Original Article

Evaluation of Efficacy of Curcumin along with Lycopene and Piperine in the Management of Oral Submucous Fibrosis

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Abstract

Context: Oral submucous fibrosis (OSMF) is a high-risk premalignant condition of the oral cavity and oropharynx. Complete regression of the disease is still not possible with available treatment modalities. **Aims:** The aim of the study was to evaluate the efficacy of curcumin, lycopene, and piperine as a combination in the management of OSMF. **Settings and Design:** Efficacy was evaluated on the basis of improvement in clinical parameters (i.e., visual Analog Scale [VAS]) score for burning sensation, mouth opening (MO), mucosal flexibility (MF), and tongue protrusion [TP]). **Materials and Methods:** Forty patients clinically and histopathologically diagnosed with OSMF were included in the study; patients were administered with the above-stated drug combination, and clinical parameters were evaluated at regular intervals to compare the pre- and post-treatment measurements. **Statistical Analysis Used:** Paired *t*-test was done to evaluate significance of the results. **Results:** Highly significant improvement was observed for posttreatment reduction in VAS score for burning sensation and increase in MO ($P < 0.001$). Significant improvement was also observed in the increase of MF and TP. Posttreatment histopathological evaluation also revealed reepithelialization, indicated by significant increase in the epithelial thickness as found through quantitative image analysis. Immunohistochemical studies with Col1A1 showed decrease in collagen deposition. **Conclusions:** Taken together, the present study proposes the usage of combination drug therapy for the management of OSMF as an effective and affordable way.

Keywords: *Curcumin, lycopene, mouth opening, mucosal flexibility, oral submucous fibrosis, piperine, visual Analog Scale score for burning sensation*

Introduction

Oral submucous fibrosis (OSMF) is a chronic progressive scarring disease of oral mucosa, associated with juxtaepithelial inflammatory reaction followed by fibroelastic changes in lamina propria, leading to stiffness of oral mucosa, causing restricted mouth opening (MO) and tongue movement (trismus), burning sensation in the oral cavity, and difficulty in eating.[1] The fibrotic change may involve hypersalivation/xerostomia and mucosal blanching with fibrous bands in the labial mucosa, buccal mucosa, retromolar pads, soft palate, uvula, and floor of oral cavity, as well as pharynx, esophagus, and paratubal muscles of Eustachian tubes.[2] The disease most commonly affects habitual areca nut, betel quid, and gutkha chewers and most frequently involved age group is 20–30 years, though etiopathogenesis of the disease is considered to be multifactorial, including excessive chilly consumption, Vitamin B and iron deficiency, genetic, immunological, and environmental causes.[3] Commonly prevalent among Asians, the disease provides high risk for development of oral malignancy, with a transformation rate of around 7.6%.[4]

Different treatment modalities, both medicinal and surgical, have been advocated for relieving signs and symptoms of the disease, though complete regression has not been reported till date. Therefore, the search for an effective treatment modality still continues. A number of studies have attempted to find the efficacy of different natural plant extracts, antioxidants, synthetic drugs, etc., for the management of OSMF.[5-8] One such plant is *Curcuma longa*, which is used as an Indian spice derived from the rhizomes of the plant. Its principal active constituent curcumin promotes wound healing and also has anti-inflammatory, immune-modulatory, and antioxidant properties;[9] it has been studied

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for its effectiveness against cancer and various other diseases such as diabetes, hypertension, and Alzheimer's disease.[10] Curcumin showed inhibitory properties against lipooxygenase and cyclooxygenase (COX) activities that can induce inflammation,[11] and lowers the activity of smokeless tobacco extract or nicotine-derived nitrosamine ketone-induced nuclear factor kappa-light-chain-enhancer of activated B-cells and COX-2 in oral premalignant and malignant cells.[12] Lycopene, a nonpro-vitamin A carotenoid, predominantly found in tomatoes, pink grapefruit, watermelon, papaya, guava, and other fruits showing high antioxidant and singlet-oxygen-quenching ability twice that of beta-carotene and ten times higher than that of alpha-tocopherol 2, is described as the most potent radical scavenger in various *in vivo* and *in vitro* studies.[13,14] Again, the alkaloid piperine from *Piper nigrum* has shown to increase the bioavailability of various compounds, especially curcumin by 20 folds.[15]

