stomatitis: A randomized, controlled clinical trial	To compare the efficacy regarding the administration of 5% of curcumin (new concentration) and 0.1% of triamcinolone acetanide (standard control) for treating recurrent aphthous stomatitis	RAS	Group A: curcumin 5% orabase Group B: triamcinolone acetanide 0.1% orabase	1. Significant difference in pain severity in both group, but no significant in between 2. Average size of lesion decrease significant in both groups	Effectiveness of 5% curcumin = 0.1% triamcinolone acetanide

12	Shah et al, 2020 ²¹	Effectiveness of curcumin mouthwash on radiation-induced oral mucositis among head and neck cancer patients: A triple-blind, pilot randomised controlled trial	To compare the effectiveness and safety of 0.1% curcumin (freshly prepared using nanoparticles) and 0.15% benzydamine mouthwash	Oral mucositis	Group A: 0.1% curcumin mouthwash Group B: 0.15% benzydamine mouthwash	1. Benzydamine group: none presented with score 4. Curcumin group: none scored 3 and 4 2. The risk of getting the onset was 50% lower in curcumin. 3. Onset of RIOM was also significantly delayed in the test group by 2 weeks, no significant difference between two groups. 4. Both the mouthwashes were equally effective in preventing the occurrence of severe form of RIOM	Use of curcumin 0.1% mouthwash was able to significantly delay the onset of RIOM
13	Bohra et al, 2021 ²²	Black Turmeric and Aloe Vera in the Management of Oral Submucous Fibrosis: A Prospective Clinical Study	To determine the therapeutic efficacy of Kali haldi in the management of oral submucous fibrosis (OSMF) v/s steroid therapy	OSMF	Group A: Kali Haldi and aloe vera gel Group B: intralesional injection of hydrocortisone and hyaluronidase for 6 weeks with oral antioxidant supplements for 3 months.	1. A remarkable decrease in burning sensation in Group A in comparison with Group B at the end of the 3rd month. Interincisal mouth opening did not differ significantly 2. An increase in cheek flexibility and tongue protrusion was significantly higher in Group B	Combination therapy works wonders in the case of OSMF in stages I, II, III and can be a good option, comparatively safe and with negligible side effects, but potent and equally effective management of oral submucous fibrosis.
14	Chandrashekar et al, 2021 ²³	A clinicobiochemical evaluation of curcumin as gel and as buccal mucoadhesive patches in the management of oral submucous fibrosis	To evaluate and compare the efficacy of topical curcumin gel and buccal mucoadhesive patches in the management of oral submucous fibrosis (OSMF)	OSMF	Group I: 2% curcumin gel Group II: curcumin patches	1. Significant reduction in burning sensation Group I 77% Group II 78% 2. Increase in tongue protrusion max 6 mm, cheek flexibility max 5 mm in both group 3. No adverse effect in two groups	Curcumin gel and curcumin patches were effective in improving mouth opening and reducing burning sensation in OSMF
15	Kia et al, 2021 ²⁴	Effects of nanomicelle curcumin capsules on prevention and treatment of oral mucositis in patients under chemotherapy with or without head and neck radiotherapy: a randomized clinical trial	To investigate the effects of nanomicelle curcumin on OM related chemotherapy and head and neck radiotherapy	Oral mucositis	Group A: curcumin nanomicelle capsules 80 mg Group B: placebo capsules	1. The pain score was lower in the study group than the control group in week 7 2. The OM severity was significantly lower in the study group than the control group	Nanomicelle curcumin capsules is effective on prevention and treatment of head and neck radiotherapy and especially chemotherapy induced OM
16	Nerkar Rajbhoj et al, 2021 ²⁵	A Comparative Study to Evaluate Efficacy of Curcumin and Aloe Vera Gel along with Oral Physiotherapy in the Management of Oral Submucous Fibrosis: A Randomized Clinical Trial	To compare the efficacy of Curcumin gel with Aloe vera gel when both the gel are supplemented along with oral physiotherapy in the management of OSMF	OSMF	Group A: curcumin gel Group B: Aloe vera gel	1. Reduction of burning sensation Group B > Group A 2. IID increase Group A > Group B	Curcumin gel and Aloe vera gel are effective in improving OSMF symptoms, but Aloe vera gel is more efficacious in burning sensation improvement without any side effects
17	Adhikari et al, 2022 ²⁶	Efficacy of Curcumin in Combination with Intralesional Dexamethasone with Hyaluronidase in the Treatment of Oral Submucous Fibrosis: A Randomized Controlled Trial	To determine the efficacy of curcumin in combination with intralesional dexamethasone with hyaluronidase in the treatment of oral submucous fibrosis (OSF)	OSMF	Group A: inj. Dexamethasone + hyaluronidase with curcumin capsule (6 weeks) Group B: inj. Dexamethasone + hyaluronidase with placebo capsule (6 weeks)	1. The statistically significant improvement in all the parameters better efficacy of curcumin in combination with intralesional dexamethasone and hyaluronidase in the treatment of OSF than using it alone 2. 100% improvement in burning sensation for both groups	Curcumin in combination with intralesional dexamethasone with hyaluronidase is efficacious in the treatment of OSF

