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EFFICACY OF CURCUMIN IN ORAL SUBMUCOUS FIBROSIS - A RANDOMIZED CONTROLLED CLINICAL TRIAL

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Keywords:

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ABSTRACT: Introduction: Oral submucous fibrosis (OSMF) is a potentially malignant disorder carrying a high risk of malignant transformation. A wide range of treatment modalities have been proposed for OSMF but none have proved curative or reduced the morbidity significantly. *In-vitro* and *in-vivo* studies suggested curcumin as an anticancer, antioxidant and anti-inflammatory agent. Thus based on this literature survey the study was undertaken. **Aim:** To evaluate the efficacy of curcumin for the treatment of clinical stage 2 OSMF patients and to compare it with patients receiving placebo drugs. **Study Design and Sample Size:** A randomized single blinded placebo controlled clinical trial was conducted in 100 clinical stage 2 OSMF patients with clinically and histopathologically confirmed diagnosis. **Materials and Methods:** 100 clinical stage 2 patients selected for the study were divided into 2 groups with 50 patients each. Group 1 patients were given placebo capsules**.** Group 2 patients were given curcumin capsules of 500 mg. The primary outcome measures were to note the subjective symptoms and objective parameters. These parameters were analyzed at baseline and 6^{th} month. Patients were also evaluated histopathologically after 6 months. ANOVA, students t test and p value were utilized for statistical inferences. **Results:** Patients in group 2 showed statistically significant improvement in all the subjective signs and symptoms and histopathological changes with p value of < 0.001 when compared with group 1 patients. **Conclusion:** It is evident from the study that curcumin holds good promise in the treatment of OSMF.

INTRODUCTION: OSMF was first described by Schwartz in 1952 as a fibrosing condition in five Indian women and in Kenya and he called it as atrophica idiopathica tropica [1].

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Subsequently Joshi in 1953 is credited to have coined the term Oral submucous fibrosis. Epidemiological studies show a unique prevalence of this premalignant condition in India and South East Asia [1]. It has a specific geographic distribution and predominantly affects the Asians [2]. Pindburg has summed up the clinical and histopathological features in his definition for OSMF as "an insidious chronic disease affecting oral mucosa or any part of the oral cavity and occasionally extending into pharynx and Esophagus, although occasionally

preceded by and/or associated with vesicle formation, it is always associated with juxtraepithelial inflammatory reaction followed by fibro elastic change in the lamina propria with epithelial atrophy leading to stiffness of oral mucosa causing trismus and inability to eat [1]. The pathogenesis of the disease is thought to be multifactorial, the exact etiology and pathogenesis is still obscure, with chewing of pan masala/gutka, arecanut being recognized as one of the most significant risk factors for OSMF. It is predominantly seen in the second or third decade, and recent data suggest a male predominance. The onset is insidious and the clinical presentation depends on the stage of the disease [2]. A wide range of treatment modalities have been proposed for OSMF but none have proved curative or reduced the morbidity significantly. Hence, the search for effective treatment modality still continues [1, 3].

The wisdom and scientific credentials of curcumin have been corroborated by numerous studies conducted over the past 30 years [3]. Curcumin (diferuloylmethane), an orange-yellow component of turmeric is a polyphenol natural product isolated from the rhizome of the plant Curcuma longa. Its effects are diverse and appear to involve the regulation of various molecular targets [4]. Thus, due to its efficacy and regulation of multiple targets, as well as its safety for human use, curcumin has received considerable interest as a potential therapeutic agent for the prevention and treatment of various potentially malignant disorders, malignant diseases, and inflammatory illnesses. Only sixteen clinical trials on curcumin are currently listed in the national cancer institute website [4, 5].

Thus based on this thorough literature survey, lack of curative treatment the study was undertaken to evaluate the efficacy of curcumin for treatment of clinical stage 2 OSMF patients and to compare it with patients receiving placebo drugs both clinically and histopathologically.

MATERIALS AND METHODOLOGY:

Study Design: A randomized single blinded placebo controlled clinical trial study was conducted at HKE'S S.N institute of dental sciences and research center, Gulbarga. Informed consent was obtained from all the subjects who were included in the present study. The study was approved by Institutional Ethical Committee, Dental College and Hospital as per Rajiv Gandhi University of Health Sciences, Karnataka, India (ECM/HKES/SNDCH/2012-2013) and was registered under clinicaltrials.gov (NCT03511261).

