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Review Article

CURCUMIN IN ORAL MUCOSAL LESIONS: AN UPDATE

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ABSTRACT

The phytopharmaceutical curcumin - the Indian golden spice has been widely researched for its pharmaceutical properties. It exhibits a big promise as a therapeutic agent due to its properties such as antioxidant, analgesic, anti-inflammatory, antiseptic activity, anticarcinogenic activity, chemopreventive, chemotherapeutic activity, antitumor, antiviral, antibacterial, and antifungal and is currently in human trials for a variety of conditions. The applications of curcumin in dentistry include its use as pit and fissure sealant, dental plaque detection system, subgingival irrigant, and intracanal medicament. The aim of the present paper is to review the current literature for the use of curcumin in oral mucosal lesions. A thorough review of the existing literature encompassing PubMed, Ovid, Embase, and Google scholar was made using the keywords curcumin, turmeric, oral, mucosal, oral submucous fibrosis (OSMF), oral lichen planus (OLP), aphthous, recurrent aphthous stomatitis (RAS), leukoplakia, mucositis, reverse smoking, tobacco-associated lesions, and premalignant. No filters in relation to language or publication year were used and only *in vivo* studies on humans were selected. Reference lists of retrieved journal articles were searched for publications missed during the primary search. Finally, the Google search engine was used to do a comprehensive search of the World Wide Web to ensure completeness of the search. The review of the literature revealed evidence of the use of curcumin in tobacco-associated conditions of the oral cavity-OSMF, oral leukoplakia, oral lesions associated with reverse smoking and ulcerative conditions of the oral cavity- OLP, RAS, and oral mucositis has been studied. Curcumin provides the basis for a simple, safe, acceptable, and cost-effective intervention for oral mucosal disorders.

Keywords: Curcumin, Oral leukoplakia reverse smoking, Oral lichen planus, Oral mucosal lesions, Oral mucositis, Oral potentially malignant disorders, Oral submucous fibrosis, Oral ulcers, Premalignant, Recurrent aphthous stomatitis, Recurrent aphthous, Tobacco-associated lesions, Treatment-induced oral mucositis, Turmeric.

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INTRODUCTION

In this era of herbal renaissance, the use of herbal agents in medicine and dentistry is gaining importance worldwide. One such nutraceutical is turmeric which has come all the way from the kitchen to clinic. Turmeric is a perennial herb of Zingiberaceae family [1]. Its botanical name is *Curcuma longa*. The rhizomes of this plant are dried and powdered to yield the spice turmeric. The name turmeric originates from the Persian word "kirkum," meaning saffron, given due to its effervescent yellow-orange color [2].

Turmeric has been used in several ancient medicinal systems such as Ayurveda, Sidhha, Unani, and Chinese systems of medicine. Its documented use dates back to 6000 years [3]. The medicinal properties of turmeric were later discovered. Turmeric is indigenous to Southeast Asia. Indian contribution to the total world production of turmeric is 93.3% [3]. The estimated size of the Indian turmeric industry is 2500–3000 crores [4].

Several components, >100, have been isolated from turmeric. The major constituent of the root is a volatile oil which is composed of turmerone, and coloring agents called curcuminoids [5]. Curcuminoids include curcumin, demethoxycurcumin, 5'-methoxycurcumin, and dihydrocurcumin, which are natural antioxidants [6]. Curcumin, the principal curcuminoid, comprises approximately 2–5% of turmeric [7]. It owes its importance by providing the yellow color to turmeric and also accounts for most of its pharmacological effects. Curcumin possesses numerous pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial properties, chemopreventive, and chemotherapeutic activity [8]. Recently, apoptosis induction effect of curcumin and its analogs on cancer cell lines have been shown [9]. A recent review has highlighted the role of curcumin as a potent anticarcinogenic polyphenol [10].

Several papers have reviewed the role of turmeric or curcumin in dentistry. The applications of curcumin in dentistry include its use as pit and fissure sealant, dental plaque detection system, subgingival irrigant, and intracanal medicament [11]. The aim of the present paper is to review the current literature for the use of curcumin in oral mucosal lesions. The antioxidant, anticarcinogenic, and anti-inflammatory properties of curcumin make it appropriate to explore the role of curcumin in oral mucosal disorders. A thorough review of the existing literature encompassing PubMed, Ovid, Embase, and Google scholar was made using the keywords curcumin, turmeric, oral, mucosal, oral submucous fibrosis (OSMF), oral lichen planus (OLP), aphthous, recurrent aphthous stomatitis (RAS), leukoplakia, mucositis, reverse smoking, tobacco-associated lesions, and premalignant. No filters in relation to language or publication year were used and only *in vivo* studies on humans were selected. Reference lists of retrieved journal articles were searched for publications missed during the primary search. Finally, the Google search engine was used to do a comprehensive search of the World Wide Web to ensure completeness of the search. The review of the literature revealed evidence of the use of curcumin in oral mucosal lesions such as OSMF, oral leukoplakia, oral lesion associated with reverse smoking, RAS, OLP, and oral mucositis. This first half of this review will focus on the use of curcumin in tobacco-associated lesions such as OSMF, oral leukoplakia, and lesion associated with reverse smoking. Reddy *et al.* have also highlighted the role of curcumin as an anti-cancer spice in their recent review [12].

Curcumin in OSMF

Pindborg defined OSMF as "insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx, occasionally preceded by vesicle formation, always associated with juxtaepithelial inflammatory reaction followed by a fibroelastic change of lamina propria with

epithelial atrophy leading to stiffness of the oral mucosa, trismus and inability to eat." [13]. It is a potentially malignant disorder mainly caused due to areca nut chewing characterized by restricted mouth opening, burning sensation on having hot and spicy food, and stiffness and blanching of the oral mucosa. The malignant transformation rate of OSMF has been reported to be around 27% over several years [14].