(Continued)

Table 2 (Continued).

No	Reference	Title	Aim	Oral disease	Intervention	Outcome	Result
18	Bakhshi et al, 2022 ²⁷	COMPARATIVE EFFICACY OF 1% CURCUMIN NANOMICELLE GEL AND 2% CURCUMIN GEL FOR TREATMENT OF RECURRENT APHTHOUS STOMATITIS: A DOUBLE-BLIND RANDOMIZED CLINICAL TRIAL	To compare the efficacy of topical application of 1% curcumin nanomicelle gel and 2% curcumin gel for treatment of RAS.	RAS	Group A: 1% curcumin nanomicelle gel Group B: 2% curcumin gel	1. At 7 days, the mean of lesions size were 2.87±2.03 in the curcumin gel and 1.29 ±0.91 in the curcumin nanomicelle gel group; this difference was statistically 2. Pain score was zero in both groups at 7 days, and was not significant between 2 group 3. Efficacy indices of lesion size and VAS 100% in both group,	The 1% nanomicelle gel can be effectively used to enhance the healing of RAS
19	Fardad et al, 2022 ²⁸	A comparative study to assess the effectiveness of curcumin, mucosamin, and chlorhexidine in chemotherapy-induced oral mucositis	To evaluate the efficacy of curcumin, mucosamin, and chlorhexidine in the treatment of chemotherapy-induced oral mucositis	Oral mucositis	Group A: mucosamin spray Group B: curcumin gel 0.5% Group C: chlorhexidine mouthrinse 0.2%	1. Gradual reduction in all three groups, full recovery was observed only in curcumin group 2. OMAS intensity score erythema and ulceration reduce faster in curcumin group than control group 3. No adverse reactions related to all products, except for eight patient experienced a stinging sensation in the chlorhexidine group	Curcumin result in faster recovery in comparison with mucosamin and chlorhexidine
20	Fathima et al, 2022 ²⁹	Comparison of Efficacy of Topical Application of Bleomycin with Adjuvant Antioxidants vs Topical Curcumin Oral Gel with Adjuvant Antioxidants in the Treatment of Oral Leukoplakia	To compare the effectiveness of topical bleomycin with that of topical curcumin in patients with oral leukoplakia (OL)	Oral leukoplakia	Group A: bleomycin solution Group B: Curcumin gel	Group A (n = 10): complete resolution of the lesions, Group B: resolution of the clinical lesion was not substantial	Bleomycin was more efficient producing clinical and histopathologic resolution of oral leukoplakia than curcumin
21	Ramezani et al 2023 ³⁰	Efficacy of curcumin for amelioration of radiotherapy-induced oral mucositis: a preliminary randomized controlled clinical trial	To assess the effect of both oral and topical formulations of curcumin on ROM	Oral mucositis	Group A: curcumin mouthwash 0.1% Group B: curcumin tablet 40 mg Group C: placebo	1. More than 33% and 15% of curcumin mouthwash and curcumin nanocapsule group remained ulcer free compared with none of the placebo-treated subjects 2. WHO and NRS scales in each of the curcumin-treated groups were significantly reduced at the study periods of week 3 compared to the placebo group	Both curcumin mouthwash and nanocapsule were effective, safe, and well tolerated in the treatment of RIOM

proliferation and differentiation to repair the tissue.³³ Curcumin reduced ROS production and suppressed the cytokines.³⁴ Cytokines are modified by NF- κ B which can cause mucosal injury.³⁵ Two articles from Shah et al (2020) and Rao et al (2014) showed curcumin mouthwash inhibits and reduces mucositis compared with benzydamine and povidone iodine ($p<0.0001$).^{10,21} Nanocurcumin capsules from articles Kia et al (2021) and Delavarian et al (2019) showed curcumin reduced the grade of mucositis compared with the intervention group ($p<0.001$).^{10,16,21,24,28,30}