Meanwhile, combination therapy comprising a treatment modality that combines two or more therapeutic agents has evolved as a cornerstone of cancer therapeutics.[16] Toxicity produced through combination therapy of chemotherapeutic drugs can be significantly less because different pathways will be targeted. Working in a synergistic or additive manner, combination therapy eventually provides with a lower therapeutic dosage of each individual drug. In addition, combination therapy can induce simultaneous prevention of toxic effects on normal cells and cytotoxic effects on cancer cells. Emerging approach of restrictive combinations (RC) of drugs focuses on strategic dosing and drug administration based on the molecular differences between cancer cells and normal cells. In this approach, additional drugs can be added to improve the therapeutic potency in a synergistic manner but without undesirable side effects. As a result, combination therapy has emerged as potential therapeutic modality with limited treatment resistance and toxicity and increased efficacy. On the other hand, synergistic effect of curcumin or lycopene with irradiation has been evidenced upon oral squamous cell carcinoma cells,[17] whereas lycopene has been found to work synergistically with natural antioxidants.[18] In a number of studies, curcumin and lycopene has been separately applied for the management of OSMF;[19-24] however, a combinational approach has not been attempted yet. Thus, for the present study, we have intended for management of OSMF patients with a combination drug constituted by curcumin, lycopene, and piperine for having a meaningful success level for the said purpose.

Materials and Methods

Selection of participants

The study was conducted in the Department of Oral Pathology, Dr. R. Ahmed Dental College and Hospital, Kolkata, India. As participants, forty patients clinically diagnosed with OSMF (without malignancy) were selected for this study; all these patients belong to the Bengali population of West Bengal, India. Patients with any other oral malignant or premalignant lesions (e.g., hypertrophic lichen planus, candidiasis, etc.), any infectious or contagious disease process, or intractable medical or radiological abnormalities were excluded from the study. After clinical evaluation and collection of written informed consent, histopathological evaluation was done in ten randomly selected patients who had no contraindication for performing incisional biopsy. Clearance certificate of this study was obtained from the institutional ethics committee.

Inclusion and exclusion criteria

Patients having oral habits for >6 months with clinical sign of OSMF were included in the study. OSMF clinical diagnostic symptoms included burning sensation in the mouth while eating spicy or hot food, dryness of mouth, occasional vesicle formation and ulceration, and restricted MO with difficulty in swallowing.

Patients who were medically compromised such as patients suffering from any infectious or contagious disease or with any intractable medical or radiological abnormality, any other white patch-like candidiasis, hypertrophic oral lichen planus and lichenoid-like lesions, and scleroderma were not included in the present study. Furthermore, patients who received previous treatment or with previous history of surgery, radiotherapy or chemotherapy, or patients using vitamin or dietary supplement were excluded from the study. Cases complaining of difficulty in opening the mouth due to other reasons such as inflammation, etc., were excluded from the study.

Drug treatment and clinical evaluation

Each patient was motivated to stop chewing areca nut or tobacco 1 month prior to the commencement of the treatment, and then prescribed with commercially available combination drug BIOCUMIN (Biochem India) twice a day for 3 months. Each tablet comprised curcumin (500 mg), piperine (5 mg), and lycopene (25 mg). The responses were assessed clinically every 15 days up to a follow-up period of 3 months. Parameters used for this clinical evaluation were MO, tongue protrusion (TP), mucosal flexibility (MF), and Visual Analog Scale (VAS) score of burning sensation (VAS). For MO, interincisal distance was measured using vernier calipers; TP was measured from the margin of the lower incisor to the tip of the tongue. To determine the MF or cheek flexibility, the point of intersection of the two imaginary lines, one joining the tragus of the ear and angle of the mouth and another perpendicular line from the outer canthus of the ipsilateral eye extended downward, was marked as the reference point on both sides of the face; the distance between the two reference points at normal centric occlusion was recorded as m_1. The patient was asked to blow the cheeks fully with lips closed and the distance between the reference points was recorded as m_2.

The difference between the two values (m_2–m_1) was used as measure of MF. Burning sensation was recorded on VAS ranging from 0 to 10, with ten-grade showing maximum burning sensation. The OSMF patients were divided into four subgroups based on their MO (Group I: >35 mm; Group II: 30.1–35 mm; Group III: 20-30 mm; Group IV: <20 mm) following Lai's classification (1995).[25]

All the patients were having areca chewing habits. Habit counseling was done before start of the treatment. Patients were advised to stop oral habits and certain dietary modifications such as elimination of spicy food including high consumption of chillies.

Histopathology

Pre- and post-treatment biopsy specimens collected from OSMF patients were processed for paraffin embedding. Sections of 4–5-μm thickness were evaluated qualitatively and quantitatively following hematoxylin and eosin (H and E) staining and visualization under LEICA DM 3000 microscope (Leica Microsystems, Switzerland). Image-J analysis system (National Institutes of Health, Bethesda, MD, USA) was used to measure the epithelial thickness from multiple sections.