Curcumin exhibits several properties such as anti-inflammatory, antioxidant and proapoptotic activities, which account for its chemopreventive action and is, therefore, desirable for OSMF. Curcumin is a dual inhibitor of arachidonic acid metabolism and, therefore, inhibits the products of inflammation such as prostaglandins and leukotrienes [15]. Curcumin also has a role in the suppression of tumor necrosis factor (TNF)-induced nuclear factor-κB (NF-κB) activation and NF-κB-dependent reporter gene expression [16]. Downregulation of several products involved in cellular proliferation (cyclooxygenase 2, cyclin D1, and c-myc), anti-apoptosis (IAP1, IAP2, XIAP, Bcl-2, Bcl-xL, Bfl-1/A1, TRAF1, and cellular cFLIP), and metastasis (vascular endothelial growth factor [VEGF], matrix metallopeptidase 9 [MMP-9], and intercellular adhesion molecule 1) by curcumin has been previously reported [17]. Rao *et al*. have demonstrated a very interesting effect of curcumin, namely the scavenging effect on superoxide radicals, hydroxyl radicals, and lipid peroxidation, considered a major etiopathogenetic factor of OSMF [18]. Recently, Zhang *et al.* demonstrated anti-fibrotic activity of curcumin in TGF-β1-induced myofibroblasts from human oral mucosa, suggesting its utility in OSMF patients [19]. It has also been previously demonstrated that curcumin possesses fibrinolytic action in liver and lung fibrosis and is regarded as a fibrinolytic agent in Chinese medicine [20]. Li *et al*. have attributed the fibrinolytic action of curcumin to its three properties, namely inhibition of lipid peroxidation, checking cellular proliferation, and inhibition of collagen synthesis [21]. Curcumin also suppresses bleomycin-induced pulmonary fibrosis in rats [22].

The review of the literature reveals eight research papers which have been published assessing the efficacy of curcumin in OSMF patients (Table 1). Of these four are randomized control trials (RCTs), three are observational studies, and one is a pre-post study design. The most recently published literature is an RCT by Pipalia *et al*. [23]. This study evaluated the effectiveness of turmeric with black pepper and *Nigella sativa* in OSMF patients. Tumeric with black pepper and *N. sativa* improved mouth opening, burning sensation, and superoxide dismutase levels in OSMF patients. The rationale behind the use of black pepper was it prevents the metabolism of turmeric and therefore increases the bioavailability of turmeric. *N. sativa* due to its antioxidant, anti-inflammatory, anticarcinogenic, immunomodulatory, and anti-fibrotic properties was used. Furthermore, it has been tried in human studies for type II diabetes mellitus for glycemic control.

Hazarey *et al.* evaluated the efficacy of curcumin over standard medicinal management modality for OSMF [24]. The curcumin group was given Longvida lozenges (400 mg lozenges) with a total daily dose of 2 g and was compared to topical clobetasol propionate 0.05% to be applied 3 times daily for 3 months. The mean decrease in the Visual analogue scale score and increase in mouth opening was statistically significant in the curcumin group as compared to the control group. The authors proposed that curcumin being antioxidant and anti-inflammatory may enhance the neoangiogenic and antifibrotic potential of the OSMF patients.

The observational study by Srivastava *et al.* investigated the clinical efficacy of 1 g tulsi and 1 g turmeric mixed in glycerine base for the treatment of OSMF patients and found statistically significant improvement in both burning sensation and mouth opening in the study population [25]. They have hypothesized that ursolic acid (UA), a pentacyclic triterpene acid from *Ocimum sanctum* (Tulsi) has been reported to suppress NF-κB activation-induced by various carcinogens. In addition, UA prevents proliferation and induces apoptosis and cell arrest in the G1-G0 phase of the cell cycle [15]. Synergistic action of these two herbs resulted in potent anti-OSMF treatment characterized by an early, sustained and significant fall in burning sensation and improvement in mouth opening for severe cases reflecting its higher efficacy.

Table 1: Review of literature showing eight research papers assessing the efficacy of curcumin in OSMF patients

S. No.	Author(s)	Type of evidence	n	Interventions	Outcomes	Results
1.	Pipalia *et al*.	RCT	23	Group A received turmeric (400 mg) with black pepper (100 mg), 2 capsules TID for 3 months. Group B received *Nigella sativa*, two capsules of 500 mg TID for 3 months	The mouth opening and burning sensation were the primary treatment outcome endpoints. Cheek flexibility was also measured. Patients' serum SOD levels were assessed before and after treatment and also compared with healthy controls	After the treatment Groups A and B showed 3.85±0.22 mm and 3.6±0.07 mm improvement in mouth opening, respectively; 87.90% and 78.91% reduction in burning sensation, respectively; and +0.62 U/ml and +0.74 U/ml improvement in serum SOD levels, respectively
2.	Hazarey *et al*.	RCT	30	Test group patients were treated with Longvida (curcumin) lozenges and control group with tenovate ointment (clobetasol propionate (0.05%)	IID on maximum mouth opening, VAS for normal food, and VAS for spicy food	The test group showed 5.93 (±2.37) mm increase in mouth opening compared to 2.66 (±1.76) mm of the control group. In relation to VAS scale with spicy and normal food, the average reduction was 64 (42–73) and 77 (70.5–82) as compared to 34 (14.5–64.5) and 64 (46–75.5), respectively in control group
3.	Srivastava *et al*.	Observational study	41	1 g tulsi and 1 g turmeric mixed in glycerine base applied 3–4 times a day for 3 months	Burning sensation and mouth opening	Mean burning sensation was 6.07±1.75 before the treatment and 2.22±1.41 after the treatment (t=15.52; p<0.001). Mean mouth opening was 24.46±4.0 mm before the treatment and 27.85±3.39 mm after the treatment (t=9.06; p<0.001)

(*Contd*...)