Leukoplakia is an oral potentially malignant disorder lesion characterized with white plaque, not clinically or pathologically like other diseases.³⁶ Leukoplakia is characterized by epithelial keratosis with or without dysplasia.³⁷ Impaired differentiation of oral epithelium is the pathogenesis of leukoplakia.³⁸ Curcumin functions as an antioxidant by inhibiting the production of reactive oxygen species (ROS). It significantly elevates the levels of vitamins C and D in saliva and aids in protecting against lipid peroxidation and DNA damage.³⁹ Curcumin regulates cell division by regulating cell proliferation and inhibiting nuclear factor NF- κ B. In addition, curcumin prevents invasion and metastasis in the epithelium towards the mesenchyme by suppressing excessive TGF β receptor signalling.⁴⁰ One article from Kuriakose et al (2016) stated significant results in clinical and histologic response between systemic curcumin and intervention group. Fathima et al (2022) used curcumin gel and bleomycin in the study. Clinical findings showed downgrading dysplasia into hyperkeratosis in both groups. Bleomycin group has better result in the treatment of leukoplakia compared with curcumin gel. 40% of dysplasia cases downgraded into hyperkeratosis in the bleomycin group, but in the turmeric group only 20% of dysplasia cases turned into hyperkeratosis with P value 0.01. Systemic curcumin showed significant result in improve clinical and histopathologic response compared with the placebo group ($P=0.02$).^{12,29}

RAS is a mucosal tissue damage caused by various aetiologies. The stimulus triggers inflammatory process in the epithelium and initiate lymphocyte infiltration. Lymphocytes release cytokines and oedema develops as an immune response. The ulceration occurs and triggers chemotaxis process. CD8+ lymphocytes, neutrophils, and plasma cells infiltrate followed by epithelial regeneration.⁴¹ Curcumin inhibits the enzymes cyclooxygenase-2 (COX-2) and 5-lipoxygenase, which play a role in triggering inflammation. It reduces the inflammatory response by blocking the production of pro-inflammatory cytokines such as tumour necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6). Additionally, by suppressing the activation of nuclear factor-kappa B (NF- κ B), curcumin decreases the transcription factors that regulate gene expression related to inflammation.⁴² There were two studies used topical curcumin from Bakhshi et al (2022) with 1% curcumin nanomicelle and 2% curcumin gel, and articles from Kia et al (2020) used 5% curcumin gel. Nanomicelle curcumin is greater in absorption. Two articles showed a decrease in VAS and diameter of lesion. Nanocurcumin gel showed significant result compared with curcumin gel in reducing pain score and size of lesion ($p<0.05$). One study found 5% curcumin effective as 0.1% triamcinolone and insignificant results between two groups. Systemic curcumin is used when the lesion is resistant.^{20,27}

OLP is an oral lesion caused by infiltration of cytotoxic CD8+ T lymphocytes and production of cytokines for apoptosis in keratinocytes of the basal cell layer.⁴³ Curcumin plays a role as a free radical scavenger that exhibits antioxidant effects via Nrf-2 activation. Nrf2 is a gene that promotes transcription of antioxidant. Curcumin diminishes inflammation by blocking nitric oxide synthase, which may lower the activation of the TNF- α -induced NF- κ B signalling pathway and inflammatory enzymes such as COX-2.⁴⁴ Curcumin inhibit pathogenesis of OLP by its antioxidant effects and immunomodulatory effect. The immunomodulatory effect activates macrophage, natural killer cells, and modulates T cell proliferation to reduce severity of OLP.⁴⁵ One article from Kia et al (2020) used 80 mg nanocurcumin capsules for the treatment. The decrease in VAS scores and lesion size observed in both the curcumin and prednisolone groups is statistically significant ($p<0.001$); however, there are no notable differences between the two groups.²⁴

