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Review Article

Therapeutic Effects of Curcumin on Different Types of Oral Diseases: Evidence from Preclinical Animal Studies and Clinical Trials

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Abstract

Background: The present study aims to review and summarize the therapeutic effects of curcumin on different types of oral diseases, along with the mechanisms of action based on evidence.

Methods: A comprehensive review of preclinical animal studies and clinical trials published from 2014 to 2024 in PubMed, Scopus, ScienceDirect, Web of Science, Wiley Online Library, and Google Scholar was conducted. Risk of bias was assessed using SYRCLE's RoB tool for preclinical animal studies and Cochrane RoB 2 for clinical trials.

Results: Based on the review, we highlight that curcumin has strong potential as a promising adjuvant therapeutic agent for various oral diseases, such as periodontal diseases (gingivitis and periodontitis), recurrent aphthous stomatitis, oral mucositis, oral lichen planus, oral leukoplakia, oral submucous fibrosis, and oral cancer, as evidenced by both preclinical animal studies and clinical trials. These effects are attributed to curcumin's reported anti-inflammatory, antioxidant, antifungal, antimicrobial, immunomodulatory, and anticancer activities. We also found that no significant adverse side effects were reported from subjects given curcumin compared with those given conventional therapy. However, although curcumin offers significant therapeutic effects on oral diseases, we found limitations in clinical trials of curcumin on some diseases, especially oral cancer. Therefore, future studies related to clinical trials on some oral diseases with rigorous methods may be warranted.

Conclusion: Curcumin seems promising as a therapeutic agent for oral diseases. However, further clinical trials with more rigorous methods and larger samples are strongly needed.

Keywords: curcumin, periodontitis, recurrent aphthous stomatitis, oral mucositis, oral lichen planus

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1. Introduction

Oral disease is a condition affecting both the hard and soft tissues of the oral cavity. It is a health issue that is often overlooked, despite being a major global public health problem affecting around 3.5 billion people worldwide [1, 2], with dental caries, periodontal disease, and tooth loss being the most prominent oral diseases in 2017 [3]. Several studies indicate that oral diseases and oral microbiota can influence overall health and are related to the development of various systemic diseases [4–11]. Since dental and oral health are closely linked to general health, and considering the high number of oral disease cases worldwide, it is essential to address oral disease seriously.

Although conventional medical treatment of oral diseases has been practiced for a long time, herbal medications have shown rapid development due to their unique therapeutic properties. This is in addition to topical drugs used to maintain oral health, which have significant side effects. For example, chlorhexidine is the most commonly prescribed chemotherapeutic agent as an adjunct to oral disease treatment, including scaling and root planning [12, 13]. However, evidence suggests that it causes adverse effects, including tooth and tongue discoloration, antimicrobial resistance, allergic reactions, oral and tongue paresthesia, altered taste perception, oral pain, xerostomia, aphthous ulcers, taste disturbances, and glossodynia [14–16].

In addition to chlorhexidine as a mouthwash, studies report that several types of antibiotics are also given to patients with oral diseases [17, 18]. Although antibiotic administration has a major effect on the treatment of oral diseases [19, 20], they are sometimes prescribed inappropriately and excessively, leading to the development of antimicrobial resistance [21, 22]. Therefore, management of oral diseases using alternative agents that have minimal side effects, such as natural products, is necessary [23]. Previous comprehensive studies have explored and summarized various natural products from herbal plants that are used for the maintenance and treatment of different dental and oral diseases. Curcumin is one such plant [24, 25] and is known as a safe compound to use even in large doses in mammals because of its nontoxicity [26].

Curcumin or diferuloylmethane is a compound derived from turmeric (*Curcuma longa* L.), which is a constituent of polyphenols [27, 28]. It is reported to have strong potential for use in the therapy of different chronic diseases, including neurodegenerative, cardiovascular, autoimmune, metabolic, pulmonary, gastrointestinal, and psychiatric disorders [29–35], as well as various oral diseases [36]. This is proven by several studies reporting that curcumin exhibits anti-inflammatory, anticancer, antimicrobial, antiviral, antioxidant, and antimutagenic properties [37–44]. Curcumin can overcome pathogens through antioxidant mechanisms by effectively breaking down reactive oxygen species (ROS) and increasing the activity of detoxification enzymes such as glutathione-S-transferase (GST). Additionally, through anti-inflammatory mechanisms, it inhibits the formation of enzymes that catalyze inflammatory processes such as cyclooxygenase (COX)-2 and 5-lipoxygenase [45]. Thus, curcumin is considered to have strong potential in inhibiting or treating various diseases, and is helpful as a medicinal agent for oral diseases.

Although the study and public interest in herbal medicine continue to increase due to its minimal

side effects, comprehensive studies related to curcumin on oral diseases are still limited and need to be updated [36, 46, 47]. This study aims to comprehensively summarize the therapeutic effects of curcumin on different types of oral diseases by conducting a comprehensive review of preclinical studies in animal models or in *in vivo* and clinical trials, along with its evidence-based mechanisms of action.

2. Methods

A comprehensive review was conducted to summarize and review the therapeutic effects of curcumin on different types of oral diseases, along with its mechanisms of action. This search employed several electronic databases, including PubMed, Scopus, ScienceDirect, Web of Science, Wiley Online Library, and Google Scholar. In the literature search, the following keyword combinations were applied: "curcumin," "diferuloylmethane," "curcuma," "Curcuma longa," "turmeric," "oral disease," "oral health," "periodontal," "gingivitis," "periodontitis," "recurrent aphthous stomatitis," "oral ulcer," "oral aphthous," "stomatitis," "oral mucositis," "oral potentially malignant," "oral lichen planus," "oral leukoplakia," "oral submucous fibrosis," "oral cancer," "oral squamous cell carcinoma," and "oral neoplasm," with Boolean operator "AND" and "OR."

Screening was performed on all search results based on title, abstract, or full-text manuscript. Inclusion criteria were applied in this process, which included peer-reviewed, written in English, and full-text papers of preclinical animal studies and clinical trials, as well as articles explaining the effects of curcumin on oral diseases. Studies were excluded if they met the exclusion criteria, such as having irrelevant information, not having fully available manuscripts, being written in languages other than English, or not having English translations available. Review articles, letters to the editor, commentaries, and *in vitro* and computational studies were also excluded. Additionally, to prevent outdated studies and ensure that our review remains relevant, we limited our search to studies published in the last 10 years, from January 2014 to May 2024.

All included articles were subsequently evaluated for risk of bias. Two authors (FMR and AJS) independently performed the risk of bias assessment, which was then validated by a senior researcher (AI). Systematic review center for laboratory animal experimentation's risk of bias (SYRCLE's RoB) tool was used for risk of bias assessment in preclinical animal studies, with judgments of "Yes," "Unclear," and "No" indicating low, unclear, and high risk of bias, respectively [48]. Meanwhile, the included clinical trials were evaluated using the Cochrane risk of bias 2 (RoB 2) with assessments of "low risk of bias," "some concerns," and "high risk of bias" [49].

Finally, three authors (FMR, WEW, and RA) read all included studies and extracted important information in tables containing types of oral disease, subjects (strains or patients with oral disease), curcumin (dose and mode), control, outcomes, mechanism of action, and reference. The extracted data were analyzed qualitatively in the discussion.

3. Results

The search results in electronic databases identified, after removing duplicates and publications prior to 2014, a total of 3673 potential records.