Study Samples and Sample Size: OSMF patients from the department of oral medicine and radiology from HKE'S S.N institute of dental sciences and research center and Al-Badar rural dental college and hospital were selected by simple random sampling technique. The study sample included a total of 100 clinical stage 2 OSMF patients with clinically and histopathologically confirmed diagnosis.

Inclusion Criteria: 100 clinical stage 2 OSMF patients selected randomly with clinically and histopathologically confirmed diagnosis were divided into 2 groups with 50 patients each.

Exclusion Criteria: Clinical stage 1 and 3 OSMF patients, oromucosal disorders with clinical features same as OSMF, patients who are under treatment, clinically diagnosed cases not ready for incisional biopsy, patients suffering from medically compromised conditions.

Procedure: The study was conducted by strictly adhering to the ethical protocols. Patient's personal history of habits was recorded. Diagnosis of OSMF was done by the criteria given by Bailoor D.N and Nagesh (2005) [6] for presence of burning sensation, blanching of the oral mucosa, restricted mouth opening, restricted tongue protrusion and palpable fibrous bands. Clinical staging of OSMF was done according to Mathurand Jha [7], Bailoor and Nagesh [8]. Clinical stage 2 cases were included in the study. Patients were encouraged for habit cessation and were subjected to oral prophylaxis to motivate them for abstinence. Symptoms like burning sensation, difficulty in mouth opening, difficulty in swallowing, intolerance to spicy food was noted. After 1 month of discontinuation of habits they were selected for commencement of treatment. Routine hematological examination was done for all the patients before subjecting them to incisional biopsy for histopathological examination. The biopsies were obtained from the buccal mucosal region in all the cases, since all the cases exhibited

clinically evident changes in this area and also taking the consideration of accessibility for biopsy procedures. The specimens were preserved in 10% formalin for further laboratory procedures. The tissue sections were made and studied under microscopy after staining with haematoxylin and eosin. The histopathological grading of OSMF was done according to Pindburg and Sirsat [9].

After histopathological diagnosis of OSMF, 100 clinical stage 2 patients selected for the study were divided into 2 groups with 50 patients each. Baseline parameters were recorded. Group 1 patients were given placebo capsules and were instructed to take 2 capsules per day. Group 2 patients were given curcumin capsules of 500 mg and were instructed to take 2 capsules per day making a daily dose of 1 gram.

The primary outcome measures were to note the subjective symptoms like burning sensation, difficulty in mouth opening, intolerance to spicy food and difficulty in swallowing, signs like shrunken uvula, hockey stick appearance of uvula, and objective parameters like blanching, sites of fibrosis, burning sensation, pain, mouth opening, tongue protrusion and cheek flexibility. Patients were explained about visual analog scale (VAS) and were asked to mark the severity of burning sensation (BS) and pain on it. The patients were enquired for the improvement of burning sensation and pain at the subsequent visits and were asked to mark it again on a VAS scale. Burning sensation and pain was then recorded on a percentage reduction basis. The parameters like Interincisal distance (IID), tongue protrusion and cheek flexibility were recorded as mentioned by Ranganathan *et al*., [10]. Interincisal distance (IID) was measured with vernier caliper between the right maxillary and mandibular central incisors on maximum opening. If these teeth were missing, they were measured on the corresponding teeth of the left arches. The measurements at subsequent visits were done at the previously recorded sites only, to avoid misinterpretation. Tongue protrusion was measured with a scale as the distance of movement of the tongue beyond the incisal tips of the lower incisors. Cheek flexibility was measured by a line joining tragus of the ear and angle of the mouth was drawn. An imaginary perpendicular line from the outer canthus of the ipsilateral eye was extended downwards to intersect the ala-tragus line using a protractor at 90º. The point of intersection was marked as a reference point. This was done on both right and left sides. The distance between the two reference points was recorded at normal centric occlusion as C1. The subjects were asked to blow the cheeks fully with lips closed and the distance between the reference points was recorded as C2. The difference between the 2 values (C2-C1) was used as measure of cheek flexibility. Subjective and objective parameters were entered as scores in the proforma. All measurements were taken by the same examiner to avoid observer variability [10.]

Follow up: These parameters were analyzed at baseline and 6th month. Patients were also evaluated histopathologically after 6 months.