Table 1: (*Continued*)

S. No.	Author(s)	Type of evidence	n	Interventions	Outcomes	Results
4.	Yadav *et al*.	RCT	40	First group - weekly intralesional injection of 4 mg dexamethasone and 1500 I.U hyaluronidase. Second group - oral administration of two tablets (turmix - tablet containing curcumin 300 mg and piperine 5 mg) per day for 3 months each	Improvement of burning sensation, IID and TP	Improvement in burning sensation was from 22.4 (8.7) to 15.6 (11.2) in Group 1 compared to 63.5 (24.7) to 0 in curcumin group. The mean increase in IID was 3.13 and 1.25 mm. Mean increase in TP was 2.56 mm and 0.38 mm in Groups 1 and 2, respectively
5.	Agarwal *et al*.	Observational study	30	Turmix (tablet containing curcumin 300 mg and piperine 5 mg) TDS for 1 month	Patient's mouth opening and burning sensation on VAS	The change in burning sensation on VAS scale was statistically significant, and maximum improvement was observed in Group B (83.33%). The overall change in mouth opening was 0.69 cm which was not statistically significant, with maximum improvement in late stages (Group D)
6.	Das *et al*.	RCT	48	Group I patients was given curcumin capsules, Group II TO, and Group III the control group was provided with multinal tablets for 3 months	Improvement of burning sensation, IID, and TP and H/P	Significant improvement was observed in the clinical signs and symptoms of patients treated with curcumin and TO when compared to those with multinal
7.	Rai *et al*.	Pre-post study	25 (100)	Curcumin 1 g caplets (900 mg curcumin and 80 mg desmethoxycurcumin, and 20 mg bisdesmethoxycurcumin)	Pain control using VAS and lesion healing measured by lesion size and mouth opening salivary and serum oxidative markers such as MDA, 8-OHdG, and Vitamins C and E were analyzed at baseline, 1 week and after clinical cure of the lesion	Salivary MDA levels decreased from 0.32 (0.16)–0.11 and serum levels decrease from 1.19 (0.37)–0.98 (0.67). Levels of 8-OhdG showed a similar decrease in salivary (0.32–0.11) and serum samples (2.12–1.89). Levels of Vitamin C increased in salivary samples (1.01–1.45) as well as in serum (8.56–9.05. A similar trend was observed in Vitamin E in salivary (0.67–0.89) and serum samples (8.08–8.97). Mouth opening increased from 24.64 (3.2) to 39.4 (3) mm ($p<0.05$)
8.	Hastak *et al*.	Observational study	90	Group 1: 15 patients received a total of 3 g/day of TE in three equal doses; 10 patients completed 3 months treatment and served as positive controls; Group 2: 22 patients were given 600 mg TOR per day mixed in 3 g of TE in three equal doses; 13 patients continued up to 3 months; and Group 3: 21 patients were given 600 mg TO per day mixed with 3 g of TE; 16 patients continued up to 3 months. 32 normal healthy subjects without chewing and smoking habits and of comparable age were studied for comparison with the treatment groups	Number of micronucleated cells in exfoliated oral mucosal cells and circulating lymphocytes	Number of micronuclei/100 cells in exfoliated buccal mucosal cells in normal patients was 2.2±0.17 and 10.2±0.28 in OSMF patients. This decreased to 3.9±0.23 in patients of Group 1, 3.8±0.23 in patients of Group 2, and 2.7±0.22 in patients of Group 3. A similar trend was observed in micronuclei/100 cells in circulating lymphocytes

OSMF: Oral submucous fibrosis, SOD: Superoxide dismutase, VAS: Visual analogue scale, IID: Interincisal distance, TP: Tongue protrusion, 8-OHdG: 8-hydroxydeoxyguanosine, MDA: Malondialdehyde, TOR: Turmeric oleoresin, RCT: Randomized control trial, TO: Turmeric oil

In the study by Yadav *et al.*, complete, rapid, and early improvement of burning sensation was observed with curcumin compared to a mean 15.6% residual burning sensation at the end of therapy in the steroid group [26]. Improvement in mouth opening and tongue protrusion was less as compared to intralesional steroids. The authors recommended that early use of curcumin in OSMF patients provides rapid symptomatic relief and, therefore, is beneficial and effective in the management of early OSMF. Similar results have been obtained by Srivastava *et al.* who reported significant improvement in burning sensation only, not mouth opening, in OSMF patients following treatment with curcumin [25]. In their study, maximum improvement in mouth opening was observed in the late stage while maximum improvement in burning sensation was observed in early stages.

The study by Das *et al.* compared curcumin, turmeric oil (TO), and multinal tablets and found that curcumin produced a quicker reduction in burning sensation and intolerance to spicy food, though TO was found to have a long-term effect on follow-up evaluation [27]. Complete relief of pain was reported with both curcumin and TO, while pain persisted in 5 patients in the multinal group. Statistically significant and equal increase in mouth opening of patients in Groups I and II was observed. The remarkable reduction in clinical scoring after 15 days of treatment with curcumin and TO was observed and was confirmed histopathologically as well. They also reported that curcumin and TO were well-tolerated without adverse events.

The study by Rai *et al.* studied 25 patients each of OSMF, oral leukoplakia, and OLP and 25 controls and assessed oxidative stress markers in serum and saliva [28]. The mean and median values of serum and salivary Vitamins C and E showed an increase, while malondialdehyde (MDA) and 8-hydroxydeoxyguanosine (8-OHdG) levels showed decreases in OSMF patients 1 week after intake of curcumin. These values were statistically significant after curing of OSMF in an average of 211 (17) days. A similar trend of increase in Vitamins C and E levels and a decrease of MDA and 8-OHdG levels were observed when the comparison of OSMF patients with healthy controls was made, at baseline and after 209 days. Improvement in pain scores, size of the lesion, and mouth opening was also significant. This research suggested that curcumin significantly increases the local and systemic antioxidant status and the levels of Vitamins C and E, while it decreases the lipid peroxidation and DNA damage of patients with potentially malignant disorders. Curcumin quenches reactive oxygen species (ROS) production at low concentrations and induces ROS production at high concentration.

Hastak *et al.* did a combination of *in vitro* and *in vivo* study in OSMF patients and showed that there is increased the incidence of micronuclei (Mn) in exfoliated oral mucosal cells and circulating lymphocytes of patients suffering from OSMF [29]. In this study, the authors report non-mutagenicity of TO and turmeric oleoresin (TOR) on the basis of the fact that TO and TOR did not induce an increase in Mn in lymphocytes when treated individually. They also report the chemoprotective effect of TO and TOR in lymphocytes of normal healthy subjects *in vitro* and recovery from DNA damage in OSMF patients *in vivo*.

Curcumin in oral leukoplakia

According to the World Health Organization (WHO) workshop consensus "the term leukoplakia should be used to recognize white plaques of questionable risk having excluded (other) known diseases or disorders that carry no risk for cancer" [30]. Oral leukoplakia is the most commonly encountered oral potentially malignant disorder and presents as homogenous form and non-homogeneous forms [31].