Initial screening was carried out by evaluating the titles, resulting in 2602 articles being excluded and 1071 reports remaining. We then performed further screening based on title and abstract, resulting in the exclusion of 747 reports, leaving 324 articles remaining. The remaining studies were then subjected to an eligibility evaluation by reading the entire manuscript, resulting in 276 being excluded for the following reasons: being review studies, using curcumin derivatives or in combination with other agents, using photodynamic therapy, having issues with methodology, study objectives being irrelevant, the full-text manuscript not being available, and being written in languages other than English. Finally, a total of 48 studies were included in this review. The entire study selection process is shown in the PRISMA flowchart in Figure **1**.

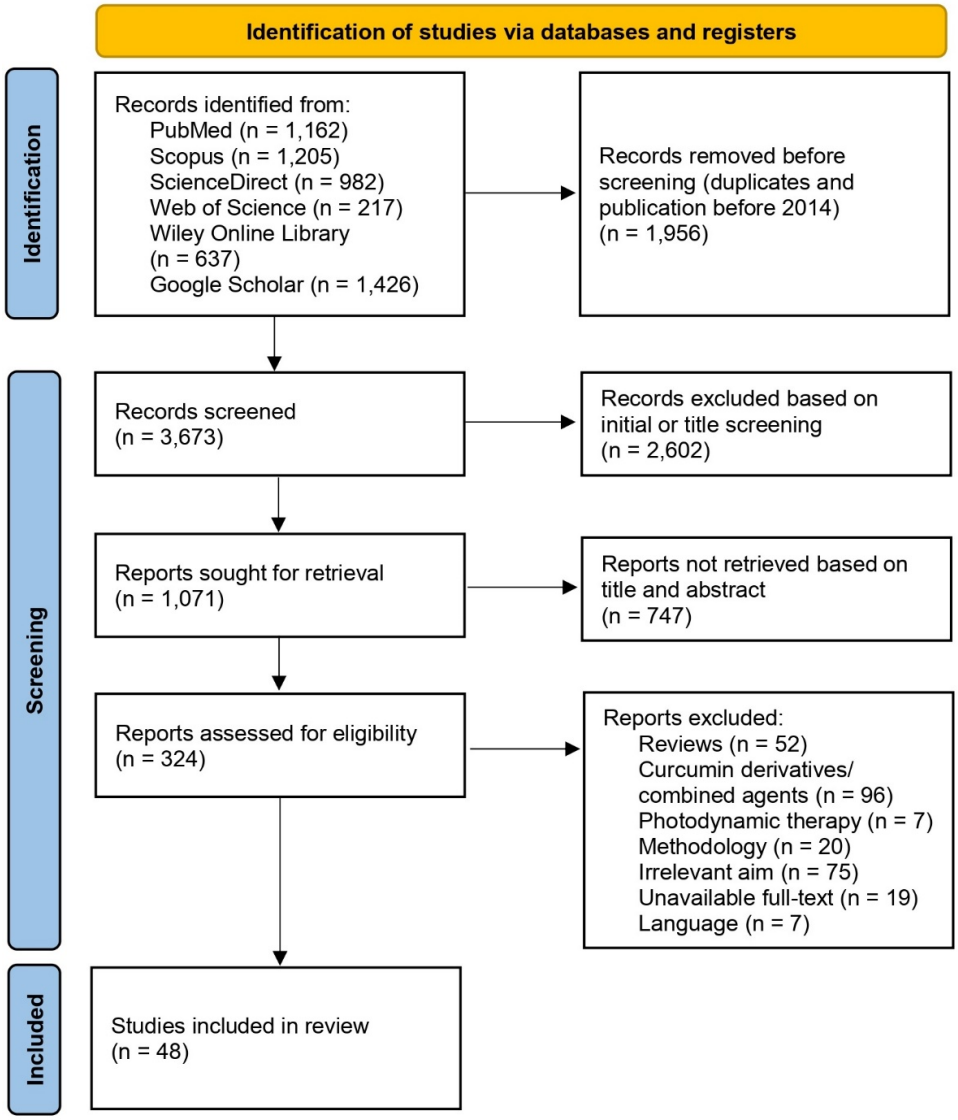

Figure 1: PRISMA flowchart.

The included studies consisted of 14 preclinical animal studies and 34 clinical trials. All studies investigated the potential and effects of curcumin on various types of oral diseases, including gingivitis [50–53], periodontitis [54–67], recurrent aphthous stomatitis (RAS) [68–72], oral

mucositis [73–78], oral lichen planus (OLP) [79–83], oral leukoplakia [84, 85], oral submucous fibrosis (OSF) [86–94], and oral cancer [95–97]. The characteristics of the included studies are described in Table **1**. In addition, the mechanism and summary of the therapeutic effects of curcumin on oral diseases are depicted in Figure **2**.

Table 1: Characteristics and summary of the included studies.

Oral disease	Subjects	Curcumin (dose and mode)	Control	Outcomes and mechanism of action	Reference
Gingivitis	30 patients with generalized chronic gingivitis	Curcumin mouthwash 0.1%, gargled 2 times a day for 28 days	I: Saline II: Chlorhexidine mouthwash 0.2%	Curcumin reduced GI, PI scores, and ROM levels.	[50]
Gingivitis	60 patients	Curcumin mouthwash 0.1%, gargled 2 times a day for 28 days	I: Chlorhexidine mouthwash 0.12% II: Scaling and polishing	Curcumin significantly decreased PI, GI, and BOP scores, and decreased salivary IL-1β levels.	[52]
Gingivitis	60 patients	Curcumin gel 1%, topically twice a day for 29 days	I: Chlorhexidine gel 1% II: Chlorhexidine 0.25% and metronidazole gel	Curcumin significantly reduced IL-1β and CCL28.	[53]
Gingivitis	15 Wistar rats	Curcumin suspension 1%, orally daily for 8 days	No treatment	Curcumin decreased the number of lymphocytes and MMP-13 expression.	[51]
Periodontitis	21 Wistar rats	Curcumin gel 2%, topically once every 2 days for 6 days	I: No treatment II: Plain gel	Curcumin lowered GI scores.	[58]
Periodontitis	40 Wistar rats	Curcumin 100 mg/kg, via gavage daily and observed for 30 days	I: Placebo II: Resveratrol 10 mg/kg	Curcumin decreased IL-1β levels and increases IL-4 levels.	[56]
Periodontitis	60 Holtzman rats	Curcumin 300 mg/kg, via oral gavage daily for 15 days	I: No treatment II: Vehicle	Curcumin inhibited NF-κB activity.	[57]
Periodontitis	16 Holtzman rats	Nano-curcumin 3 µL, injected 3 times a week for 28 days	Empty nanoparticles	Curcumin decreased the number of PMN and mononuclear cells, and inhibited p38 MAPK and NF-κB activation.	[67]
Periodontitis	60 patients with chronic periodontitis	Curcumin solution 1% 10 mL, irrigated subgingivally for 7 days	I: SRP II: Chlorhexidine 0.12%	Curcumin reduced serum ALP and CRP levels.	[60]
Periodontitis	20 patients	Nano-curcumin 50 µg, applied once after SRP and observed for 180 days	Empty nanoparticles	Curcumin inhibited the increase in IL-1α, and reduced IL-6 and TNF-α levels.	[62]
Periodontitis	35 Wistar rats	Curcumin 30 mg/kg, via oral gavage daily for 15 days	DMSO	Curcumin decreased IL-6 and IL-1β.	[66]
Periodontitis	54 patients with stage II grade A periodontitis	Curcumin gel 2%, applied once a week after SRP and observed for 42 days	I: Healthy patients (negative control) II: SRP (positive control)	Curcumin reduced salivary PCT levels.	[54]
Periodontitis	50 Wistar rats	Curcumin gel 12.5 µg/mL, applied to the pocket twice daily for 7 days	I: Healthy rats II: No treatment III: Tetracycline gel 6 µg/mL IV: SRP	Curcumin decreased the concentration of IL-6, CRP, ALP, and MMP-8 activity.	[61]

Table 1: Continued.