Denture stomatitis is an inflammation of the oral mucosa that occurs due to long-term use of removable dentures. One of the factors contributing to denture stomatitis is *Candida albicans*. According to Tatapudi et al, topical curcumin has been demonstrated to be as effective as clotrimazole therapy in treating denture stomatitis.⁴⁶ Improper denture caused trauma to the mucosa leading to an inflammatory response. Poor oral hygiene develops biofilms and plaque on the surface of denture contain bacteria and fungi.⁴⁷ *Candida albicans* attached to the surface of the denture colonizes and then develops from yeast to hyphae, infiltrates mucosal tissue, and causes inflammation.⁴⁸ Moreover, it has anti-inflammatory and wound-healing qualities that support the healing of erythema.¹⁷ Curcumin inhibits virulence factors by reducing proteinase and phospholipase enzymes by *Candida albicans* which play a role in tissue degradation, hyphal

formation, and host invasion, which are important factors in the pathogenesis process. Curcumin modulates inflammatory response by reducing pro-inflammatory cytokines.⁴⁹ Mustafa et al (2019) used curcumin mouthwash for denture stomatitis therapy compared to chlorhexidine mouthwash. Over 14 days of treatment, curcumin has a better result than chlorhexidine on site activity response compared with chlorhexidine and chitosan group ($p<0.05$). Three groups showed an insignificant decrease in *Candida* counts.¹⁷

Curcumin has not been associated with severe side effects in several conducted studies. However, one study mentioned mild digestive issues, including bloating and flatulence, as well as slight yellow discolouration observed on the buccal mucosa, lips, and tongue, which gradually fades over time. This study has various limitations, including a small sample size, a brief duration, varying grades of oral illness, different ratios used, diverse types of interventions, and related costs. Therefore, this investigation cannot determine the long-term negative effects and efficacy of curcumin. Hewlings et al noted that one study indicated that administering curcumin for four months led to nausea and diarrhoea.⁵⁰

Conclusion

Retrieved from 21 articles, curcumin showed anti-inflammatory, antioxidant, inhibiting collagenase, antifungal, and wound healing properties for reducing severity of lesion, pain score, and size of the lesion as the therapeutic effects in the patients with oral disease including OSMF, mucositis, leukoplakia, RAS, OLP, and denture stomatitis. Curcumin was most commonly used for OSMF with the most effective formulation being a combination of curcumin and black pepper. This combination demonstrated statistically significant improvements in mouth opening, burning sensation, tongue protrusion, cheek flexibility, and SOD (superoxide dismutase) levels ($p<0.01$). This systematic review showed curcumin as a therapeutic agent for oral diseases, but its efficacy is hindered by limitations like poor water solubility, limited distribution, and inadequate absorption in the intestines, leading to low bioavailability. More clinical trials in different formulation and combination is warranted to confirm the results. Furthermore, this systematic review can provide important information as a basis for further research in the field of oral medicine, particularly related to herbal medicine for treating oral diseases and formulations that can be effectively used in daily practice. More research is required to evaluate the safest and most effective dosage and formulation of curcumin that is economically feasible, readily available, and appropriate for prolonged usage.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Umapathy VR. Effects of turmeric (*Curcuma longa*) on oral health. *Bioinformation*. 2022;18(6):538–542. doi:10.6026/97320630018538
2. Cory H, Passarelli S, Szeto J, Tamez M, Mattei J. The role of polyphenols in human health and food systems: a mini-review. *Front Nutr*. 2018;5:5. doi:10.3389/fnut.2018.00005
3. Salehi B, Lopez-Jornet P, Pons-Fuster López E, et al. Plant-derived bioactives in oral mucosal lesions: a key emphasis to curcumin, lycopene, chamomile, aloe vera, green tea and coffee properties. *Biomolecules*. 2019;9(3):106. doi:10.3390/biom9030106
4. Sood S, Nagpal M. Role of curcumin in systemic and oral health: an overview. *J Nat Sci Biol Med*. 2013;4(1):3. doi:10.4103/0976-9668.107253
5. Salehi B, Stojanović-Radić Z, Matejić J, et al. The therapeutic potential of curcumin: a review of clinical trials. *Eur J Med Chem*. 2019;163:527–545. doi:10.1016/j.ejmech.2018.12.016
6. Urošević M, Nikolić L, Gajić I, Nikolić V, Dinić A, Miljković V. Curcumin: biological activities and modern pharmaceutical forms. *Antibiotics*. 2022;11(2):135. doi:10.3390/antibiotics11020135
7. Omidian H, Wilson RL, Chowdhury SD. Enhancing therapeutic efficacy of curcumin: advances in delivery systems and clinical applications. *Gels*. 2023;9(8):596. doi:10.3390/gels9080596
8. Inchingolo F, Inchingolo AD, Latini G, et al. The role of curcumin in oral health and diseases: a systematic review. *Antioxidants*. 2024;13(6):660. doi:10.3390/antiox13060660
9. Bučević Popović V, Karahmet Farhat E, Banjari I, Jeličić Kadić A, Puljak L. Bioavailability of oral curcumin in systematic reviews: a methodological study. *Pharmaceuticals*. 2024;17(2):164. doi:10.3390/ph17020164
10. Rao S, Dinkar C, Vaishnav LK, et al. The Indian spice turmeric delays and mitigates radiation-induced oral mucositis in patients undergoing treatment for head and neck cancer. *Integr Cancer Ther*. 2014;13(3):201–210. doi:10.1177/1534735413503549