Curcumin suppresses mutagenesis and has been used as a chemopreventive agent in a variety of cancers including those arising in the oral cavity [32]. Several mechanisms are involved in the prevention of carcinogenesis by curcumin. It involves upregulation of carcinogen-detoxifying enzymes such as glutathione S-transferases [33,34] antioxidation [35,36], and suppression of expression of the isoenzyme cyclooxygenase-2 [37,38]. It shows greater modulation of translational mechanism in immortalized normal, premalignant, and malignant cells as compared to normal cells [39].

Review of existing literature shows that apart from the study by Rai *et al*. [28] which also included 25 oral leukoplakia patients, two other reports have studied the effect of curcumin on oral leukoplakia (Table 2).

A prospective phase-I study was conducted to evaluate the biologically effective dose of curcumin in humans and study the toxicology and pharmacokinetics of curcumin [40]. Patients with five high-risk conditions, namely recently resected urinary bladder cancer, arsenic Bowen's disease of the skin, uterine cervical intraepithelial neoplasm, oral leukoplakia, and intestinal metaplasia of the stomach, were recruited. Curcumin was administered orally in 25 patients for 3 months at a starting dose of 500 mg/day. The dose was escalated to a higher level up to 12,000 mg/day if no toxicity ≥Grade II was noted in at least three successive patients. Results after 3 months showed the histological improvement of precancerous lesions in 1 of 2 patients with recently resected bladder cancer, 2 of 7 patients of oral leukoplakia, 1 of 6 patients of intestinal metaplasia of the stomach, 1 of 4 patients with contrast-induced nephropathy (CIN), and 2 of 6 patients with Bowen's disease suggesting role of curcumin in chemoprevention. One patient with CIN and another with oral leukoplakia developed frank malignancies even after receiving curcumin treatment. No treatment-related toxicity up to the dose of 8000 mg/day was reported. The bulky volume of the drug was a deterrent to the patients on giving higher dosage.

In an intervention study from Sri Lanka, 72 betel quid chewers with oral potentially malignant lesions were randomly divided into two groups and were given either curcumin-coated chewing gum or placebo chewing gum [41]. The patients were followed every month while the sizes of lesions were measured every 6 months. The results showed that oral potentially malignant lesions of the curcumin group were significantly smaller within 6 months ($p<0.05$) and quitting betel quid chewing, and the use of curcumin had synergistic effects on the reduction of the lesion size.

Curcumin in treating palatal changes associated with reverse smoking

The term "palatal changes" describes the reaction of the palatal mucosa to reverse chutta smoking, a form of smoking more prevalent among females of Andhra Pradesh [42]. It encompasses several entities such as palatal keratosis, excrescences, altered pigmentation, erythematous areas, white or mixed red and white patches, and palatal ulcers. The study by Vijayalaxmi *et al.* evaluates the efficacy of curcumin preparation on the palatal changes associated with reverse smoking in 20 patients [43]. The study group was advised to use curcumin oral gel on an acrylic palatal plate along with instructions to quit smoking whereas control group patients were instructed about the benefits of smoking cessation only. Clinical and cytological smear examinations were performed for three visits at 15 days interval. Clinical improvement was graded as mild (¼ reduction in the clinical presentation), moderate (½ reduction in the clinical presentation), and fully improved if there was no evidence of the clinical lesion or no improvement if the lesion was persisting as it was. Evident improvement with reduction in size and severity of the clinical lesion was observed among the study group at both the first and third visits. However, the cytological appearances remained the same in all the cases, except for three cases from the study group, which demonstrated a transition from moderate dysplastic features to milder dysplastic features.

Curcumin on OLP

OLP is an immunologically mediated mucocutaneous disorder. Lichen planus affects the skin, oral mucosa, nail, genital mucosa, and scalp [44]. Skin lesions are classically described as purple, pruritic, and polygonal papules usually affecting the flexor surface of extremities [45]. Oral

Table 2: Review of literature showing three research papers assessing the efficacy of curcumin in oral leukoplakia patients

S. No.	Author(s)	Type of evidence	n	Interventions	Outcomes	Results
1.	Cheng *et al*.	Phase I clinical trial	25 (7)	The starting dose was 500 mg/day for 3 months. If no toxicity ≥Grade II was noted in at least three successive patients, the dose was then escalated to another level in the order of 1000, 2000, 4000, 8000, and 12,000 mg/day	The concentration of curcumin in serum and urine was determined by high-pressure liquid chromatography. Biopsy of the lesion sites was done immediately before and 3 months after starting curcumin treatment	The average peak serum concentrations after taking 4000 mg, 6000 mg, and 8000 mg of curcumin were 0.51±0.11 μM, 0.63±0.06 μM, and 1.77±1.87 μM, respectively. Urinary excretion of curcumin was undetectable. 1 of 4 patients with CIN and 1 of 7 patients with oral leukoplakia proceeded to develop frank malignancies in spite of curcumin treatment. Histologic improvement of precancerous lesions was seen in 2 of 7 patients of oral leukoplakia
2.	Chiba *et al*.	RCT	72	Curcumin-coated chewing gum and placebo chewing gum	The sizes of lesions were measured every 6 months	The oral precancerous lesions of the curcumin group were significantly smaller within 6 months ($p<0.05$). Quitting betel quid chewing and the use of curcumin had synergistic effects on the reduction of the lesion size ($p<0.05$)
3.	Rai *et al*.	Pre-post study	25 (100)	Curcumin 1 g caplets (900 mg curcumin, 80 mg desmethoxycurcumin, and 20 mg bisdesmethoxycurcumin)	Pain control using VAS and lesion healing measured by lesion size and mouth opening salivary and serum oxidative markers such as MDA, 8-OHdG, and Vitamins C and E were analyzed at baseline, 1 week and after clinical cure of the lesion	Salivary MDA levels decreased from 0.32 (0.16) to 0.11 and serum levels decrease from 1.19 (0.37) to 0.98 (0.67). Levels of 8-OhdG showed a similar decrease in salivary (0.32–0.11) and serum samples (2.12–1.89). Levels of Vitamin C increased in salivary samples (1.01–1.45) as well as in serum (8.56–9.05). A similar trend was observed in Vitamin E in salivary (0.67–0.89) and serum samples (8.08–8.97). Mouth opening increased from 24.64 (3.2) to 39.4 (3) mm ($p<0.05$)

CIN: Contrast-induced nephropathy, MDA: Malondialdehyde, 8-OHdG: 8-hydroxydeoxyguanosine, RCT: Randomized control trial

lesions can present as reticular, erosive, atrophic, plaque-like, popular, or bullous type [46]. Reticular lichen planus is associated with better prognosis [47]. The occurrence and distribution of lesion in the oral mucosa are 80% in the buccal mucosa, 65% in the tongue, 20% lips, and <10% seen in the floor of mouth and palate [48]. The follow-up studies of OLP reveal the malignant transformation of this condition to be up to 5.3% [49].