Oral disease	Subjects	Curcumin (dose and mode)	Control	Outcomes and mechanism of action	Reference
Periodontitis	48 Wistar rats	Curcumin 1%, irrigated once every 3 days for 14 days	No treatment	Curcumin inhibited MMP-7 activity.	[59]
Periodontitis	25 patients with chronic periodontitis	Curcumin gel 1%, applied locally along with SRP at baseline, 1, 3, and 6 months	SRP	Curcumin improved PI, BOP, PPD, and CAL.	[55]
Periodontitis	45 C57/BL mice	Curcumin 50, 100, and 200 mg/kg daily, via oral gavage for 10 days	I: Healthy mice II: Untreated	Curcumin increased SOD activity and GSH content, and reduced MDA levels.	[65]
Periodontitis	24 Wistar rats	Curcumin gel 12.5 µg/mL, applied once a day for 30 days	Chlorhexidine gel 0.2%	Both curcumin and chlorhexidine decreased the number of osteoclast cells, as well as IL-1β and RANKL levels.	[64]
Periodontitis	20 patients with chronic periodontitis	Curcumin gel 10 mg, applied subgingivally and evaluated after 30 days	Ornidazole gel 1%	Both curcumin and ornidazole significantly reduced PD, CAL, and PI when compared to baseline, but the reduction was more significant with curcumin when compared to control.	[63]
RAS	58 patients	Curcumin orabase 5%, applied 3 times a day for 10 days	Triamcinolone acetonide 0.1%	Both curcumin and control reduced the sizes of RAS lesions. Curcumin produced RAS lesions without pain, burning sensation, or impaired taste function.	[70]
RAS	48 patients with minor RAS	Curcumin oral gel 2%, applied to the lesions 4 times a day and observed for 180 days	Topical amlexanox paste 5%	Curcumin reduced erythema and pain scores, lesion size, and RAS recurrence rate better than controls.	[69]
RAS	105 patients with minor RAS	Curcumin gel, topically 3 times a day for 7 days	I: Honey II: Orabase	Curcumin reduced lesion size, pain, erythema, and exudate more effectively than controls.	[71]
RAS	60 patients with minor RAS	Curcumin gel 1%, applied 3 times a day for 7 days	Triamcinolone acetonide gel 0.1%	Curcumin reduced pain, size, number, and duration of RAS.	[68]
RAS	40 patients	Curcumin gel, applied 3 times daily for 7 days	Triamcinolone acetonide gel	Curcumin reduced pain and lesion count.	[72]
Oral mucositis	37 patients with mild to moderate radiation-induced oral mucositis	I: Curcumin mouthwash 0.1%, gargled 3 times a day for 21 days II: Curcumin soft gel, 1 capsule once a day for 21 days	Placebo mouthwash	Curcumin (mouthwash or topical gel) reduced the severity and pain or burning sensation.	[76]
Oral mucositis	37 patients with radiation-induced oral mucositis	Curcumin gel 0.5%, applied thinly over entire mouth 3 times a day for 21 days	Placebo gel	Curcumin effectively reduced the symptoms of oral mucositis, and significantly reduced the lesion size, burning sensation, and erythema.	[75]

Table 1: Continued.

Oral disease	Subjects	Curcumin (dose and mode)	Control	Outcomes and mechanism of action	Reference
Oral mucositis	71 patients with chemotherapy-induced oral mucositis	Curcumin gel 0.5%, applied thinly over entire mouth 4 times a day for 14 days	I: Oral spray containing hyaluronic acid with amino acid II: Chlorhexidine mouthwash 0.2%	Curcumin repaired and recovered lesions faster, improved erythema effectively, and reduced pain faster, compared to the two controls.	[74]
Oral mucositis	74 patients with radiation-induced oral mucositis	Curcumin mouthwash 0.1%, gargled 3 times a day for 7 days	Benzydamine mouthwash 0.15%	Curcumin delayed the appearance and reduced the severity of lesions significantly compared to controls.	[78]
Oral mucositis	72 golden Syrian hamsters with 5-fluorouracil-induced oral mucositis	Mucoadhesive formulation containing curcumin, topically 2 times a day and observed for 14 days	I: No treatment II: Mucoadhesive formulation without any active compound III: Chamomilla extract	Curcumin reduced the severity of lesions, showed complete healing of lesions, and accelerated re-epithelialization on day 8 characterized by decreased angiogenesis and TGF-β1 levels.	[77]
Oral mucositis	31 patients with radiation-induced oral mucositis	Curcumin gel 1%, applied 3 times a day and observed for 21 days	Dexamethasone-based mouthwash	Curcumin effectively reduced lesion severity and pain level and increased salivary EGF.	[73]
OLP	57 patients	Curcumin capsule 80 mg, taken once a day and observed for 28 days	Prednisolone capsule 10 mg, and the dose is tapered off	Curcumin was effective in reducing the severity of pain, the burning sensation, and the size of the lesions.	[81]
OLP	50 patients with atrophic or ulcerative OLP	Curcumin oral paste 5%, applied 3 times a day and observed for 28 days	Triamcinolone acetonide 0.1%	Curcumin was effective in reducing pain severity and lesion appearance scores.	[82]
OLP	27 patients with atrophic or erosive OLP	Curcumin ointment, applied 3 times a day and observed for 14 days	Triamcinolone acetonide 0.1%	Curcumin reduced pain levels, erythema, and lesion size.	[80]
OLP	40 patients	Mucoadhesive paste containing curcumin, applied 3 times a day and observed for 84 days	Betamethasone local lotion 0.1%	Curcumin reduced lesion size, severity, and pain levels.	[83]
OLP	40 patients	Curcumin gel 1%, applied 3 times a day and observed for 90 days	Triamcinolone acetonide 0.1%	Curcumin effectively reduced the burning sensation, size and extension of lesions, and erythema and ulceration.	[79]
Oral leukoplakia	223 patients	Curcumin capsule 600 mg, taken 2 times a day 3 capsules (3.6 g/day) and observed for 365 days	Placebo	Curcumin provided significant clinical and histological responses.	[85]
Oral leukoplakia	30 patients	Curcumin capsule 250 mg, once a day and observed for 30 days	No control	Curcumin decreased the size and number of lesions, and increased serum SOD levels.	[84]

Table 1: Continued.