11. Yadav M, Aravinda K, Saxena VS, et al. Comparison of curcumin with intralesional steroid injections in Oral Submucous Fibrosis – a randomized, open-label interventional study. *J Oral Biol Craniofac Res.* 2014;4(3):169–173. doi:10.1016/j.jobcr.2014.11.003
12. Kuriakose MA, Ramdas K, Dey B, et al. A randomized double-blind placebo-controlled phase IIB trial of curcumin in oral Leukoplakia. *Cancer Prev Res.* 2016;9(8):683–691. doi:10.1158/1940-6207.CAPR-15-0390
13. Pipalia PR, Annigeri RG, Mehta R. Clinicobiochemical evaluation of turmeric with black pepper and nigella sativa in management of oral submucous fibrosis—a double-blind, randomized preliminary study. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2016;122(6):705–712. doi:10.1016/j.oooo.2016.07.023
14. Piyush P, Mahajan A, Singh K, Ghosh S, Gupta S. Comparison of therapeutic response of lycopene and curcumin in oral submucous fibrosis: a randomized controlled trial. *Oral Dis.* 2019;25(1):73–79. doi:10.1111/odi.12947
15. Saran G, Umapathy D, Misra N, et al. A comparative study to evaluate the efficacy of lycopene and curcumin in oral submucous fibrosis patients: a randomized clinical trial. *Indian J Dent Res.* 2018;29(3):303. doi:10.4103/ijdr.IJDR_551_16
16. Delavarian Z, Pakfetrat A, Ghazi A, et al. Oral administration of nanomicelle curcumin in the prevention of radiotherapy-induced mucositis in head and neck cancers. *Special Care Dentistry.* 2019;39(2):166–172. doi:10.1111/scd.12358
17. Mustafa MW, Ungphaboon S, Phadoongsombut N, Pangsombon K, Chelae S, Mahattanadul S. Effectiveness of an alcohol-free chitosan–curcuminoid mouthwash compared with chlorhexidine mouthwash in denture stomatitis treatment: a randomized trial. *J Altern Complementary Med.* 2019;25(5):552–558. doi:10.1089/acm.2018.0459
18. Bhowate RR, Lanjekar AB, Bakhle S, Narayane A, Pawar V, Gandagule R. Comparison of efficacy of topical curcumin gel with triamcinolone-hyaluronidase gel individually and in combination in the treatment of oral submucous fibrosis. *J Contemp Dent Pract.* 2020;21(1):83–90. doi:10.5005/jp-journals-10024-2726
19. Kia SJ, Basirat M, Mortezaie T, Moosavi MS. Comparison of oral Nano-Curcumin with oral prednisolone on oral lichen planus: a randomized double-blinded clinical trial. *BMC Complement Med Ther.* 2020;20(1):328. doi:10.1186/s12906-020-03128-7
20. Kia SJ, Mansourian A, Basirat M, Akhavan M, Mohtasham-Amiri Z, Moosavi MS. New concentration of curcumin orabase in recurrent aphthous stomatitis: a randomized, controlled clinical trial. *J Herbs Med.* 2020;22:100336. doi:10.1016/j.hermed.2020.100336
21. Shah S, Rath H, Sharma G, Senapati S, Mishra E. 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.* 2020;31(5):718. doi:10.4103/ijdr.IJDR_822_18
22. Bohra A, Maheswari TN, Harsh A, Garg A. Black turmeric and aloe vera in the management of oral submucous fibrosis: a prospective clinical study. *Asian Pac J Cancer Prev.* 2021;22(12):3941–3947. doi:10.31557/APJCP.2021.22.12.3941
23. Chandrashekar A, Annigeri RG, U VA, Thimmasetty J. A clinicobiochemical evaluation of curcumin as gel and as buccal mucoadhesive patches in the management of oral submucous fibrosis. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2021;131(4):428–434. doi:10.1016/j.oooo.2020.12.020
24. Kia SJ, Basirat M, Saedi HS, Arab SA. Effects of nanomicelle curcumin capsules on prevention and treatment of oral mucositis in patients under chemotherapy with or without head and neck radiotherapy: a randomized clinical trial. *BMC Complement Med Ther.* 2021;21(1):232. doi:10.1186/s12906-021-03400-4