The review of the literature reveals five research papers which have been published assessing the efficacy of curcumin in OLP patients (Table 3). Of these, three have been authored by Chainani-Wu *et al.* [50]. First was a phase-II randomized, double-blind, and placebo-controlled trial evaluating the efficacy and safety of curcuminoids as an adjunct to short-course corticosteroids for the treatment of patients with atrophic or erosive OLP. The trial was conducted between February 2003 and September 2004, curcuminoids at 2000 mg/day for 7 weeks and prednisone at 60 mg/day for the first 1 week were given. The first interim analysis conducted in October 2004 using data from the first 33 subjects did not show a significant difference between the placebo and curcuminoids groups. Therefore, the study was ended early for futility. The initial course of prednisone was used in this trial due to ethical concerns regarding a placebo-controlled trial extending for 7 weeks among patients with significant oral discomfort. It was concluded that an RCT of a shorter duration, using a higher dose of curcuminoids without an initial course of prednisone, should be considered.

As a next step, randomized, double-blind, and placebo-controlled clinical trial were conducted in 2007 through 2008 with 20 patients of OLP [51]. Curcuminoids at doses of 6000 mg/day (3 divided doses) were given, and the curcuminoids group showed a greater reduction in clinical signs and symptoms as compared with the placebo group. Although the small sample size resulted in the limited power of the study, curcuminoids at doses of 6000 mg/day in 3 divided doses are well-tolerated.

In their third paper, the authors summarized the long-term open-label use of curcuminoids and experience of side effects (SEs) in 53 patients with OLP who had previously participated in RCTs of curcuminoids [52]. Of the 53 eligible patients, data were available for 44 (25/33) (75%) from the first and 19/20 (95%) from the second RCT. 18/25 participants from the first trial and 19/19 from the second trial took over-the-counter curcuminoids after completion of the trial period. The mean total daily dose was 2137.5 mg for 18/25 patients and 5058 mg for the 19/19 patient group. 10/18 (56%) reported that

Table 3: Review of literature showing five research papers assessing the efficacy of curcumin in OLP patients

S. No.	Author(s)	Type of evidence	n	Interventions	Outcomes	Results
1.	Chainani-Wua *et al*.	RCT	100	Study subjects were randomized to receive either placebo or curcuminoids at 2000 mg/day for 7 weeks. In addition, all subjects received prednisone at 60 mg/day for the first 1 week	The primary outcome was a change in symptom score from the baseline to the last follow-up visit at week 7. Secondary endpoints included changes in symptom scores from baseline at weeks 1 and 4, and changes in clinical signs from baseline at weeks 1, 4, and 7, as well as the occurrence of adverse effects. Five assessments - VAS, NRS, CSS, MOMI, and SEs (10-item questionnaire) were at 0, 1, 4, and 7 weeks	The first interim analysis (33 patients) did not show a significant difference between the placebo and curcuminoids groups. The changes in NRS values from baseline to 7 weeks in the placebo and curcuminoids groups were −1.996 and −1.666, respectively; changes in VAS values were −19.743 and −15.476, respectively; and changes in MOMI values were −2.8 and −3.583, respectively
2.	Chainani-Wua *et al*.	RCT	20	Study subjects were randomized to receive either placebo or curcuminoids at 6000 mg/day	Measurement of symptoms and signs of OLP using NRS and MOMI, CBC, liver enzymes; C-reactive protein; and IL-6 levels were done at baseline and day 14	In the placebo group, the percentage changes from baseline in NRS (median [interquartile range] =0.00 [−29–16.7], p>0.99), erythema (0.00 [−10–16.7], p=0.98), ulceration (0.00 [0.00–26.7], p=0.63), and total MOMI scores (−3.2 [−13–9.09], p=0.95) were not statistically significant, whereas they were statistically significant in the curcuminoids group: NRS (−22 [−33–−14], p=0.0078); erythema (−17 [−29–−8.3], p=0.0078), ulceration (−14 [−60–0.00], p=0.063), and MOMI (−24 [−38–−11], p=.0039). The curcuminoids group showed a greater reduction in clinical signs and symptoms as compared with the placebo group, measured by percentage change in erythema (p=0.05) and total MOMI score (p=0.03), and proportion showing improvement in NRS (0.8 vs. 0.3, p=0.02) and total MOMI score (0.9 vs. 0.5, p=0.05). Adverse effects were uncommon in both groups
3.	Chainani-Wua *et al*.	A descriptive retrospective cohort study	44 (25/33 [75%] from the first and 19/20 [95%] from the second RCT)	Collected information from clinic charts and patient interview on the OTC use of curcuminoids during a 1–5-year follow-up period	18/25 (72%) participants from the first trial - mean total daily dose was 2137.5 mg (SD=793, range 500–3000 mg) and mean duration of use was 30 months (SD=27.5). 19/19 (100%) patients from the second trial - mean total daily dose was 5058 mg (SD=1445, range 1000–6000 mg) and mean duration was 9.6 months (SD=8.04)	10/18 (56%) reported that curcuminoids controlled OLP symptoms, mean duration - 35.8 months (SD=27.4). 8/18 (44%) - unsure, mean duration of use was 21.0 months (SD=27.3). 2/18 patients (11%) reported a SE of diarrhea

(*Contd*...)