Statistical Analysis: The mean scores of 2 groups were statistically tested using ANOVA. The differences in clinical parameters from baseline and 6th month and histopathological parameters from baseline and 6th month were compared between groups 1 and 2 by students't' test. For all tests, a 'p' value of 0.05 or less was utilized for statistical significance.

RESULTS:

Age, Sex and Habits: There were equal numbers of patients in both the groups. The mean age of the patients in group 1 was 25.44 ± 5.43 and group 2 was 25.42 ± 7.38. Female: Male ratio in the study group was 1:13.3.

There were 2(4%) females, 48(96%) males in group 1 and 5(10%) females, 45(90%) males in group 2. Majority of patients were habituated to eat gutka 36(72%) and 28(56%) in group 1 and 2 respectively followed by arecanut 10(20%) and 9(18%) in group 1 and 2 respectively.

Comparison of Signs and Symptoms between Group 1 and Group 2 Subjects from Baseline to 6th Month: There were 47(94%) of patients with difficulty in mouth opening 45(90%) with burning sensation, 14(28%) with intolerance to spicy food, 4(8%) with difficulty in swallowing, 9(18%) with shrunken uvula and 2(4%) with hockey stick appearance of uvula at baseline and even after 6th month in group 1 patients with p value as 1.000 which was statistically not significant.

In group 2 patients there were 46(92%) patients with difficulty in mouth opening 46(92%) with burning sensation, 21(42%) with intolerance to spicy food, 4(8%) with difficulty in swallowing, 14(28%) with shrunken uvula and 5(10%) with hockey stick appearance of uvula at baseline. After 6 months when these signs and symptoms were compared there were 2(4%) of patients with difficulty in mouth opening, 1(2%) of patients with burning sensation, no patients reported intolerance to spicy food and, difficulty in swallowing, there were 9(18%) of patients with shrunken uvula in group1 patients with p value as <0.001 which was statistically significant except for hockey stick appearance of uvula there was no change with p value as 1.000 **Table 1**.

TABLE 1: COMPARISON OF SIGNS AND SYMPTOMS BETWEEN GROUP 1 AND GROUP 2 SUBJECTS FROM BASELINE TO 6th MONTH

Signs & symptoms	Group 1				p value	Signific-ance	Group 2				p value	Signific-ance
	Baseline		6th month				Baseline		6th month			
	n	%		%			n	%	n	%		
Difficulty in mouth opening	47	94.0%	47	94.0%	1.000	NS	46	92.0%	2	4.0%	< 0.001	VHS
Burning sensation	45	90.0%	45	90.0%	1.000	NS	46	92.0%	1	2.0%	< 0.001	VHS
Intolerance to spicy food	14	28.0%	14	28.0%	1.000	NS	21	42.0%	0	0.0%	< 0.001	VHS
Difficulty in swallowing	4	8.0%	4	8.0%	1.000	NS	4	8.0%	0	0.0%	< 0.001	VHS
Shrunken uvula	9	18.0%	9	18.0%	1.000	NS	14	28.0%	9	18.0%	< 0.001	VHS
Hockey stick uvula	2	4.0%	2	4.0%	1.000	NS	5	10.0%	5	10.0%	1.000	NS

n= no. of patients, NS=Non significant, VHS=Very highly significant, S=Significant

Comparison of Objective Parameter like Blanching between Group 1 and Group 2 Subjects from Baseline to 6th Month: There was blanching noted in 50(100%) of patients in buccal mucosa, 39(78%) in labial mucosa, 19(38%) in hard palate, 43(86%) in soft palate, 5(10%) in floor of mouth and 4(8%) in tongue at baseline and even after 6th month in group 1 with p value as 1.000 which was statistically notsignificant. In group 2, 49(98%) of patients had blanching of buccal mucosa, 32(64%) of labial mucosa, 14(28%) of hard palate, 40(80%) of soft palate, 1(2%) of floor of mouth and 4(8%) of tongue at baseline. After 6 months when these patients were evaluated 10(20%) of patients had blanching of buccal mucosa, 1(2%) of labial mucosa, 9(18%) of soft palate, 1(2%) of tongue, there was no blanching of hard palate and floor of mouth with p value as <0.001 which was statistically significant except for floor of mouth and tongue with p value of 0.523 and 0.032 respectively **Table 2**.