Oral disease	Subjects	Curcumin (dose and mode)	Control	Outcomes and mechanism of action	Reference
OSF	30 patients	Curcumin lozenges 400 mg (total dose 2 g/day), accompanied by physiotherapy with mouth exercise device, observed for 180 days	Clobetasol propionate 0.05%, accompanied by physiotherapy with mouth exercise device	Curcumin and physiotherapy were effective in reducing burning sensation and increasing mouth opening.	[88]
OSF	119 patients	I: Curcumin tablets 300 mg (and piperine 5 mg), orally 3 times a day, observed for 84 days II: Curcumin tablets orally 3 times a day along with curcumin mouthwash 0.1% gargled 2 times a day, observed for 84 days	Antioxidant capsule	Both curcumin tablets and mouthwash were effective in improving mouth opening and tongue protrusion, as well as in reducing burning sensation.	[92]
OSF	40 patients	I: Curcumin gel 2%, applied twice a day, observed for 56 days II: Curcumin mucoadhesive patch 2%, applied to the buccal mucosa twice a day, observed for 56 days	No control	Curcumin, either gel or patch, were effective in reducing burning sensation, improving mouth opening and tongue protrusion, and decreasing serum LDH levels.	[86]
OSF	30 patients	Curcumin tablets 500 mg, orally 2 times a day and observed for 180 days	Triamcinolone acetonide gel 0.1%	Curcumin improved mouth opening and reduced burning sensation.	[87]
OSF	120 patients	I: Curcumin tablets 350 mg, orally 3 times a day and observed for 60 days II: Curcumin capsule 500 mg, orally 2 times a day and observed for 60 days III: Curcumin oil 10 mL, topically 2 times a day and observed for 60 days	Multivitamin tablet	Curcumin improved mouth opening and tongue protrusion and reduced burning sensation.	[93]
OSF	42 patients	I: Curcumin capsule 400 mg, orally 2 times a day and observed 90 days II: Curcumin capsule 400 mg, orally 2 times a day combined with betamethasone intralesional injection 4 mg/mL, and observed for 90 days	Placebo tablet	Curcumin improved mouth opening and reduced burning sensation.	[90]
OSF	40 patients	Curcumin tablets 300 mg (and piperine 5 mg), orally 2 tablets once a day and observed for 90 days	Intralesional injection of dexamethasone 4 mg/mL, hyaluronidase 1500 IU, along with lignocaine hydrochloride 2% (1:80,000) 0.5 mL	Curcumin eliminated burning sensation and improved mouth opening.	[94]

Table 1: Continued.

Oral disease	Subjects	Curcumin (dose and mode)	Control	Outcomes and mechanism of action	Reference
OSF	120 patients with Grade II OSF	Curcumin capsule 500 mg, orally 2 times a day and observed for 84 days	I: *Aloe vera* gel II: Lycopene capsule 8 mg	Curcumin improved mouth opening, and reduced the severity of pain, burning sensation, and discomfort.	[91]
OSF	150 patients	I: Curcumin capsule 500 mg, orally 2 times a day with stopping betel nut habitual, and observed for 28 days II: Curcumin capsule 500 mg, orally 2 times a day without stopping betel nut habitual, and observed for 28 days	I: OSF patients with bad habit cessation II: Patient with betel nut habitual without OSF III: Healthy controls	Curcumin reduces serum MDA levels.	[89]
Oral cancer	35 Sprague Dawley rats	Curcumin 80 mg/kg, orally 3 times a day and observed for 28 days	No treatment	Curcumin decreases the expression of COX-2 and NF-κB.	[97]
Oral cancer	50 Holtzman rats with 4-nitroquinoline 1-oxide-induced oral cancer	Curcumin 30 and 100 mg/kg, via gavage once daily and observed for 84 days	I: Euthanasia at baseline (negative control) II: Vehicle	Curcumin decreased the expression of BCL-2, PCNA, SOCS1 and 3, and STAT3.	[95]
Oral cancer	Mice injected with HEp-2 cells	Curcumin 200 mg/kg, orally for 4 weeks and observed for 28 days	Vehicle	Curcumin slowed tumor growth, drastically reduced Ki-67 expression, increased p-ATM expression, induced Chk1 and Cdc25c phosphorylation, decreased CD31 and MVD expression, and decreased HIF-1*α*, VEGF, MMP-2, and MMP-9 expression.	[96]

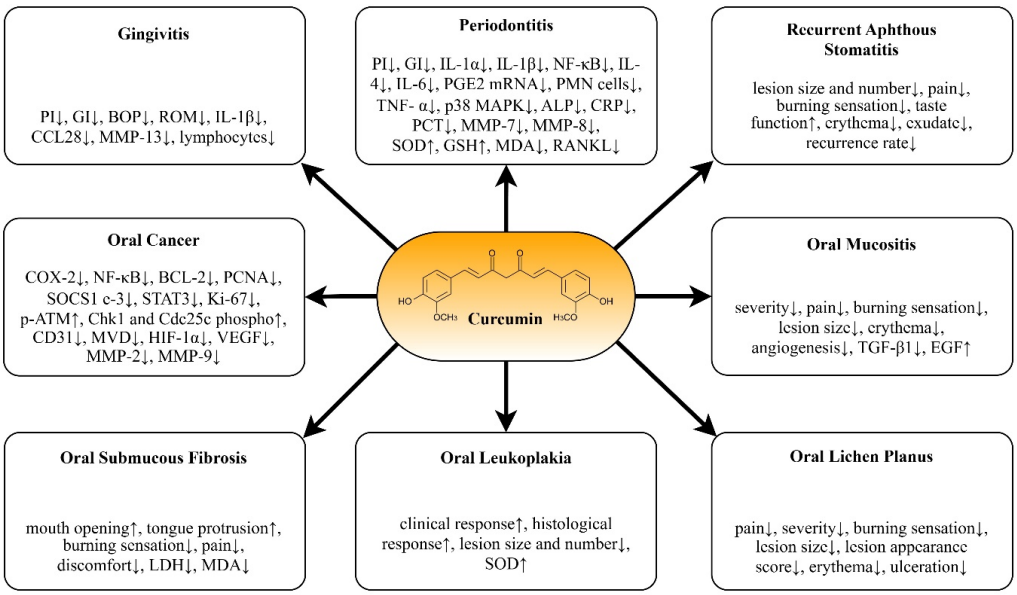

Figure 2: Summary of the therapeutic effects of curcumin on oral diseases based on evidence from preclinical animal studies and clinical trials.

Based on the results of the risk of bias assessment in preclinical animal studies using the SYRCLE's RoB tool, the majority of studies were assessed as having a low risk of bias in the domains of baseline characteristics (selection bias), random housing (performance bias), and selective outcome reporting (reporting bias). Meanwhile, the other sources of bias (other) domain in all studies were assessed as unclear because the entire study was unclear in reporting other possible biases. Additionally, two domains, allocation concealment (selection bias) and blinding (performance bias), were the domains most often considered to have a high risk of bias. All details of the risk of bias assessment results for preclinical animal studies are presented in Figure **3**.