Table 3: (*Continued*)

S. No.	Author(s)	Type of evidence	n	Interventions	Outcomes	Results
4.	Rai *et al.*	Pre-post study	25 (100)	Curcumin 1 g caplets (900 mg curcumin, 80 mg desmethoxycurcumin, and 20 mg bisdesmethoxycurcumin)	Pain control using VAS and lesion healing measured by lesion size and mouth opening salivary and serum oxidative markers such as MDA, 8-OHdG, and Vitamins C and E, were analyzed at baseline, 1 week and after clinical cure of the lesion	Salivary MDA levels decreased from 0.32 (0.16) to 0.11 and serum levels decrease from 1.19 (0.37) to 0.98 (0.67). Levels of 8-OhdG showed a similar decrease in salivary (0.32–0.11) and serum samples (2.12–1.89). Levels of Vitamin C increased in salivary samples (1.01–1.45) as well as in serum (8.56–9.05). A similar trend was observed in Vitamin E in salivary (0.67–0.89) and serum samples (8.08–8.97). Mouth opening increased from 24.64 (3.2) to 39.4 (3) mm ($p<0.05$)
5.	Singh *et al.*	Pilot study	10	Extract of turmeric in the ointment form was made at NBRI, used for local application twice/day for a period of 3 months	Reduction in sign score (Thongprasom), pain score (VAS) lesion before and after treatment	Sign score was 5 in 8 patients and 4 in 2 patients initially which changed to score 0 in 9 patients and 1 in 1 patient. Initially, pain on VAS for all 10 patients was between 2 and 4 which changed to 0–2 after the treatment

RCT: Randomized control trial, CSS: Change in symptoms scale, MOMI: Modified oral mucositis index, OLP: Oral lichen planus, VAS: Visual analogue scale, CBC: Complete blood count, IL-6: Interleukin-6, NRS: Numeric rating scale, OTC: Over-the-counter, SD: Standard deviation, SE: Side effect

curcuminoids controlled OLP symptoms, and the mean duration of use among these patients was 35.8 months. 12/19 (63%) reported that curcuminoids controlled OLP symptoms, and the mean duration of use was 14.1 months. It was concluded that total of 22/37 (60%) of patients reported a reduction of symptoms with curcuminoids, 13/37 (35%) were unsure and 2/37 (5%) reported that it did not help in reduction of symptoms. SEs included abdominal discomfort and diarrhea; however, the occurrence was dose-related, and complaints were mild.

Rai *et al.* [28] studied 25 patients each of OSMF, oral leukoplakia, and OLP, and 25 controls and proved that anti-precancerous effects of curcumin are mediated through prooxidant and antioxidant pathways.

In a pilot study, topical application of curcuminoids was studied on 10 patients of OLP [53]. The extract of turmeric in the ointment form was used for local application twice/day for a period of 3 months. Significant improvement was noted in the signs and symptoms in the follow-up period. It was suggested that curcumin has an immune modulatory effect which could prove beneficial in the management of this cell-mediated autoimmune disorder.

Curcumin in RAS

RAS is a common condition characterized by the presence of recurring oval or round ulcerative lesions affecting oral mucosa [54]. Multifactorial etiology has been proposed involving various predisposing factors such as stress, trauma, food, hormonal imbalance, nutritional deficiency, and smoking [55]. RAS has been classified by Stanley in three variants - minor RAS, major RAS, and herpetiform ulceration [56].

The possible mechanism of action of the curcumin in RAS involves the decreased rate of release and metabolism of arachidonic acid, leading to diminished activities of phospholipase A2, cyclooxygenase, and lipoxygenase [57]. Previous studies show that curcumin could downregulate the expression of cytokines such as interleukin (IL)-6, TNF-α, and various other chemokines. Thus, curcumin suppresses inflammation through multiple pathways [58]. Animal studies have shown that oral administration of curcumin in instances of acute inflammation was found to be equally effective as cortisone or phenylbutazone and half as effective in cases of chronic inflammation [59]. The activity of curcumin in acute ulcer model in rats has been studied [60]. It causes re-epithelization and accelerated the healing process and protected gastric ulcer through attenuation of MMP-9 activity and amelioration of MMP-2 activity. In an animal study, curcumin increased cellular proliferation and collagen synthesis at the wound site [61]. An immunohistochemical study evaluating the impact of curcumin on oral ulcer healing in rats proved that administration of curcumin in normal rats with tongue ulcer leads to increased expression of TGF-β and increased expression of α SMA associated with increased migration of epithelial cells, which lead to smaller ulcer size in the first 9 days [62]. Thorat *et al.* have formulated a thermoreversible mucoadhesive gel containing curcumin for the treatment of mouth ulcer and characterized it [63].

A literature search for use of curcumin in RAS patients revealed five trials, of which four are RCT, and one is a controlled study (Table 4).

Deshmukh *et al.* [64] compared the efficacy of curcumin with triamcinolone acetonide in the gel form in the treatment of minor RAS. Their study showed that there was a significant difference between the pain score, size, number, and duration of ulcers from day 0 to day 7 in both the groups, respectively. Statistical significance was not noted between all the parameters when both the groups were compared with each other. The results of this study provide positive evidence that curcumin gel can be used as an effective and safer alternative to steroids in the treatment of minor RAS. A similar study comparing turmeric and triamcinolone was conducted by Halim *et al.* [65]. There were significant differences in the pain score and ulcer size on days 1 and 5 in both the groups, but there is no significant difference between turmeric and triamcinolone for the treatment of minor RAS. Even though the differences were not significant, for mean comparison, the

Table 4: Review of literature showing five research papers assessing the efficacy of curcumin in recurrent aphthous ulcer patients