TABLE 2: COMPARISON OF OBJECTIVE PARAMETER LIKE BLANCHING BETWEEN GROUP 1 AND GROUP 2 SUBJECTS FROM BASELINE TO 6th MONTH

Blanching	Group 1				p value	Signi-ficance	Group 2				p value	Signi-ficance
	Baseline		6th month				Baseline		6th month			
	n	%	n	%			n	%	n	%		
Buccal mucosa	50	100%	50	100.0%	1.000	NS	49	98.0%	10	20.0%	< 0.001	VHS
Labial mucosa	39	78.0%	39	78.0%	1.000	NS	32	64.0%	1	2.0%	< 0.001	VHS
Hard palate	19	38.0%	19	38.0%	1.000	NS	14	28.0%	0	0.0%	< 0.001	VHS
Soft palate	43	86.0%	43	86.0%	1.000	NS	40	80.0%	9	18.0%	< 0.001	VHS
Floor of mouth	5	10.0%	5	10.0%	1.000	NS	1	2.0%	0	0.0%	0.523	NS
Tongue	4	8.0%	4	8.0%	1.000	NS	4	8.0%	1	2.0%	0.032	NS

Comparison of Objective Parameter like Fibrosis Between Group 1 and Group 2 Subjects from Baseline to 6th Month: 50(100%) of patients had fibrosis of buccal mucosa, 31(62%) of labial mucosa, 39(78%) of retro molar area, 22(44%) of soft palate, 21(42%) of uvula and 9(18%) of tongue at baseline and even after 6th month in group 1with p value as 1.000 which was statistically non-significant. In group 2, 49(98%) of patients had fibrosis of buccal mucosa, 26(52%) of labial mucosa, 41(82%) of retro molar area, 24(48%) of soft palate, 21(42%) of uvula and 23(46%) of tongue at baseline.

After 6 months when these patients were evaluated 31(62%) of patients had fibrosis of buccal mucosa,

19(38%) of retro molar area, 3(6%) of soft palate, 3(13) of uvula and 1(2%) of tongue, there was no fibrosis of labial mucosa with p value as <0.001 which was statistically significant **Table 3**.

TABLE 3: COMPARISON OF OBJECTIVE PARAMETER LIKE FIBROSIS BETWEEN GROUP 1 AND GROUP 2 SUBJECTS FROM BASELINE TO 6th MONTH

Sites of Fibrosis	Group 1				p value	Signific-ance	Group 2				p value	Signific-ance
	Baseline		6th month				Baseline		6th month			
	n	%	n	%			n	%	n	%		
Buccal mucosa	50	100.0%	50	100.0%	1.000	NS	49	98.0%	31	62.0%	< 0.001	VHS
Labial mucosa	31	62.0%	31	62.0%	1.000	NS	26	52.0%	0	0.0%	< 0.001	VHS
Retromolar area	39	78.0%	39	78.0%	1.000	NS	41	82.0%	19	38.0%	< 0.001	VHS
Soft Palate	22	44.0%	22	44.0%	1.000	NS	24	48.0%	3	6.0%	< 0.001	VHS

Comparison of Objective Parameters like Burning Sensation, Pain, Interincisal Distance, Tongue Protrusion and Cheek Flexibility between Group 1 and Group 2 Subjects from Baseline to 6th Month: In group 1 patients the mean value of burning sensation was 7.76 ± 2.75 at baseline. There was increase in burning sensation with mean value of 8.32 ± 0.239 after 6th month with p value of 0.239. In group 2 patients the mean value of burning sensation was 6.26 ± 3.5 at baseline. There was statistically significant reduction in burning sensation with mean value of 0.02 ± 0.14 after 6th month with p value of <0.001.

In group 1 patients the mean value of pain was 4.22 ± 4.23 at baseline with a similar mean value after 6th month with p value of 0.984. In group 2 patients the mean value of pain was 3.16 ± 4.23 at baseline. There was statistically significant complete reduction of pain after 6th month with p value of <0.001.

Mean value of IID in group 1 patients at baseline was 24.42 ± 3.30 mm and 23.54 ± 2.79 mm after 6th month with p value of 0.754. There was 0.88 ± 0.51 mm decrease in IID. In group 2 patients mean value of IID at baseline was 23.42 ± 3.64 mm and 32.66 ± 3.4 mm after 6th month which was statistically significant with p value of <0.001. There was mean increase of 10.47 mm in IID.