Immunohistochemistry

Biopsy specimens collected from OSMF patients were paraffin-embedded and 4–5 μm thickness sections were collected on poly-L-lysine-coated slides, after paraffin removal using xylene and rehydration (100%, 90%, and 70% of ethanol for 5 min, treated with deionized water for 10 min), the slides were treated with citrate buffer for unmasking the antigen. Further immunostaining was performed using Novolink polymer detection system ((Novocastra™, UK). The endogenous peroxidase and protein were blocked using supplied blockers. The expression Col1A1 protein was detected with primary antibody of Col1A1 (1:100, Novus Biologicals, USA). After postprimary blocking, sections were incubated with Novolink polymer and were then developed with DAB using supplied DAB substrate buffer. The sections were counterstained with hematoxylin and were observed under LEICA DM 3000 microscope (Leica Microsystems, Switzerland).

Statistical analysis

All the statistical analysis was done using Statistical software SPSS v.16.0. (statistical package for social science by International Business Machines Corporation, Armonk, New York, United States). The results for each group, their clinical parameters and epithelial thickness (pre- and post-therapy) were calculated as mean ± standard deviation. Paired *t*-test was done to evaluate significance of the results. $P \leq 0.05$ was considered as statistically significant.

Results

For the present study, a total number of 40 OSMF patients were selected from the Outpatient Department of Dr. R. Ahamed Dental College, Kolkata. The mean age of the group under study was 34.75 years (standard deviation ± 11.53 years). The age range was 18–62 years with male: female ratio 7:1. The patients were further subdivided to four groups based on the interincisal distance following Lai's classification (Group I: >35 mm, Group II: Between 30.1 and 35 mm; Group III: Between 20 and 30 mm; and Group IV: <20 mm), so that ten patients belonged to each of the four groups. The efficacy of the treatment was evaluated based on the pre- and post-treatment values of four clinical parameters (i.e., VAS) score for burning sensation, MO, MF, and TP) measured from each of the patient under study [Figure 1]. Again, tissue sections from ten randomly selected patients were collected through biopsy procedure at pre- and post-treatment stage and were evaluated for expression of collagen-1 protein by immune-histochemistry technique. All the samples were collected after getting informed consent from the patient. The study was approved by the ethical committee of the Institution.

All the four clinical parameters under consideration showed improvement at the posttreatment stage [Table 1]. The average VAS score for burning sensation of all the patients showed significant reduction at the posttreatment stage. In Group I, the mean VAS score reduced from 8.7 to 0.28; Group II showed a reduction from 8.1 to 0.37; Group III revealed a reduction of VAS score from 7.4 to 0.46, and VAS score in Group IV reduced from 7.6 to 0.46. The reduction in the VAS scores in all the subgroups was statistically significant ($P < 0.001$). Again, the MO was significantly increased in all the subgroups at the posttreatment stage; the mean MO was significantly increased from 27.21 mm to 30.83 mm. In Group I, the average MO was increased from 38.93 mm to 43.37 mm; Group II showed increase in MO from 32.38 mm to 36.5 mm; an increase from 24.67 mm to 28.05 mm of MO was observed in the Group III; while the Group IV showed increased MO from 12.86 mm to 15.38 mm. The increase in the MO in all the subgroups was also statistically significant ($P < 0.001$). For TP in Group I, posttreatment TP increased from 28.3 mm to 31.4 mm; Group II showed increase from 34.4 mm to 37.6 mm; Group III showed an increase from 29.5 mm to 32 mm of TP; whereas in Group IV, the TP increased from 21.3 mm to 23.5 mm. MF was significantly improved in all the four subgroups (6.5 mm to 7 mm in Group I, 5.7 mm to 6.2 mm in Group II, 4.97 mm to 5.65 mm in Group III, and 5.3 mm to 6.09 mm in Group IV, respectively); the increase in mean MF also increased from 5.62 mm to 6.24 mm, which is statistically significant ($P < 0.001$).