S. No.	Author(s)	Type of evidence	n	Interventions	Outcomes	Results
1.	Deshmukh *et al*.	RCT	60	Group I - Curcumin gel group (10 mg of *C. longa* extract/g) and Group II - triamcinolone acetonide (0.1%) gel group patients in either group were asked to apply the gel 3 times a day on each ulcer	Ulcer size measured along its longest diameter, number of ulcers, duration of healing, and pain score was 0–10 using the VAS on day 0, 3, 5, and 7	Reduction in pain (4.7±1.53 in Group I and 4.5±1.43 in Group II), size (−3.8±1.08 in Group I and −3.7±1.53 in Group II), and the number of ulcers (−1.2±0.38 in Group I and −1.5±0.77 in Group II) and duration of ulcers (3.9±1.18 in Group I and 4.1±1.18 in Group II) was statistically significant in both the groups from day 0 to day 7, respectively; but on the comparison between Groups I and II, no statistical significance was noted
2.	Halim *et al*.	RCT	20	Group I received turmeric powder, and Group II received triamcinolone acetonide, to be applied for 5 min twice per day	The VAS has been used to assess the pain score, and the ulcer size was measured by sliding caliper on day 1 and 5	The statistically significant difference in reduction in pain score from day 1 (4.40±1.713) to 5 (0.80 ±2.530) in Group II and the Group I (5.7±1.767 day 1; 1.1±1.287 day 5) was observed. A similar difference in size of the ulcer for the Group I (mean 23.7042±82.05465) and Group II (mean 51.4677±60.71060) were observed. No significant difference between turmeric and triamcinolone for the treatment of minor recurrent aphthous ulcer observed
3.	Manifer *et al*.	RCT	57	Group I received placebo gel, and Group II received curcumin gel 2%, to be applied twice per day	Size of ulcers measured by the investigator, pain evaluated based on perceived pain rating scale before drug application (day 0) and at days 4, 7, and 14 as well as subject overall satisfaction score at the end of treatment on four-point description scale (poor=1, moderate=2, good=3, and excellent=4)	Mean ulcer pain of two groups matched well at baseline but was significantly relieved in the turmeric group at day 4 ($p<0.05$). Ulcer size of the treatment group and the placebo group matched well at the study entry ($p>0.05$), significant group differences appeared at the later visits (days 4 and 7; $p<0.05$). Highly significant group differences appeared at the end of the trial regarding the overall satisfaction of the patients ($p\leq0.01$)
4.	Antharjanam and Balan	Controlled trial	20	Group I - antiseptic gel topically twice daily. Group II - instructed to hold 2.5 ml of curcumin oil (1 ml of curcumin oil contained 250 mg curcumin) mixed with 10 ml of milk for 1–2 min and spit, twice daily	The number of ulcers, the intensity of pain, the period of healing and frequency of recurrence through log diaries given to the patient. Pain was assessed using VAS	Patients who used curcumin oil reported that ulcers started healing earlier than in previous attacks; there was also an early reduction in pain. A follow up for 1 year has shown no recurrence in these patients

(*Contd*...)

Table 4: (*Continued*)

S. No.	Author(s)	Type of evidence	n	Interventions	Outcomes	Results
5.	Al-Saffar	RCT	83	Group A: 30 patients received a viscous solution of curcumin 10%; Group B: 33 patients received a viscous solution of curcumin 50%; Group C: 10 patients without treatment (control negative); and Group D: 10 patients received glycerin treatment (control positive)	Healing time and symptomatic relief of individual treatment. Appearance of lesion, zone of inflammation and pain was recorded at each visit during the healing phase	There was a significant difference in the percentage of complete healing between control negative group and groups of patients using a viscous solution of curcumin 10% and 50% ($p<0.05$), and there was a significant difference in the percentage of complete healing between control positive group, groups of patients using a viscous solution of curcumin 10% and those using viscous solution of curcumin 50% ($p<0.05$). While there is no significant difference between groups of patients using a viscous solution of curcumin 10% of those using a viscous solution of curcumin 50% ($p>0.05$)

RCT: Randomized control trial, VAS: Visual analogue scale, *C. longa: Curcuma longa*

triamcinolone had a greater value of mean for ulcer size, indicating turmeric was better in reducing the size of the ulcer. Similarly, for pain score, turmeric was the better medicament for relieving the pain of the ulcer compared to triamcinolone.

In a randomized, double-blind, and placebo-controlled trial of patients with minor RAS efficacy of curcumin gel containing 2%, curcumin was studied [66]. Curcumin gel significantly reduced pain intensity and size of aphthous ulcer compared to placebo. Significant group differences were also observed at the end of the trial regarding overall satisfaction of the patients. A study focusing on the therapeutic effects of curcumin in RAS in comparison to conventional antiseptic gel found that curcumin could produce a remarkable reduction in recurrence of RAS (follow-up for 1 year) [67]. In addition, ulcers treated with curcumin healed faster and were associated with early relief in pain.

Al-Saffar [68] studied the efficacy of two different concentrations of the viscous curcumin solution on the healing of ulcer in patients with RAS and compared it with a positive and negative control. Complete recovery occurred from 5 days (73% patients in curcumin solution 10% and 78.7% in curcumin solution 50%) to 11 days (6.6% in curcumin solution 10% and 3.2% in curcumin solution 50%). However, in control negative group (without treatment), the complete recovery occurred from 5 days (20%) to 11 days (40%) only. In control positive group (received glycerin vehicle treatment), the complete recovery occurred from 5 days (30%) to 11 days (20%).

Curcumin in oral mucositis

Oral mucositis refers to erythematous and ulcerative lesions of the oral mucosa observed in patients treated with chemotherapy, and/or with radiation therapy to fields involving the oral cavity. Lesions of oral mucositis are extremely painful and compromise nutrition and oral hygiene, thereby increase the risk for local and systemic infection [69]. Fractionated radiation dosage increases the risk of mucositis to >70% of patients in most trials [70].

The pathophysiology of mucositis is multifarious and involves direct cellular effects brought about by DNA damage and generation of ROS. Amplification of signaling pathways, for example, TNF-α release, NF-κB activation, and ROS potentiates cell death, mediating mucosal damage. Polymicrobial flora in the oral cavity potentiates proinflammatory cytokine release [71]. Curcumin offers potential preventive and therapeutic benefit in oral mucositis due to its anti-inflammatory and antibacterial properties. Lüer *et al.* [72] assessed the *in vitro* extent of bactericidal activity of curcumin on pharyngeal cells. Complete suppression of the release of TNF-α, IL-6, IL-8, monocyte chemoattractant protein 1, granulocyte macrophage-colony stimulating factor, and VEGF was observed. Repetitive exposure to curcumin resulted in repetitive suppression of cytokine/chemokine expression lasting from 4 to 6 h. Therefore, the authors concluded that through reduction of oral microbial concentration and suppression of inflammation cascades, curcumin may play a role in oral mucositis.