Mean value of tongue protrusion in group 1 patients at baseline was 15.06 ± 4.85 mm with a similar mean value after 6th month with p value of 0.992. In group 2 patients mean value of tongue protrusion at baseline was 15.66 ± 5.08 mm and 25.26 ± 4.96 mm after 6th month which was statistically significant with p value of <0.001. There was mean increase of 9.6 mm tongue protrusion.

Mean value of cheek flexibility in group 1 patients at baseline was 7.34 ± 2.99 mm with a similar mean value after 6th month with p value of 0.999. In group 2 patients mean value of cheek flexibility at baseline was 6.80 ± 2.85 mm and 14.84 ± 1.97 mm after 6th month which was statistically significant with p value of <0.001. There was mean increase of 8.04mm cheek flexibility **Table 4**.

TABLE 4: COMPARISON OF OBJECTIVE PARAMETERS LIKE BURNING SENSATION, PAIN, INTER INCISAL DISTANCE, TONGUE PROTRUSION & CHEEK FLEXIBILITY BETWEEN GROUP 1 AND GROUP 2 SUBJECTS FROM BASELINE TO 6th MONTH

Objective parameters	Group 1				p value	Signi-ficance	Group 2				p value	Signi-ficance
	Baseline		6th month				Baseline		6th month			
	Mean	S D	Mean	S D			Mean	S D	Mean	S D		
Burning sensation	7.76	2.57	8.32	1.93	0.239	NS	6.26	3.25	0.02	0.14	< 0.001	VHS
Pain	4.22	4.23	4.22	4.23	0.984	NS	3.16	4.23	0.00	0.00	< 0.001	VHS
IID	24.42	3.30	23.54	2.79	0.754	NS	23.42	3.64	32.66	3.41	< 0.001	VHS
Tongue protrusion	15.06	4.85	15.06	4.85	0.992	NS	15.66	5.08	25.26	4.96	< 0.001	VHS
Cheek flexibility	7.34	2.99	7.34	2.99	0.999	NS	6.80	2.85	14.84	1.97	< 0.001	VHS

Comparison of Clinical Staging between Baseline to 6th Month: All the cases in group 1 were in clinical stage 2 at baseline and even after 6th month with p value of 1.000 In group 2 there was a statistically significant change in the clinical staging between Baseline to 6th month with p value of <0.001 **Table 5**.

TABLE 5: COMPARISON OF CLINICAL STAGING BETWEEN BASELINE TO 6th MONTH

Clinical staging	Pre treatment (base line)				p value	Signi ficance	Post treatment (6 month)				p value	Signi-ficance
	Group 1		Group 2				Group 1		Group 2			
	n	%	n	%			n	%	n	%		
Stage I	0	0	0	0			0	0	43	86		
Stage II	50	100	50	100	1.000	NS	47	94	7	14	<	VHS
Stage III	0	0	0	0			3	6	0	0	0.001	
Total	50	100	50	100			50	100	50	100		

Comparison of Histopathological Grading between Base Line to 6th month: All the cases in group 1 showed same histopathological grading at baseline and even after 6th month with p value of 1.000. There was improvement in histopathological parameters which was statistically significant when comparison was done between Base line and 6th month in group 2 patients with p value of <0.001 **Table 6**.

TABLE 6: COMPARISON OF HISTOPATHOLOGICAL GRADING BETWEEN BASE LINE AND TO 6th MONTH

Histopathological grading	Pre treatment (base line)				p value	Signi ficance	Post treatment (6 month)				p value	Signi-ficance
	Group 1		Group 2				Group 1		Group 2			
	n	%	n	%			n	%	n	%		
Grade I	4	8	9	18			4	8	19	38		
Grade II	34	68	25	50	0.057		34	68	28	56	<	VHS
Grade III	5	10	13	60		NS	5	10	3	6	0.001	
Grade IV	7	14	3	12			7	14	0	25		
Total	50	100	50	100			50	100	50	100		

DISCUSSION: The mean age of the patients in group 1 was 25.44 ± 5.43 and group 2 was 25.42 ± 7.38. Thus most of our patients were in the second and third decades of life. Our study shows a male predominance. This male predominance in our study could be due to the arecanut and gutka chewing habit which is practiced by younger individuals in this part of the country.