25. Nerkar Rajbhoj A, Kulkarni TM, Shete A, Shete M, Gore R, Sapkal R. A comparative study to evaluate efficacy of curcumin and aloe vera gel along with oral physiotherapy in the management of oral submucous fibrosis: a randomized clinical trial. *Asian Pac J Cancer Prev.* 2021;22(S1):107–112. doi:10.31557/APJCP.2021.22.S1.107
26. Adhikari S, Rimal J, Maharjan I, Shrestha A. Efficacy of curcumin in combination with intralesional dexamethasone with hyaluronidase in the treatment of oral submucous fibrosis: a randomized controlled trial. *Asian Pac J Cancer Prev.* 2022;23(9):3125–3132. doi:10.31557/APJCP.2022.23.9.3125
27. Bakhshi M, Mahboubi A, Jaafari MR, Ebrahimi F, Tofangchiha M, Alizadeh A. Comparative efficacy of 1% curcumin nanomicelle gel and 2% curcumin gel for treatment of recurrent aphthous stomatitis: a double-blind randomized clinical trial. *J Evidence-Based Dent Pract.* 2022;22(2):101708. doi:10.1016/j.jebdp.2022.101708
28. Fardad F, Ghasemi K, Ansarinjad N, Khodakarim N, Nasiripour S, Farasatinasab M. A comparative study to assess the effectiveness of curcumin, mucosamin, and chlorhexidine in chemotherapy-induced oral mucositis. *EXPLORE.* 2023;19(1):65–70. doi:10.1016/j.explore.2022.04.009
29. Fathima AS, Manoharan GVMG. Comparison of efficacy of topical application of bleomycin with adjuvant antioxidants vs. Topical curcumin oral gel with adjuvant antioxidants in the treatment of oral leukoplakia. *J Indian Acad Oral Med Radiol.* 2022;34(4):409. doi:10.4103/jiaomr.jiaomr_201_22
30. Ramezani V, Ghadirian S, Shabani M, Boroumand MA, Daneshvar R, Saghaei F. Efficacy of curcumin for amelioration of radiotherapy-induced oral mucositis: a preliminary randomized controlled clinical trial. *BMC Cancer.* 2023;23(1):354. doi:10.1186/s12885-023-10730-8
31. Rai A, Siddiqui M, Parveen S, Parveen S, Rasheed A, Ali S. Molecular pathogenesis of oral submucous fibrosis: a critical appraisal. *Biomed Pharmacol J.* 2019;12(04):2027–2036. doi:10.13005/bpj/1835
32. Zhang SS, Gong ZL, Li WH, Wang X, Ling TY. Antifibrotic Effect of Curcumin in TGF- β 1-induced myofibroblasts from human oral mucosa. *Asian Pac J Cancer Prev.* 2012;13(1):289–294. doi:10.7314/APJCP.2012.13.1.289
33. Georgiou M, Patapatiou G, Domoxoudis S, Pisteveu-Gompaki K, Papanikolaou A. Oral Mucositis: understanding the pathology and management. *Hippokratia.* 2012;16(3):215–216.
34. Idrees M, Kujan O. A curcumin-based oral gel has potential protective efficacy against oral mucositis: in vitro study. *J Pers Med.* 2023;14(1):1. doi:10.3390/jpm14010001
35. Punatar S, Katti K, Rajamanickam D, et al. Role of curcumin in reducing toxicities associated with mucosal injury following melphalan-based conditioning in autologous transplant setting. *Cell Transplant.* 2022;31:096368972210869. doi:10.1177/09636897221086969
36. Parlatescu I, Gheorghe C, Coculescu E, Tovar S. Oral leukoplakia - an update. *Maedica.* 2014;9(1):88–93.
37. Guimarães LM, Diniz MG, Rogatto SR, Gomez RS, Gomes CC. The genetic basis of oral leukoplakia and its key role in understanding oral carcinogenesis. *J Oral Pathol Med.* 2021;50(7):632–638. doi:10.1111/jop.13140
38. Villa A, Woo SB. Leukoplakia—A Diagnostic and Management Algorithm. *J Oral Maxillofacial Surg.* 2017;75(4):723–734. doi:10.1016/j.joms.2016.10.012
39. Rai B, Kaur J, Jacobs R, Singh J. Possible action mechanism for curcumin in pre-cancerous lesions based on serum and salivary markers of oxidative stress. *J Oral Sci.* 2010;52(2):251–256. doi:10.2334/josnusd.52.251