To further evaluate the effect of the therapy, H and E staining was performed before and after the completion of the therapy [Figure 2]. Pretherapy microphotograph showed thin atrophic epithelium with subepithelial hyalinization and homogenization with a few blood vessels,

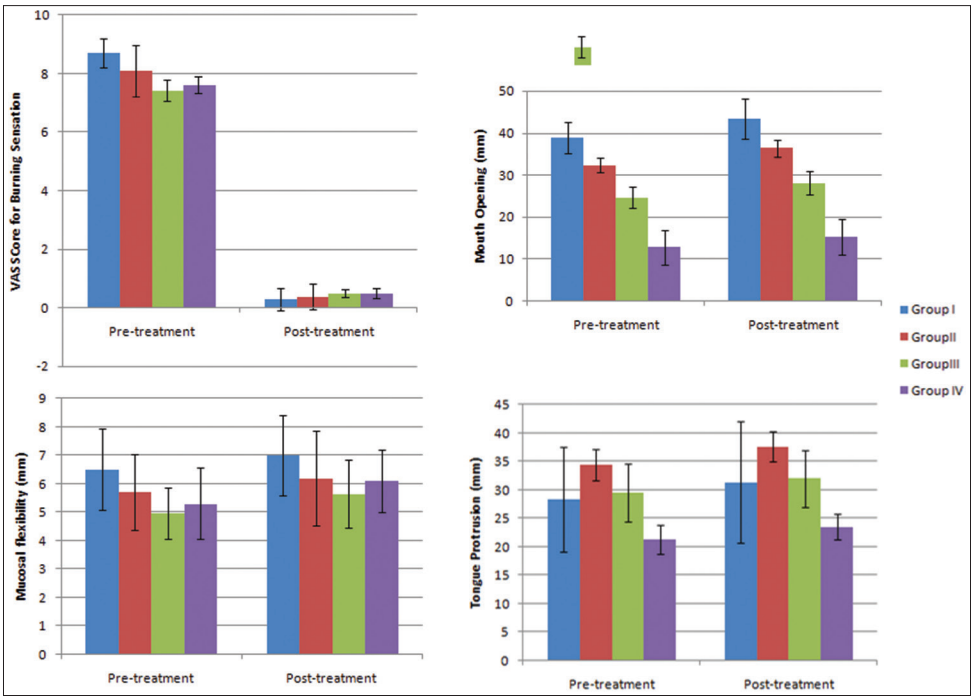

Figure 1: Posttreatment improvement of Visual Analog Scale score of burning sensation, mouth opening, mucosal flexibility, and tongue protrusion (TPin different groups of oral submucous fibrosis patients)

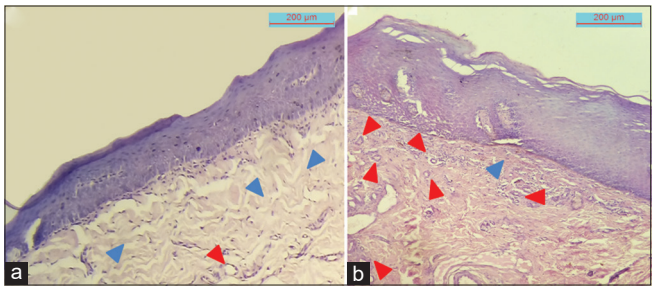

Figure 2: Representative image of hematoxylin and eosin-stained histopathological section of oral submucous fibrosis tissues at × 10 magnification (a) pretreament; (b) posttreatment, showing reduced hyalinization (blue arrow) and increased number of blood vessels (red arrow) after treatment

whereas posttherapy micrographs revealed increased thickness of epithelium along with reduced hyalinization and increasing number of blood vessels in the connective tissue. The epithelial thickness was measured in multiple H and E-stained histopathological sections of pre- and post-therapy biopsy samples with image analysis software Image-J (National Institutes of Health, Bethesda, MD, USA) [Table 2]. The results distinctly indicated a significant MO increase in the epithelial thickness in posttherapy samples (pretreatment: 0.22, ±0.036; posttreatment: 0.38, ±0.088) ($t = -29.826$; $P \leq 0.001$).

Efficacy of the combinational drug treatment was further evaluated by determining the expression of Col1A1 by immune histochemistry to determine the collagen density before and after therapy [Figure 3]. As shown in Figure 3a, Col1A1 expression was observed throughout the thickness of stratified squamous epithelium, lamina propria, submucosal layer, and connective tissue. An overall reduction in collagen expression was noticed following the therapy [Figure 3b].

Discussion

Clinical management of OSMF is symptomatic and aimed primarily at improving MO. Various methods, such as intralesional injection of corticosteroid/interferon-gamma, micronutrient supplement, physiotherapy, and surgical interventions, have been used to alleviate burning sensation, improving MO, and reducing fibrous bands. All the patients of the present study had a history of consuming gutkha, accompanied by occasional smoking and alcohol consumption which can be considered as the major factor for the development of the disease. Before starting any regime of treatment, initial management strategy should mandatorily be the discontinuation of associated detrimental oral habits along with patient counseling and education, which was followed in the present study. Again, the choice of treatment modality is significant; topical application provides for direct availability of the drug to the primary affected buccal site, but chances of washing out by the saliva may hinder the efficacy.