It was noted that the majority of subjects in the study chewed only gutka. Gutka is a mixture of arecanut, tobacco, lime, catechu and flavouring compounds which are marketed in small sachets or pouches. The habit-forming process of gutka chewers is due to tobacco and areca nut, which if consumed for longer duration and frequencies is responsible for causing addiction, leading to OSMF [11]. Hence we presume that gutka and arecanut plays an important role in the etiology of OSMF.

Patients in group 2 (curcumin group) showed statistically significant improvement in all the signs and symptoms like difficulty in mouth opening, burning sensation, intolerance to spicy food, difficulty in swallowing and shrunken uvula when compared with group 1 patients (placebo group) where patients had similar signs and symptoms at baseline and 6th month.

Statistically significant improvement in blanching was noted in buccal mucosa, labial mucosa, hard and soft palate in group 2 patients. There was improvement of blanching in floor of the mouth and tongue also but was not statistically significant. When comparison was done with group 1 patients there was no improvement and all patients showed similar findings at baseline and 6th month. Our study showed similar results with the study of Das *et al.*, [1] which showed change in color of the oral mucosa from blanched to erythematous. This improvement in blanching could be due to the increase in vascularity brought about by the curcumin regimen [1]. Other authors have not considered blanching in their outcome measure. Statistically significant improvement in fibrosis was noted in buccal mucosa, labial mucosa, retro molar area, soft palate, uvula and tongue in group 2 patients. When comparison was done with group 1 patients there was no improvement and all patients showed similar findings at baseline and 6th month.

Visual analog scale (VAS) was used to record severity of burning sensation (BS) and pain. The patients were enquired for the improvement of burning sensation and pain at the subsequent visits and were asked to mark it again on a VAS scale. Burning sensation and pain was then recorded on a percentage reduction basis. There was complete reduction of burning sensation and pain in group 2 patients which was statistically significant when compared to group 1 patients where all the patients

had persistent pain and mean score of burning sensation increased from 7.76 ± 2.57 at baseline to 8.32 ± 1.93 after 6th month.

Statistically significant reduction of burning sensation was also observed in different studies. With inter-group comparison in Kopuri *et al*., [12] study patients under curcumin group showed a better reduction in severity of burning sensation but did not differ enough to be statistically significant (*P*>0.05), where as in Das *et al*., [1] study statistically significant quicker reduction of burning sensation was noted. Agarwal *et al*., [13] study showed the change in burning sensation on VAS was statistically significant (*P*<0.001). Hazarey *et al*., [14] study reported 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. Yadav *et al*., [15] reported that burning sensation improved in turmix group at the end of 1st month mean values of 63.5, to 0 at the end of 3rd month. Complete resolution of burning sensation was noted with turmix. Reduction in burning sensation with turmix was statistically significant when compared with conventional therapy (P<0.001).

Pindburg and Sirsat have defined OSMF as juxtraepithelial inflammatory reaction followed by fibro elastic change of lamina propria. So inflammation is definitely a component of OSMF. The amelioration of signs and symptoms could be attributed to the anti-inflammatory property of curcumin [1]. Curcumin offers anti-inflammatory effect through inhibition of NF-kB activation [16, 17, 18]. Curcumin blocks the IK-mediated phosphorylation and degradation of IBα, thus, NF-kB remains bound to IkBα in the cytoplasm and is not able to enter the nucleus to activate transcription [19]. Curcumin modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2 (COX-2), lipo-oxygenase, and inhibits the production of the inflammatory cytokines, tumor necrosis factor-alpha (TNF-alpha), interleukin 1, 2, 6, 8, and 12, monocyte chemo attractant protein(MCP), and migration inhibitory protein [15, 17, 20]. Curcumin has been described as a dual inhibitor of arachidonic acid metabolism, as it inhibits both cyclooxygenase and lipooxygenase pathways of inflammation, thus inhibiting the products of inflammation such as prostaglandins and leukotriens [1, 21]. Curcumin inhibits lipid peroxidation using linoleate, a polyunsaturated fatty acid that is able to oxidize and form a free fatty acid radical. Curcumin acts as a chain breaking radical and causes neutralization of lipid radicals. In addition to inhibiting lipid peroxidation, curcumin demonstrates free radical-scavenging activity.