40. Bose S, Panda AK, Mukherjee S, Sa G. Curcumin and tumor immune-editing: resurrecting the immune system. *Cell Div.* **2015**;10(1):6. doi:10.1186/s13008-015-0012-z
41. Rivera C. Essentials of recurrent aphthous stomatitis (Review). *Biomed Rep.* **2019**. doi:10.3892/br.2019.1221
42. Idrees M, Kujan O. Curcumin is effective in managing oral inflammation: an in vitro study. *J Oral Pathol Med.* **2024**;53(6):376–385. doi:10.1111/jop.13547
43. Glick M, Greenberg MS, Lockhart PB. *Challacombe SJ*. editors.. Burket's Oral Medicine. Wiley; **2021**.
44. Khosrojerdi M, Gumprich E, Jamialahmadi T, Kesharwani P, Sahebkar A. Is curcumin a safe and effective therapeutic in the treatment against oral lichen planus? *Curr Med Chem.* **2023**;30(15):1684–1688. doi:10.2174/0929867330666221202150727
45. Lv KJ, Chen TC, Wang GH, Yao YN, Yao H. Clinical safety and efficacy of curcumin use for oral lichen planus: a systematic review. *J Dermatological Treat.* **2019**;30(6):605–611. doi:10.1080/09546634.2018.1543849
46. Tatapudi R, Abdul Samad S, Manyam R, Dasari D, Lakshmi R. Efficacy of curcumin in the treatment of denture stomatitis: a randomized double-blind study. *J Oral Maxillofacial Pathol.* **2021**;25(2):286. doi:10.4103/0973-029X.325128
47. Gendreau L, Loewy ZG. Epidemiology and Etiology of Denture Stomatitis. *J Prosthodontics.* **2011**;20(4):251–260. doi:10.1111/j.1532-849X.2011.00698.x
48. Abuhajar E, Ali K, Zulfiqar G, et al. Management of chronic atrophic candidiasis (denture stomatitis)—a narrative review. *Int J Environ Res Public Health.* **2023**;20(4):3029. doi:10.3390/ijerph20043029
49. Chen E, Benso B, Seleem D, et al. Fungal-host interaction: curcumin modulates proteolytic enzyme activity of *Candida albicans* and inflammatory host response *In Vitro.* *Int J Dent.* **2018**;2018:1–7. doi:10.1155/2018/2393146
50. Hewlings S, Kalman D. Curcumin: a review of its effects on human health. *Foods.* **2017**;6(10):92. doi:10.3390/foods6100092

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