Curcumin, the principal curcuminoid found in turmeric and considered as its most active constituent, as well as lycopene, the high potent antioxidant found in tomatoes and green vegetables, were studied for their effectiveness against cancer and also in wide range of other conditions. A number of studies have attempted the use of curcumin or

Table 1:Posttreatment efficacy of curcumin on Visual Analog Scale score of burning sensation (Visual Analog Scale), cheek flexibility, mouth opening, and tongue protrusion

Parameter	Cases (n=40)			Group I (n=10)			Group II (n=10)			Group III (n=10)			Group IV (n=10)		
	Pretreatment	Posttreatment	*P**	Pretreatment	Posttreatment	*P**	Pretreatment	Posttreatment	*P**	Pretreatment	Posttreatment	*P**	Pretreatment	Posttreatment	*P**
VAS score for burning sensation	7.95±0.93	0.39±0.43	<0.001	8.7±0.48	0.28±0.38	<0.001	8.1±0.88	0.37±0.43	<0.001	7.4±0.84	0.46±0.46	<0.001	7.6±0.97	0.46±0.46	<0.001
MO	27.21±10.29	30.83±11.99	<0.001	38.93±3.75	43.37±4.67	<0.001	32.38±1.65	36.5±1.99	<0.001	24.67±2.55	28.05±2.77	<0.001	12.86±4.16	15.38±4.27	<0.001
TP	28.38±7.14	31.13±9.1	<0.001	28.3±9.15	31.4±10.68	0.009	34.4±2.68	37.6±2.68	<0.001	29.5±5.15	32±4.99	<0.001	21.3±2.49	23.5±2.27	<0.001
Mucosal flexibility	5.62±1.33	6.24±1.4	<0.001	6.5±1.43	7±1.41	0.014	5.7±1.34	6.2±1.67	0.023	4.97±0.91	5.65±1.2	0.002	5.3±1.25	6.09±1.11	<0.001

*Significance level $P \leq 0.05$. VAS: Visual Analog Scale; MO: Mouth opening

Table 2: Posttreatment efficacy of curcumin on epithelial thickness

Parameters	Mean pretreatment epithelial thickness (mm)	Mean posttreatment epithelial thickness (mm)	*P**
Mean±SD	0.217±0.036	0.382±0.088	<0.001
Maximum	0.284	0.574	
Minimum	0.124	0.119	

*Significance level $P \leq 0.05$. SD: Standard deviation

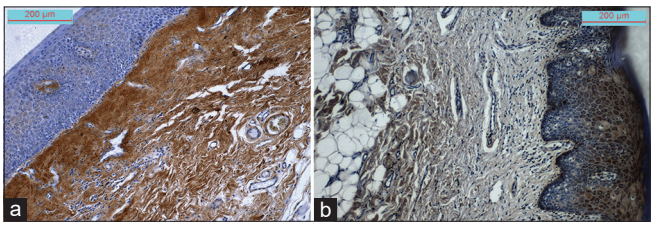

Figure 3: Representative image of Immunohistochemistry for localization of Col1A1 in histopathological section of oral submucous fibrosis tissues at × 10 magnification (a) pretreament; (b) posttreatment, showing reduced expression of Col1A1 after treatment

lycopene in different forms for the management of OSMF, as well as three standard treatment modules, which have been summarized in Table 3. Most of these studies have evaluated the clinical parameters of burning sensation and MO; however, none of them have considered the MF, which is a significant parameter for evaluation of the diseased mucosa.[32] Again, few of the studies have noted some limitations in the topical application of curcumin.[5,22,27] In our study, we have attempted to find out the efficacy of a combinational modality combining curcumin, lycopene, and piperine on the improvement over the burning sensation, MO, TP, and MF. All the patients of this study had a history of consuming gutkha, accompanied by smoking also in some cases. Similar to previous studies, all forty patients, administered with combination of curcumin, lycopene, and piperine revealed a general improvement with reduction of burning sensation and increase in MO, MF, and TP. MO in Group III showed highest improvement (1.14-fold increase), whereas MF increased 1.2 fold in Group IV which were the highest among all four groups. For TP, nearly equal improvement was observed for all the subgroups. The improvement in reduction of burning sensation was also significant for the OSMF patients. Analysis of the VAS score for burning sensation showed 0.03-, 0.04-, 0.06-, and 0.06-fold reduction in Groups I, II, III, and IV, respectively. When the overall improvement was considered, the combinational herbal drug therapy showed statistically significant posttreatment improvement ($P < 0.001$).