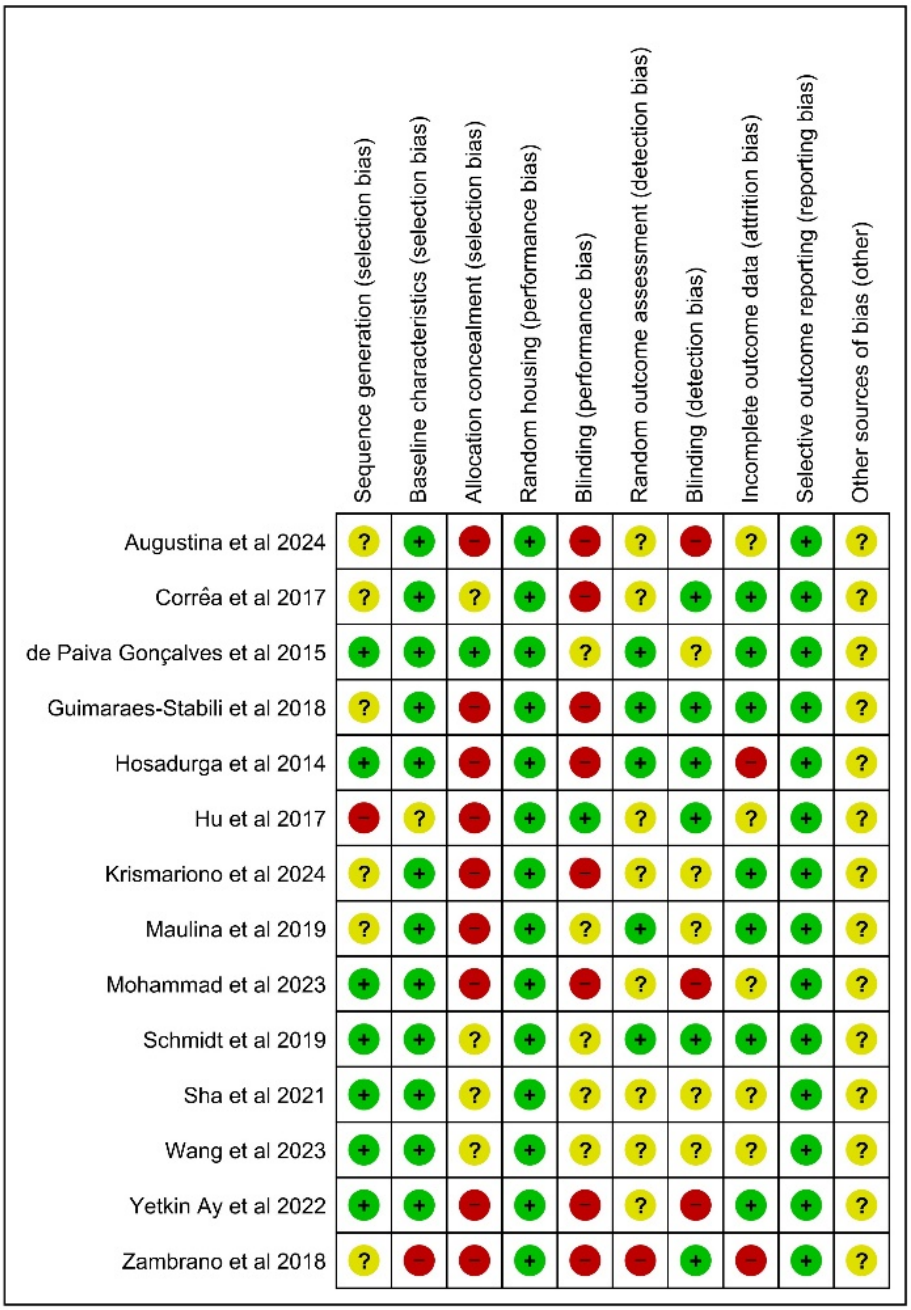

Figure 3: Summary of risk of bias for preclinical animal studies using the SYRCLE's RoB.

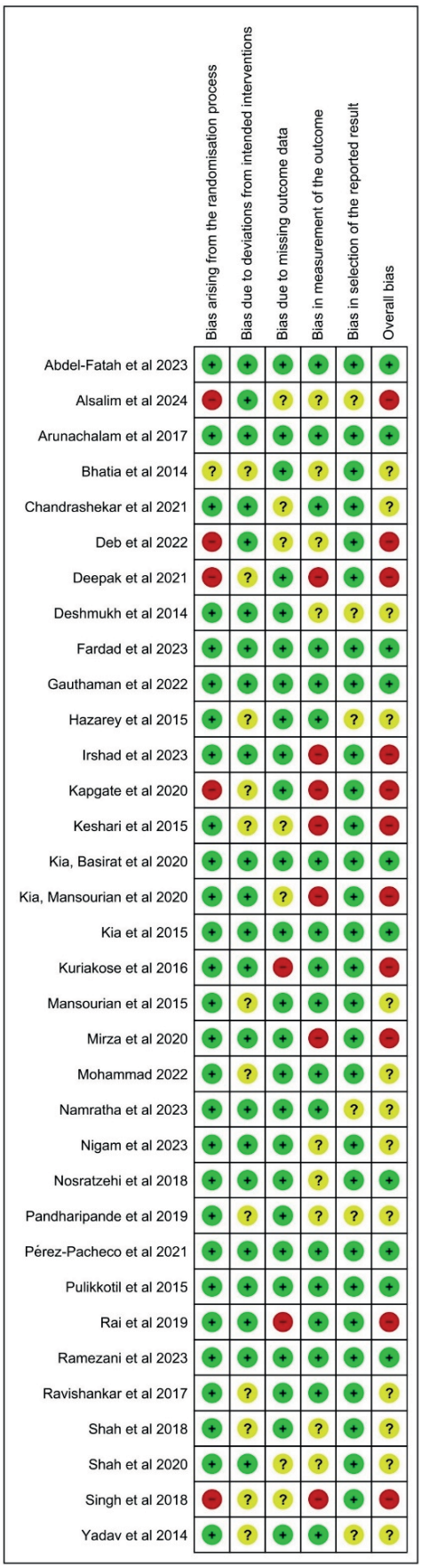

Figure 4: Summary of risk of bias for clinical trials using the Cochrane RoB 2.

The results of the evaluation of the risk of bias of clinical trials using the Cochrane RoB 2 tool showed that most studies received a low risk assessment for the randomization process and selection of the reported results domains. Based on overall bias, 10 studies had a low risk of bias, 13 had a moderate risk of bias, and 11 had a high risk of bias. Risk of bias assessment for clinical studies is shown in Figure **4**.

4. Discussion

4.1. Curcumin and gingivitis

Gingivitis is an inflammatory disorder that causes gingival erythema and edema but does not result in periodontal attachment loss. In general, this condition is caused by the accumulation of microbial biofilm [98, 99]. In assessing the quality of gingival tissue, measuring the severity and location of changes in the area that forms the marginal gingival perimeter, the gingival index (GI) score is used. The higher the GI score, the more severe the level of gingival inflammation and its tendency to be accompanied by spontaneous bleeding [100]. Two randomized clinical trials (RCTs) reported that curcumin mouthwash showed effectiveness in reducing GI, Plaque Index (PI), and bleeding on probing (BOP) scores [50, 52]. These clinical parameters are linked to the presence of pro-inflammatory cytokines, one of which is interleukin (IL)-1β.

Periodontal diseases, including gingivitis, result in increased levels of IL-1β, a pro-inflammatory cytokine [101, 102]. IL-1β contributes to the development of periodontal disease, also inducing cell chemotaxis, collagen destruction, and bone resorption [103]. Two RCTs concluded that curcumin shows efficacy in reducing salivary IL-1β levels [52, 53]. The decrease in IL-1β levels by curcumin causes matrix metalloproteinase (MMP)-13 stimulation to be inhibited [104]. Interestingly, curcumin also results in a reduction of MMP-13 [51], a compound that has a crucial function in periodontal tissue damage and alveolar bone resorption [105, 106]. In addition to these gingivitis markers, C-C motif chemokine ligand 28 (CCL28) has also been defined as a new marker for diagnosing oral diseases, where increased CCL28 is associated with increased epithelial inflammation [107]. CCL28 expression is also indirectly increased due to increased production of cytokines, including IL-1β, and certain bacterial products, which attract effector cells to the inflammation site [108]. In this case, one study stated that CCL28 levels were significantly inhibited by curcumin [53]. Curcumin's potent anti-inflammatory activities are thought to be responsible for this. As a result, it has great potential for usage as a mouthwash to treat gingivitis.

Additionally, one study investigated reactive oxygen metabolite (ROM) levels in chronic gingivitis patients treated with curcumin, resulting in a significant decrease in ROM levels [50]. It is known that individuals with periodontal disease have higher plasma ROM levels than those with healthy periodontal conditions [109]. In patients with periodontal disease, evidence shows that ROM level testing is deemed helpful in determining total oxidative status [110]. This is because ROM levels are regarded as a valid measure of oxidative stress and have been demonstrated to be related to the severity of periodontal disease [111]. Excessive ROM has an impact on the development of various pathological conditions and contributes to the activation of intracellular pathways such as mitogen-activated protein kinase (MAPK), phosphatases, and transcription factors such as nuclear factor

kappa B (NF-κB) and activator protein 1 (AP-1), which further enhance inflammation [112]. With the antioxidant effects contained in curcumin [113], it can reduce ROM levels and contribute to the relief of oxidative stress, further improving inflammatory conditions associated with gingivitis. In summary, current evidence indicates that curcumin demonstrates promising anti-inflammatory and antioxidant properties that contribute to the improvement of gingival health.