Review of literature revealed four studies evaluating the role of curcumin in treatment and prevention of oral mucositis (Table 5).

Patil *et al.* [73] evaluated the efficacy and safety of curcumin mouthwash in comparison with chlorhexidine in the management of oral mucositis. Curcumin was found to be better than chlorhexidine mouthwash in terms of rapid wound healing and better patient compliance. No oral or systemic complications were reported in this study.

Saldanha and Almeida [74] compared turmeric and saline mouthwash on oral mucositis. There was a significant difference in the score of oral mucositis between pre-intervention on day 1 morning and post-intervention score on day 5 evening in both turmeric and saline group but on comparison it was found that turmeric mouthwash was more effective than saline mouthwash in all the days except in day 3 where there was no significant difference found.

Elad *et al.* [75] undertook a pilot study to assess the tolerability of a curcumin mouthwash for the management of oral mucositis. They had originally designed a placebo-controlled study, but gastrointestinal adverse events (nausea and vomiting) affected the compliance of the first three participants who were receiving placebo. Due to ethical issues, the control group was discontinued and the authors reported their results as a case series. In this study, the authors suggested that curcumin mouthwash was safe and well-tolerated.

Table 5: Review of literature showing four research papers assessing the efficacy of curcumin in oral mucositis patients

S. No.	Author(s)	Type of evidence	n	Interventions	Outcomes	Results
1.	Patil *et al*.	RCT	20 adult cancer patients undergoing radiochemotherapy	Study subjects were randomized to receive either chlorhexidine mouthwash 0.2% or freshly prepared curcumin mouthwash; each to be used thrice daily	The WHO scale, the OMAS, and NRS (NRS; patient reporting scale of 0–10) were used for assessment at days 0, 10, and 20. Adverse events were tracked	On the comparison between the baseline and 2nd follow-up scores of the study and control groups, NRS ($p<0.001$), erythema ($p=0.050$), ulceration ($p<0.001$), and WHO ($p=0.003$) were found to be statistically significant
2.	Saldanha and Almeida	RCT with pre-post-test time series design	40 adult cancer patients undergoing radiochemotherapy	Group I receiving turmeric mouthwash (mouthwash solution prepared by mixing 1.5 g of turmeric powder with 50 ml of water). Group II received saline mouth, 3 times/ day for 5 days	Oral mucositis assessment checklist and pain using pain scale every morning before the intervention and evening after the intervention	The mean pre-test TIOM score of Group I was 25.35 whereas in post-test it is 18.85. The mean of pre-test TIOM score of Group II was 25.05 whereas in post-test it is 20.15. The mean post-interventional scores (day 5 evening) in Groups I and II were significantly lower than the mean pre-interventional scores (day 1 morning) In comparison, it was found that turmeric mouthwash was effective than a saline mouth in all the days except in day 3 where there was no significant difference found
3.	Elad *et al*.	Pilot study	7 pediatric and young-adult oncology patients undergoing doxorubicin-containing chemotherapy	10 drops of curcumall in a half glass (50 ml) of water twice daily (equivalent to 330 mg/day), in addition to standard preventive oral care (chlorhexidine 0.2% mouthwash) during treatment with high dose chemotherapy	The primary outcome measure was oral adverse events related to curcumin use, and secondary outcome measures were OMAS, WHO mucositis scale, and VAS. OM was assessed on days 0, 7, 10, 14, and 21 days	No oral or systemic adverse events were documented. In the four patients who fulfilled the compliance criteria, the WHO, OMAS, and VAS scores were lower than the severity of oral mucositis previously reported in the literature. 4 of the 5 participants developed OM, but the values were low, reflecting a relatively mild case. Duration of neutropenia ranged from 3 to 8 days, with an average of 4. Opioid use ranged from 0 to 4 days with an average of 1.5 days. Moreover, finally, hospitalization ranged for all subjects between 0 and 12 days with a median of 7. No parenteral nutrition was required
4.	Rao *et al*.	RCT	80 head and neck cancer patients requiring 70 Gy of radiation or chemoradiotherapy	Group I – turmeric gargle and Group II - povidone-iodine gargle during chemo/ radiotherapy during the period of treatment	Oral mucositis was assessed using the RTOG grading system before the start, during, and at the end of the treatment by an investigator unaware of the treatment. The primary endpoint of this study was the incidence of mucositis every week during the 7-week period. The secondary endpoint was the effect of turmeric gargle on the incidence of treatment breaks, loss of scheduled treatment days, and a decrease in body weight at the end of the treatment	Compared with the cohorts using povidone-iodine gargle, the group using turmeric as a mouthwash had delayed and reduced the levels of radiation-induced oral mucositis and was statistically significant at all-time points ($p<0.001$–$p<0.0001$). In addition, the cohorts using turmeric had decreased intolerable mucositis ($p<0.001$) and lesser incidence of the treatment breaks in the first half of the treatment schedule before 4 weeks ($p<0.01$) and reduced change in body weight ($p<0.001$)

NRS: Numeric rating scale, WHO: World Health Organization, OMAS: Oral mucositis assessment scale, TIOM: Treatment-induced oral mucositis, VAS: Visual analogue scale, RTOG: Radiation therapy oncology group

Rao *et al.* [76] in their single-blinded, randomized, controlled clinical trial compared turmeric gargle or povidone-iodine in head and neck cancer patients requiring 70 Gy of radiation or chemoradiotherapy (daily radiotherapy plus carboplatin once a week). They concluded that gargling with turmeric provided significant benefit by delaying and reducing the severity of mucositis.

CONCLUSION

Turmeric has been used in Ayurvedic medicine since ancient times, with various biological applications. Curcumin is a nontoxic, highly promising natural antioxidant compound having a wide spectrum of biological functions. It is expected that curcumin may find application as a novel drug in the near future to control various oral mucosal disorders. This paper reviewed the role of curcumin in tobacco-associated and ulcerative conditions. Curcumin, therefore, fulfills two roles in the putative treatment of oral mucosal disorders, as an anti-inflammatory agent, antioxidant, antimicrobial, and chemopreventive agent. It also provides the basis for a simple, safe, acceptable, and cost-effective intervention for oral mucosal disorders.

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