The other factor considered in this study was the effect of the combinational herbal drug treatment on the tissue morphology and collagen production. Curcumin exerts anti-inflammatory activity by inhibiting a number of different molecules that participate in the process of inflammation. Its ability to inhibit lipid peroxidation

Table 3: Studies showing the application of curcumin and/or lycopene for management of oral submucous fibrosis

Details of patients	Therapeutic strategy	Dose of therapy	Mode of application of curcumin/lycopene	Duration of therapy	Parameters studied	Brief result	Any adverse reaction	Authors
39 patients (15-35 years of age) from Bombay (Mumbai)	TO; TOR; alcoholic TE	Group I: TE-3 g/day Group II: 600 mg TOR + 3 g of TE/day Group III: 600 mg TO + 3 g of TE/day	Oral-systemic (capsules)	3 months	Number of MN cells in exfoliated oral mucosal cells and circulating lymphocytes	Decrease in MN observed; Reduction of MN by TOR was more in oral mucosal cells, the decrease in MN in lymphocytes was comparable in all three groups	No data	Hastak *et al.*[19]
83 patients (18-70 years of age) from Karnataka	Lycopene, lycopene + intralesional steroid injections	Group I: 16 mg lycopene/day in 2 doses Group II: 16 mg lycopene/day in 2 doses, and intralesional injections of betamethasone (2 ampoules of 4 mg/ml) two times weekly	Oral systemic (4 mg soft gels)	2 months	MO, TP, burning sensation (VAS), palpation	Improved MO and TP in both groups; Complete relief from burning sensation in both groups posttreatment	No side effects or intolerance	Kumar *et al.*[26]
48 patients (age not specified) from Trivandrum	Curcumin capsule, TO	Group I: 1 g (two capsules twice) daily Group II: 600 mg (12 drops of oil twice) daily	Oral systemic (capsules) Topical (oil to hold in mouth and swallow)	Treatment-3 months follow-up period-6 months	Burning sensation, intolerance to spicy food, MO, TP	Reduction in burning sensation and intolerance to spicy food observed at 3 months of treatment. The mean increase in MO was 0.87 cm in both the groups after the follow-up period. Increase in TP better in Group II. Curcumin produced quicker improvement; TO appeared to have long-term effect	Change of color of oral mucosa (blanched to erythematous) in Group II	Das *et al.*[27]
25 patients (age not specified) from New Delhi	Curcumin	1 g (curcumin [Cur]-900 mg, desmethoxy Cur-80 mg, bisdesmethoxyCur-20 mg)	Oral-systemic (caplets)	211 days	Pain (VAS), lesion size, MO, serum and salivary vitamins C and E; MDA; 8-OhdG	Pain score and size of lesion decreased ($P<0.05$); MO increased (24.64 [3.2]-39.4[3], $P<0.05$). Serum and salivary vitamins C and E increased, while MDA and 8-OhdG decreased	No treatment related toxic effect up to 8 g/day	Rai *et al.*[12]
46 patients (17-57 years of age) from Wardha	Lycopene	Lycopene (8 mg)/day divided in 2 doses	Oral-systemic (8 mg soft gel)	3 months	Presence of oral lesions, burning sensation (VAS) and intolerance to spice, MO	Improved MO; reduced burning sensation and intolerance to spices, and absence of erythematous areas or ulceration or erosions	No side effect or intolerance to lycopene	Karemore and Motwani (2012)[28]

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Table 3: Contd...