It has been shown to scavenge various reactive oxygen species produced by macrophages (including superoxide anions, hydrogen peroxide and nitrite radicals). Inducible nitric oxide synthase (iNOS) is an enzyme found in macrophages that generates large amounts of NO to provide the 'oxidative burst' necessary for defense against pathogens. iNOS is induced in response to an oxidative environment, and the NO generated can react with superoxide radicals to form perioxynitrite, which is highly toxic to cells. It has been shown that curcumin down regulates the iNOS activity in macrophages, thus reducing the amount of reactive oxygen species (ROS) generated in response to oxidative stress [16, 21, 22, 23].

Rai *et al*., [24] has demonstrated the scavenging effect of curcumin on superoxide radicals, hydroxyl radicals and lipid peroxidation. So the effect brought about by the curcumin could be a synergism of their anti-inflammatory and antioxidant properties. This anti-inflammatory and antioxidant activity of curcumin would have been responsible for statistically significant reduction of burning sensation and pain in our patients. In addition, the antioxidant or free-radical scavenging activity of curcumin also contributes to its anti-inflammatory properties by decreasing the amount of oxidative stress that can trigger the inflammatory cascade [21]

There was statistically significant increase of IID, tongue protrusion and cheek flexibility in group 2 patients. There was mean increase of 10.47 mm in IID, 9.6 mm of tongue protrusion. 8.04 mm of cheek flexibility. When compared with group 1 patients IID decreased by 0.56 mm, tongue protrusion and cheek flexibility parameters were similar at baseline and 6th month. Similar results were observed in studies done by Rai B *et al*., [24], Das AD *et al*., [1], Agarwal *et al*., [13], Yadav *et al*., [15], Hazarey *et al*., [14]. Rai B *et al*., [24] in their study

reported that in patients with submucous fibrosis, mouth opening recovered significantly (P<0.05) after 6 months of treatment. Das *et al*., [1] in their study reported statistically significant and equal increase in the mouth opening of patients in Groups I (curcumin capsules) and II (turmeric oil) after 1 month and 3 months of treatment and also after the follow-up period. The mean increase was 0.87 cm in both the groups which was significant when compared with the other groups. Agarwal *et al*., [13] in their study mentioned the overall improvement in mouth opening as 0.68 mm was not statistically significant (P=0.109) this could be because of the shorter duration of treatment for 3 months.

In Yadav *et al*., [15] study the mean increase in IID was 3.13 mm and 1.25 mm respectively in groups 1 and 2. Tongue protrusion showed greater recovery at the end of 1st month in group 1 when compared with group 2 (P=0.004). Mean increase in TP at the end of the study period was noted to be 2.56 mm and 0.38 mm in group 1 and 2 respectively. Hazarey *et al*., [14] in their study reported 5.93 (±2.37) mm increase in mouth opening for test group compared to 2.66 (±1.76) mm of the control group. Myofibroblasts, typically considered to be activated fibroblasts, play an important role in morphogenesis, oncogenesis, inflammation, wound healing and fibrosis in most organs and tissues (Watsky *et al*., 2010). Myofibroblast persistence is a key feature of fibrotic diseases including OSF, scleroderma, and hepatic, pancreatic, and pulmonary fibrosis (Gabbiani, 2003; Angadi *et al*., 2011).

Myofibroblasts can be detected in the OSF-affected tissues; this phenomenon is related to the severity of OSF (Angadi *et al*., 2011). Myofibroblasts not only synthesize collagen, but also produce numerous inflammatory mediators, chemokines, and growth factors (Powell *et al*., 1999), intensifying and prolonging the inflammation in OSF by activating the inflammatory corpuscles. This self-excitation of inflammation increases the expression of fibrogenic cytokines such as TGF-β1, and enhances fibrosis. The possibility of inhibiting proliferation and inducing apoptosis in myo-fibroblasts offers a new, promising therapy line in the treatment of OSF [25]. It has been reported in a study that curcumin inhibits cell proliferation in fibroblasts and myofibroblasts.

MTT assay revealed that curcumin treatment significantly decreases the proliferation of fibroblasts and myofibroblasts, in a dose-dependent manner. This effect is more pronounced in myofibroblasts; the growth inhibitory rate for myofibroblasts incubated with curcumin was double of that for the similarly treated fibroblasts. Curcumin induces cell cycle arrest in myofibroblasts. Cell cycle analysis shows that curcumin treatment results in a dose-dependent increase in the proportion of myofibroblast cells in G0/G1 phase. Curcumin induces cell apoptosis in myofibroblasts. It has been suggested that mitochondria play a role in curcumin-induced apoptosis [25].