4.2. Curcumin and periodontitis

Periodontitis is an inflammatory disease that affects the supporting tissue of the teeth, with the main etiologies being oral pathogenic bacteria, *Porphyromonas gingivalis*, and the formation of biofilm plaque [114], and the secondary etiologies being poor dental and oral conditions, systemic factors, genetics, smoking, and stress [115, 116]. Clinically, curcumin has been shown to have a significant positive effect on improving probing depth (PD), CAL, GI, PI, and BOP [58, 63]. Furthermore, since periodontitis is associated with chronic inflammatory conditions, several animal studies agree that curcumin effectively reduces C-reactive protein (CRP) and alkaline phosphatase (ALP) levels, as well as the expression of IL-6, IL-1β, and tumor necrosis factor (TNF)-α [56, 61, 64, 66]. Interestingly, common indicators of inflammatory activity, NF-κB and p38 MAPK, were also found to be decreased [57, 67]. These decreases are mediated by changes in the phenotype of fibroblast cells in the gingiva, which also affect pro-inflammatory cytokines. The decrease in NF-κB also has an impact on inhibiting prostaglandin (PG) E2 production [117]. This inhibition may be associated with curcumin's anti-inflammatory effect mediated by decreasing the expressions of COX-1 and -2, and microsomal PGES in the NF-κB pathway so that the release of PGE2 can be inhibited [118].

Furthermore, IL-6, IL-1β, and TNF-α act as strong mediators in activating NF-κB [119]. Additionally, one study reported that curcumin also increases IL-4 levels [56], where increased IL-4 acts as an anti-inflammatory factor in periodontitis [120]. Inhibition of MMP-7 and MMP-8 is also observed after mice were given curcumin [59, 61]. MMP can support pathological damage to periodontal tissue, so when MMP is inhibited, the damage can also be minimized [121]. Damage to periodontal tissue can also occur due to excessive polymorphonuclear (PMN) and mononuclear cell activity [122]. Surprisingly, the numbers of PMN and mononuclear cells decreased in mice that were given curcumin [67]. One study also reported that curcumin drastically lowered GI scores in mice, indicating its anti-inflammatory effects [58]. This study also strengthens the idea that curcumin not only works at the molecular and cellular level, but also at the tissue level.

In relation to alveolar bone destruction due to periodontitis, curcumin is effective in reducing the number of osteoclast cells and levels of receptor activator of nuclear factor-kappa B ligand (RANKL) [64]. RANKL is a major regulator of osteoclast differentiation and activation, which subsequently causes excessive alveolar bone resorption and results in alveolar bone loss [123]. By inhibiting the number of osteoclast cells and RANKL levels, curcumin has the potential to inhibit alveolar bone damage through the process of inhibiting osteoclastogenesis.

In addition, curcumin increased the activity of superoxide dismutase (SOD) and glutathione (GSH), and decreased malondialdehyde (MDA) levels [65]. MDA is a biomarker of tissue injury due to oxidative stress, while SOD is an antioxidant

that protects cells from oxidative damage, and GSH is defined as an antioxidant that functions as a substrate for lipid detoxification. Increased SOD and GSH activity strengthen the cellular antioxidant defense system, reducing ROS accumulation. This decrease in ROS indirectly reduces MDA production [65, 124]. Thus, curcumin contributes to increased activity of antioxidant enzymes, which collectively impact the protection of periodontal tissues from further damage.

In a review of several RCTs, it was revealed that curcumin can suppress or diminish the activity of pro-inflammatory cytokines such as IL-1α, IL-6, and TNF-α [62]. In addition, decreased levels of additional indicators such as serum ALP, CRP, and salivary procalcitonin (PCT) levels were also observed in periodontitis patients given curcumin [54, 60]. In conclusion, based on *in vivo* studies and clinical trials, curcumin has a high potential for use as an adjuvant treatment in treating and regenerating periodontal tissue due to periodontitis. However, RCTs involving larger populations and longer follow-ups are required to determine further curcumin's efficacy on protecting and repairing alveolar bone affected by periodontitis.

4.3. Curcumin and recurrent aphthous stomatitis (RAS)

RAS is a chronic, multifactorial inflammatory disease caused by a variety of factors such as genetics, physical and chemical trauma, bacterial and viral infection, allergies, vitamin and micronutrient deficiencies, immunological, hormonal, systemic diseases, drugs, and stress [125–127]. RAS is characterized by recurrent and painful ulceration [128, 129]. Regarding RAS-related pain, all six clinical trials included in this study reported that curcumin oral gel effectively reduced pain and burning sensation, as evidenced by a significant decrease in visual analogue scale (VAS) scores and in the number, size, and degree of erythema of lesions [68–72]. In addition, RAS is described as a recurring lesion, and one study indicated that curcumin was more efficient than topical anti-inflammatory medications in reducing the recurrence rate of RAS [69]. This is because curcumin has anti-inflammatory properties through binding to toll-like receptor (TLR) and regulating signaling pathways, including NF-κB, AP-1, MAPK, and JAK/STAT, as well as reducing levels of pro-inflammatory mediators such as interleukins, TNF-α, inducible nitric oxide synthase (iNOS), regulated upon activation normal T expressed and secreted (RANTES), granulocyte colony-stimulating factor (G-CSF), and monocyte chemoattractant protein 1 (MCP-1) [130, 131].

In the early phase, RAS usually appears with the characteristic of a round or oval ulcer with the center being a necrotic area covered by fibrinous exudate infiltrated by polymorphonuclear leukocytes with an erythematous edge [132–134]. Furthermore, individuals with oral ulcers may have changes in taste, where overgrowth of Gram-negative bacteria is believed to be a secondary cause of these changes, which are also common in patients with other necrotic oral lesions [135, 136]. Additionally, the perception of taste and comfort when eating or drinking is also believed to be influenced by the pain, burning sensation, or odynophagia that arises due to RAS [137]. Interestingly, curcumin has been shown to be effective in improving taste bud dysfunction and abnormal changes in RAS patients [70]. With its anti-inflammatory effects, curcumin also reduces exudate [71]. In fact, two studies [68, 70] reported that curcumin has the same effectiveness as triamcinolone acetonide, where triamcinolone is

the first-line topical corticosteroid in the treatment of RAS [138]. In conclusion, curcumin has strong potential to be developed into a topical agent for treating RAS due to its anti-inflammatory properties, as evidenced by six clinical trials reporting positive therapeutic benefits for RAS treatment.

4.4. Curcumin and oral mucositis

Oral mucositis is an acute adverse effect in head and neck cancer patients receiving chemotherapy or radiation [139]. Clinically, oral mucositis is defined by erythematous, erosive, and/or ulcerative lesions [140]. These lesions range in severity from asymptomatic or mildly symptomatic to severe pain that interferes with oral activities such as eating, speaking, and swallowing, increases the risk of infection, and causes delays, pauses, or termination of chemotherapy or radiation [141, 142]. Regarding these symptoms, administration of curcumin in formulations such as gel, capsules, mouthwash, and mucoadhesive decreased severity and pain, erythema, burning sensation, and size of lesions, and caused an increase in the acceleration of recovery and a delay in the onset of oral mucositis [73–78]. This can be achieved because curcumin has been proven to possess anti-inflammatory, antioxidant, and antibacterial activities. The damaged mucosal barrier due to oral mucositis makes it easier for pathogens to penetrate the mucosa. However, the antibacterial effect that inhibits the growth and kills pathogens, as well as the anti-inflammatory and antioxidant properties contained in curcumin, contribute to reducing symptoms and accelerating the healing [143, 144].