Details of patients	Therapeutic strategy	Dose of therapy	Mode of application of curcumin/lycopene	Duration of therapy	Parameters studied	Brief result	Any adverse reaction	Authors
45 patients (18-49 years of age) from Chennai	Lycopene + intralesional steroids and hyaluronidase	Lycopene 16 mg/day with biweekly intralesional injections of dexamethasone 1.5 ml and hyaluronidase 1500 IU mixed with lignocaine	Oral-systemic (capsules with lycopene 5000 µg, various micronutrients)	6 weeks	Burning sensation on VAS, MO	Significant increase in MO by lycopene+intralesional steroids and hyaluronidase compared to oral antioxidant capsule and/or intralesional steroids and hyaluronidase.	No adverse effect was found	Selvam and Dayanand[29]
30 patients (18-50 years of age) from Lucknow	Curcumin + piperine	Curcumin (900 mg) + piperine (15 mg)/day	Oral-systemic (tablet with curcumin 300 mg and piperine 5 mg)	1 month	MO, burning sensation on VAS	Statistically significant change in burning sensation on VAS; maximum improvement in MO in patients with initial MO <20 mm	No data	Agarwal *et al.*[30]
44 patients (15-60 years of age) from Lucknow, Bhilai	Lycopene, intralesional injection of betamethasone	Group I: 10,000 mcg of Lycopene daily in two equally divided doses Group II: Intralesional injection of betamethasone (4 mg) two times weekly	Oral-systemic-soft gel (lycopene-5000 mcg with vitamin A, C, E, B1, B2, B6, B12, D3, sodium selenite, chromium chloride, zinc sulfate monohydrate, manganese sulfate, folic acid, niacinamide, calcium pantothenate)	Treatment: 2 months; follow up: 4 months	MO, burning sensation on VAS	Better improvement in MO in Group I (37.62%, 12 mm) compared to group II (13%, 3.9 mm); Group I also showed more reduction of burning sensation (94.5%) than group II (54.1%)	No side effects found	Singh *et al.*[31]
41 patients (17-56 years of age) from Varanasi	Turmeric powder + tulsi powder	Turmeric powder (1 g) + tulsi powder (1 g) mixed in glycerine (paste) −4-5 times/day	Oral-topical (paste application to oral mucosa, hold for 15 min)	3 months	Burning sensation (VAS), MO as inter-incisional distance (mm)	Mean burning sensation 6.07±1.75 before treatment; 2.22±1.41 after treatment (t=15.52; P<0.001). Mean MO 24.46±4.0 mm before treatment; 27.85±3.39 mm after treatment (t=9.06; P<0.001)	Out of 41 patients, 3 patients experienced bad taste, mild headache	Srivastava *et al.* (2015)[21]
20 patients (20-40 years of age) from Lucknow	Curcumin + piperine	2 tablets containing *curcuma longa* (300 mg), piperine (5 mg) daily	Oral-systemic (tablets)	12 weeks	Burning sensation (VAS), IID, TP	The mean increase in IID was 1.25 mm; mean increase in TP at the end of the study period was 0.38 mm. Burning sensation improved	No data	Yadav *et al.*[2]
15 patients (18--50 years of age) from Nagpur	Curcumin + physiotherapy exercises by mouth exercise device	2 g of longvida lozenges (containing 400 mg curcumin) daily	Oral-topical (lozenges)	Treatment: 3 months Follow-up: 6 months	Interincisal distance, Burning sensation for normal and spicy food (VAS)	Increase in MO 5.93±2.37 mm. In relation to VAS scale with spicy and normal food the average reduction was 64 (42-73) and 77 (70.5-82)	Yellowish coating over teeth and dorsum of tongue observed in 3 patients	Hazarey *et al.*[22]

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Table 3: Contd...

Details of patients	Therapeutic strategy	Dose of therapy	Mode of application of curcumin/lycopene	Duration of therapy	Parameters studied	Brief result	Any adverse reaction	Authors
120 patients (age not specified) from Chattisgarh	Lycopene, aloe vera	Group I: 8 mg lycopene daily in two divided doses Group II: 5 mg aloe vera gel to be applied topically thrice daily	Oral-systemic (capsule)	3 months	MO, TP, VAS for burning sensation, pain associated with the lesion, and difficulty in swallowing and speech	Clinical improvements in MO and TP were significant in Group I (P<0.001). Subjective symptoms of burning sensation (P=0.007), pain associated with the lesion (P=0.005), and difficulty in swallowing and speech (P=0.003) improved in both the groups but were insignificant. There was a mild to moderate decrease in the size of the lesion	Few patients reported nausea in the early visits	Patil *et al.*[5]
30 patients (>15 years of age) from Raichur	Curcumin, lycopene	Group I: Lycopene 8 mg/day (in 2 doses) Group II: Curcumin 800 mg/day (in 2 doses)	Oral-systemic (capsule with lycopene-2000 mcg, zinc-7.5 mg, selenium-35 mcg); Haridra capsule: *Curcuma longa*-400 mg	3 months	MO; burning sensation (VAS); blanching of buccal mucosa	Group I: Better improvement in MO (6 mm) than Group II (3 mm); better improvement in reduction of fibrous bands. Group II: Better reduction in severity of burning sensation; better reduction of blanching of buccal mucosa	No data	Kopuri *et al.*[23]
60 patients (<30 years of age) from Lucknow	Lycopene, curcumin	Group I: Lycopene 4 mg/day (in 2 doses) Group II: Curcumin 900 mg/day (in 3 doses)	Oral-systemic, lycopene capsule (lycopene-4 mg, Zinc-7.5 mg, selenium-35 mg), curcumin tablet (*Curcuma longa* extract-300 mg, *Piper nigrum* 5 mg)	3 months	MO; burning sensation (VAS)	Complete cessation of burning sensation in both groups; Group I showed better improvement in MO (11.1%) than Group II (6.2%)	No data	Saran *et al.*[20]
40 patients (18-62 years of age) from Kolkata	Lycopene + curcumin + piperine	Curcumin (1 g), lycopene (50 mg), piperine (10 mg)/day in two divided doses	Oral-systemic tablet biocumin: Curcumin (500 mg), piperine (5 mg) and lycopene (25 mg	3 months	Burning sensation on VAS, MO, and TP mucosal flexibility	Complete reduction of burning sensation and significant increase in MO, TP, and mucosal flexibility	No adverse effect is found	Present study
28 patients (21-60 years of age) from Bengaluru	Hyaluronidase and dexamethasone injection	Hyaluronidase 1500 IU mixed in 1.5 ml of dexamethasone and 0.5 ml of lignocaine HCL	Intralesional injection biweekly	4 weeks	Burning sensation and MO, blanching of oral mucosa, presence of vesicles and ulcers, palpable bands, limitation of tongue movement	Improvement in the patient's MO with a net gain of 6±2 mm (92%), the range being 4-8 mm. Definite reduction in burning sensation, painful ulceration and blanching of oral mucosa and patient followed up for an average of 9 months	No data	L James *et al.* (2015)

Contd...

Table 3: Contd...

Details of patients	Therapeutic strategy	Dose of therapy	Mode of application of curcumin/lycopene	Duration of therapy	Parameters studied	Brief result	Any adverse reaction	Authors
29 patients (the mean age of the patients was 39.64±7.2 years)	Pentoxifylline therapy	Initial 400 mg tablet twice a day initial 30 days and then thrice a day for rest 6 months	Oral administration	7 months	MO, TP, fibrotic band	Improvement in MO, TP, and relief from perioral fibrotic bands subjective symptoms of intolerance to spices burning sensation of mouth, tinnitus, difficulty in swallowing and difficulty in speech were also improved significantly	Frequent complaints of dyspepsia, nausea and/or vomiting in <3% of the patients receiving 1200 mg per day in SRT form. Approximately 1% report bloating, flatus, and bleeding	R Rajendran *et al.* (2006)[33]
52 patients (10-55 years of age) from Jabalpur, MP, India	Triamcinolone therapy	Triamcinolone acetate, which was given at biweekly intervals at the dose of 40 mg for a period of 12 weeks	Local injections, on multiple sites in the oral cavity using insulin syringe	12 weeks	Interincisal MO	A highly significant improvement in the interincisal MO is seen following treatment in study group with submucosal injection of triamcinolone	No data	NT Ameer *et al.* (2012)[34]

TO: Turmeric oil; TOR: Turmeric oleoresin; TE: Turmeric extract; MN: Micronucleated; IID: Interincisal distance; TP: Tongue protrusion; VAS: Visual Analog Scale; MO: Mouth opening; MDA: Malondialdehyde; HCL: Hydrochloride; SRT: Sustained release tablet

and check cellular proliferation reduces collagen synthesis rate, conferring its fibrinolytic property. Histopathologically, all the sections, irrespective of Group, revealed reepithelialization, although the degree varied. The appearance of rete pegs was also visible with increase in blood vessels in the connective tissue region. Immunohistochemical analysis revealed decrease in collagen content following therapy. The data showed significant increase in VAS, MF, epithelial thickness, and decrease in collagen bands following therapy.

Thus, curcumin is considered as a safe nontoxic and effective alternative for many conventional drugs, due to its distinguishable therapeutic properties and multifarious effects on different systems of the body. Statistically significant improvement in the clinical sign and symptoms were observed among different group of OSMF patients treated with combination therapy of curcumin. Positive changes were also observed in pre- and post-histopathological evaluation of the therapy. The choice of combination therapy is noninvasive, beneficial, and affordable drug management in all grades of OSMF. Extensive study with a larger number of patients backed by longer periods of follow-up is necessary to arrive at a definitive conclusion. Thus, we reiterate curcumin, in combination with lycopene and piperine, has the potential of being an alternative therapeutic measure for treating all grades of OSMF patients.

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Conflicts of interest

There are no conflicts of interest.

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