Healing of damaged mucosa due to oral mucositis requires fibroblasts that form collagen, where fibroblasts are stimulated by several factors, including epidermal growth factor (EGF) and transforming growth factor (TGF)-β [145]. Meanwhile, in patients with oral mucositis, EGF levels decrease [146]. Interestingly, curcumin significantly increased salivary EGF [73]. EGF is a polypeptide that functions in tissue formation and mucosal wound healing associated with oral mucositis because it helps the proliferation, growth, and migration of epithelial cells [147, 148]. In addition, TGF-β1 is released following tissue injury, increasing the production of VEGF, which is necessary for angiogenesis during wound healing [149]. TGF-β1 and EGF also contribute synergistically to form new myofibroblasts, which aids in wound healing [150]. However, excessive TGF-β1 signaling and ongoing angiogenesis may hinder wound healing and cause scar tissue development [151, 152]. Surprisingly, curcumin accelerated re-epithelialization as indicated by decreased TGF-β1 levels and angiogenesis on day 8 [77]. It can be concluded that curcumin is believed to be significant in reducing the symptoms and accelerating the healing of wounds caused by oral mucositis. The anti-inflammatory, antioxidant, and antibacterial effects of curcumin contribute to this. In addition, it has been suggested that curcumin also exhibits radioprotective effects [153, 154], effectively treating and preventing oral mucositis in patients undergoing radiotherapy.

4.5. Curcumin and oral lichen planus (OLP)

OLP, one of the oral potentially malignant disorders (OPMDs), is defined as a chronic inflammatory illness of the oral mucosa. Autoimmune conditions are considered a possible contributing factor, where T cells mediate inflammation and cause a

response to unknown antigens on the epithelium [155, 156]. The clinical presentation of OLP is diverse, including reticular, atrophic, plaque-like, erosive, papular, and bullous patterns, with the most prevalent variety being Wickham's striae [157]. OLP lesions can appear in the form of painful, inflamed ulcerations, erythematous or non-erythematous lesions, burning sensation, and/or discomfort, affecting the patient's quality of life since they make eating, drinking, and doing activities difficult [158]. In this regard, six clinical studies reported that curcumin was beneficial in lowering pain and burning sensation levels, ulceration and erythema, and lesion size and appearance scores [79–83]. This is due to its anti-inflammatory effects that hinder the TNF-α and NF-κB signaling pathways, as well as enzymes such as COX-2 [159, 160]. Additionally, curcumin has also been shown to impede nitric oxide (NO) and ROS formation, proving its effective antioxidant effects for OLP [160, 161]. Furthermore, curcumin has immunomodulatory effects that contribute to the modulation of T cell proliferation related to OLP pathogenesis [160].

All studies we reviewed compared curcumin with several corticosteroids commonly used in the treatment of OLP, including prednisolone, triamcinolone acetonide gel, and betamethasone. Interestingly, one study reported that patients treated with corticosteroids experienced additional candidal infections, whereas no adverse effects were reported with curcumin [80]. It is believed that curcumin has antifungal effects against *Candida* spp. [162, 163], whereas OLP therapy with corticosteroids increases the adverse side effects of candidal infections [164]. Our review highlights that curcumin exhibits beneficial anti-inflammatory, antioxidant, and immunomodulatory effects in treating OLP without any significant adverse effects reported. In addition, its antifungal effects inhibit additional candidal infections that may occur in patients treated with corticosteroids as an adverse effect.

4.6. Curcumin and oral leukoplakia

Oral leukoplakia is a type of OPMDs, and it may precede the development of oral neoplasm, with tobacco and alcohol being important independent contributing factors to its development [165, 166]. Oral leukoplakia is described as a primarily white plaque or patch that cannot be clinically or pathologically distinguished from any other pathological condition [167]. It is divided into homogeneous and non-homogeneous types. Homogeneous leukoplakia has clinical criteria in the form of thin, flat, whitish lesions with a smooth surface, while non-homogeneous leukoplakia is characterized as lesions with a mixed white-red or erythroleukoplakia, nodular, speckled, granular, and verrucous or exophytic appearance [168, 169]. Histologically, oral leukoplakia has diverse characteristics ranging from squamous hyperplasia without dysplasia to mild, moderate, or severe dysplasia [170].

Two clinical trials reported that curcumin provided significant clinical and histological responses, causing a decrease in the size and quantity of plaque lesions and significant improvement in histological features [84, 85]. This is because curcumin has antioxidant effects, making it a promising chemopreventive agent by inhibiting free radicals, both ROS and reactive nitrogen species (RNS) [171]. Downregulation of molecular biomarkers associated with dysplasia in OPMD, such as Ki 67, cyclin D1, and p53, after curcumin administration has also been demonstrated in a clinical trial [172]. In addition, a study revealed

that patients with oral leukoplakia had decreased SOD levels [173]. SOD is the primary cellular antioxidant responsible for physiological defense against free radicals, especially superoxide and ROS [174, 175]. Interestingly, one study found curcumin was effective in increasing serum SOD levels [84], which in turn catalyzes the dismutation of amniotic superoxide into oxygen and water [176]. Although clinical research on curcumin's effectiveness in treating oral leukoplakia remains limited, this natural compound exhibits a potentially strong chemopreventive agent for oral leukoplakia therapy with its antioxidant effects. Future studies related to this with large samples and robust methods are needed.

4.7. Curcumin and oral submucous fibrosis (OSF)

OSF is one of the OPMDs related to the habit of chewing betel nut, characterized clinically by pale appearance, burning sensation, as well as progressive and irreversible fibrosis [177]. Other symptoms that may appear are xerostomia, ulceration, pain, and taste disorders [178]. Furthermore, the fibrotic condition of OSF limits patients' ability to open their mouths, which in turn causes difficulty in speaking and swallowing [179]. We highlight the results of eight clinical trials reporting that curcumin, whether in the form of lozenges, tablets, capsules, mouthwash, gel, mucoadhesive patches, or oil, effectively improved mouth opening and tongue protrusion and significantly lowered pain or burning sensation [86–88, 90–94]. Only one study among them [88] added physiotherapy using a mouth exercise device as an additional therapy of curcumin. This may be achieved due to curcumin's antioxidant and anti-inflammatory activities [180]. The anti-inflammatory properties cause the inhibition of the COX and lipoxygenase pathways, which in turn inhibit prostaglandins and leukotrienes [181].

Patients with OSF showed significant changes in both salivary and serum biomarker levels. Evidence reported increased lactate dehydrogenase (LDH), MDA, and lipid peroxidation (LPO) levels, as well as decreased SOD, glutathione peroxidase (GPx), vitamins C and E, and β-carotene in OSF [182, 183]. Increased LDH levels are a sign of hypoxia, fibrosis, and a shift to anaerobic glycolysis, which are included in the pathogenesis of OSF [184, 185]. In addition, LDH also contributes to the creation of an oxidative stress environment that causes the formation of ROS [183]. ROS formed in the pathogenesis of OSF attack cell membranes, which in turn induces MDA production [186]. MDA is a toxic compound that induces inter- and intramolecular collagen cross-linking, contributing to tissue stiffening and reduced tissue function. In addition, MDA facilitates mutagenic transformations in DNA that are believed to be related to carcinogenesis and mutagenesis, where increasing MDA levels are associated with increasing clinical stages of OSF [186–189]. Interestingly, there is a study reporting that curcumin significantly reduces serum LDH [86] and serum MDA levels [89] in patients with OSF. The decrease in both biomarkers resulted in inhibition of ROS production and improvement of tissue function. Finally, curcumin's anti-inflammatory and antioxidant capabilities improve mouth opening and tongue protrusion while also lowering the degree of pain and burning sensation due to OSF.

4.8. Curcumin and oral cancer

Oral cancer is the most frequent type of head and neck neoplasms and is known to be very aggressive due to its high rates of metastasis and

recurrence [190, 191]. Its development is often associated with several inflammatory mediators, including COX and MMP, which have suppressive effects on tumor suppressor genes [192, 193]. Specifically, increased COX-2 increases proliferation, invasion, metastasis, angiogenesis, and inhibits apoptosis in oral cancer [194–196]. Increased COX-2 may also be linked to increased activation of the NF-κB signaling pathway in carcinoma [197]. Interestingly, curcumin is believed to be effective in inhibiting NF-κB phosphorylation and reducing COX-2 [198]. This is in line with the study reporting a decrease in COX-2 accompanied by a decrease in NF-κB after mice were given curcumin orally [97]. This is while other inflammatory mediators, such as MMP, were also observed to decrease, especially MMP-2 and -9 [96].

In addition to matrix reduction, Hu and colleagues [96] also observed a slowing of tumor growth in mice given curcumin. As the severity increases, tumor growth will continue to develop, and in its development, tumors require vascular structures to develop and spread [199]. This condition causes the process of angiogenesis to occur, which is known as an indicator of regression and metastasis [200]. Curcumin appears to suppress angiogenesis induction through decreasing CD31, microvascular density (MVD), and hypoxia-inducible factor (HIF)-1α, common prognostic biomarkers used in cancer angiogenesis studies. Furthermore, the decrease in HIF-1α leads to a reduction in vascular endothelial growth factor (VEGF), which was also observed [96]. This may be associated with the role of HIF-1α as a specific transcription factor that regulates VEGF as an inducer of angiogenesis, along with other pro-angiogenic factors [201–203].

Other indicators, such as protein expression and phosphorylation, were also biomarkers tested in the study by Hu and colleagues [96], where curcumin was able to reduce Ki-67, a protein linked to increased differentiation of cancer tissue [204, 205]. Other proteins, cell cycle regulator proteins, Cdc25C, and checkpoint kinase 1 (Chk1) were reported to increase their phosphorylation when given curcumin. Both proteins are closely related to the cyclin-dependent kinase (CDK) complex activity. In its mechanism, Cdc25C will activate CDK1 in cells to initiate mitosis and regulate G2/M development, then regulate checkpoints if DNA damage occurs, so that DNA information transmission is better [206]. Meanwhile, Chk1 functions by inhibiting CDK activity. When CDK is inhibited, the cell cycle progression in G1-S, intra-S, and G2-M will be reduced or arrested [207].

Another critical aspect in evaluating the development of oral cancer is assessing the DNA damage factor. If damage occurs, the DNA strand breaks and creates abnormal nucleotide fragments that give rise to mutation sites. This results in the expression of dysfunctional proteins that affect cellular physiology to become unstable, causing cancer cell proliferation [208]. One study reported that curcumin increased phosphorylated ataxia telangiectasia mutated (p-ATM) expression [96], which is closely related to its role in DNA damage repair [209]. Therefore, DNA damage repair is a promising biomarker in evaluating the development of oral cancer [210]. Another research found that curcumin exhibits pro-apoptotic, anti-proliferative, and anti-invasive effects by reducing the expression of several biomarkers, including proliferating cell nuclear antigen (PCNA), suppressor of cytokine signaling (SOCS)1 and 3, and STAT3, as well as BCL-2 as a pro-apoptotic protein [95]. Direct suppression of the expression of several of these biomarkers also strengthens the

efficacy of curcumin in reducing the activity and development of oral cancer.

In conclusion, curcumin demonstrates multi-faceted therapeutic potential against oral cancer by modulating key molecular pathways involved in tumor progression. Its ability to interfere with inflammatory signaling, angiogenesis, cell cycle regulation, and DNA repair underscores its promise as a complementary agent in oral cancer therapy. However, as current evidence is predominantly based on preclinical models, future clinical investigations are warranted to confirm its traditional applicability and therapeutic value in human subjects.

5. Conclusion

Curcumin is a promising adjuvant therapeutic agent for various oral diseases, including periodontal diseases, RAS, oral mucositis, OPMDs, and oral cancer, with no significant adverse effects reported in studies. Evidence indicates its anti-inflammatory, antioxidant, antifungal, immunomodulatory, and anticancer effects, which are effective in treating oral diseases. However, although curcumin offers significant therapeutic effects on oral diseases, this review found limitations in clinical trials of curcumin on some diseases, especially oral cancer. Therefore, future studies on clinical trials of curcumin on oral diseases with rigorous methods and larger samples are needed.

Declarations

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Ethical Considerations

Not applicable.

Competing Interest

The authors declare no conflict of interest related to this work.

Availability of Data and Materials

The datasets used in the present study are available from the corresponding author upon reasonable request.

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Abbreviations and Symbols

ALP: Alkaline phosphatase

AP-1: Activator protein 1

BOP: Bleeding on probing

CAL: Clinical attachment level

CCL28: C-C motif chemokine ligand 28

CDK: Cyclin-dependent kinase

Chk1: Checkpoint kinase 1

COX: Cyclooxygenase

CRP: C-reactive protein

EGF: Epidermal growth factor

G-CSF: Granulocyte colony-stimulating factor

GI: Gingival index

GPx: Glutathione peroxidase

GSH: Glutathione

GST: Glutathione-S-transferase

HIF: Hypoxia-inducible factor

IL: Interleukin

LDH: Lactate dehydrogenase

LPO: Lipid peroxidation

MAPK: Mitogen-activated protein kinase

MCP-1: Monocyte chemoattractant protein 1

MDA: malondialdehyde

MVD: Microvascular density

MMP: Metalloproteinase

NF-κB: Nuclear factor kappa B

NOS: Nitric oxide synthase

OLP: Oral lichen planus

OPMD: Oral potentially malignant disorder

OSF: Oral submucous fibrosis

PCNA: Proliferating cell nuclear antigen

PCT: Procalcitonin

PD: Probing depth

PG: Prostaglandin

PI: Periodontal index

PMN: Polymorphonuclear

RANKL: Receptor activator of nuclear factor kappa B ligand

RANTES: Regulated upon activation normal T expressed and secreted

RAS: Recurrent aphthous stomatitis

ROM: Reactive oxygen metabolite

ROS: Reactive oxygen species

SOCS: Suppressor of cytokine signaling

SOD: Superoxide dismutase

STAT: Signal transducer and activator of transcription protein

TGF: Transforming growth factor

TLR: Toll-like receptor

TNF: Tumor necrosis factor

VEGF: Vascular endothelial growth factor

AI Use Disclosure

The authors declare that no generative artificial intelligence (AI) tools were used in the preparation of this manuscript, including writing, analysis, figure generation, or editing.

Author Contributions

Concept or design of the work: FMR, AJS; Acquisition, analysis, or interpretation of data: FMR, AJS, WEW; Methodology: RA; Project administration: FMR; Supervision: AI; Validation: AJS;

Manuscript preparation: FMR, RA, PD; Manuscript editing: WEW, RA, PD; Manuscript review: AI; Final approval of the version to be published: FMR, AJS, WEW, RA, PD, AI; Accountability for all aspects of the work: FMR, AJS, WEW, RA, PD, AI.

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