The increase in mouth opening and tongue protrusion and cheek flexibility could be a result of anti-inflammatory and antioxidant and fibrinolytic properties of curcumin. Curcumin has been reported to possess fibrinolytic action in liver and lung fibrosis in studies conducted by kuttan *et al*., Li *et al*., has attributed the fibrinolytic action of curcumin to its three properties namely inhibition of lipid peroxidation, checking cellular proliferation and inhibition of collagen synthesis [1]. This same action of curcumin would also be responsible for the statistically significant reduction of palpable fibrous bands which in turn improves mouth opening, tongue protrusion and cheek flexibility.

In group 2 there was a statistically significant change in the clinical staging between Baseline to 6th month with p value of <0.001 when compared with group 1 where all the patients were in stage 2 at baseline and even after 6th month. This was because of overall improvement in all the subjective and objective parameters in group 2 patients. There was improvement in histo-pathological parameters in all the patients which was statistically significant when comparison was done between Pretreatment (Base line) and Post treatment (6th month) follow up. Post treatment (after 6 months) histopathological changes such as hyperplasia of epithelium and reduction in inflammatory cells was observed. These findings correlate with clinical reduction in burning sensation, pain and intolerance to spicy foods.

A marked reduction in hyalinization of connective tissue along with reduction in inflammatory cells would have improved the extent of mouth opening, tongue protrusion and cheek flexibility. These findings support the anti-inflammatory and fibrinolytic actions of curcumin. Increase in number of blood vessels (prominent vascular component) presented with significant improvement in color of oral mucosa from blanched to erythematous. These post treatment histopathological findings were also similar to the study done by Das *et al*., [1]. Other studies have not taken histopathology as their secondary outcome measure. All the patients in the study tolerated the treatment regimens well. None of the patients reported any allergic or abnormal reaction nor did elicit any signs and symptoms of toxicity to the treatment modality. The CDRI and various studies have reported curcumin to be nontoxic [1].

It is of interest to note that none of the patients presented with malignant transformation. Krishnaswamy reported that curcumin inhibits carcinogenesis by polycyclic aromatic hydrocarbons and hence a prospective chemo preventive agent against oral cancer. Earlier studies have reported that curcumin to be a potent antioxidant and coupled with their ant initiating and detoxifying effects, they have proven to be effective in the chemoprevention of cancer. Along with the inhibition of arachidonic acid metabolism, they also inhibit superoxide generation, thus prevent tumor promotion. Kerry bone has stated that curcumin alters the metabolism carcinogens in liver and increases the activity of detoxifying enzyme glutathione-e-transferase, thus preventing oncogenesis [1].

More recently curcumin has been found to possess anti-cancer activities *via* its effect on a variety of biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumourigenesis and metastasis. In various studies, anti tumor-promoting effects of curcumin were studied and proved. In these studies it was proved that curcumin showed antitumor-promoting effects due to the induction of apoptosis. Investigations have shown specific inhibitory effect of cyclooxygenase. In addition, curcumin affects a variety of growth factor receptors and cell adhesion molecules involved in tumor growth, angiogenesis and metastasis [26].

Curcumin also affects both the Phase I and Phase II enzymes of the hepatic cytochrome p450 enzyme system involved in the oxidation and detoxification of toxic substances. Curcumin has been shown to inhibit the Phase I enzymes (including cytochrome p450 isoforms and p450 reductase) which are induced in response to toxin exposure and create a host of carcinogenic metabolites that contribute to DNA adduct formation during the oxidation of such substances. Conversely, curcumin induces the Phase II enzymes involved in detoxification of toxic metabolites including glutathione S-transferase, glutathione peroxidase and glutathione reductase [21].

CONCLUSION: The mean age of the patients in group 1 was 25.44 ± 5.43 and group 2 was 25.42 ± 7.38. Female: Male ratio in the study group was 1:13.3. Majority of patients were habituated to eat gutka 36(72%) and 28(56%) in group 1 and 2 respectively followed by arecanut 10(20%) and 9(18%) in group 1 and 2 respectively.

Comparison of subjective symptoms like burning sensation, difficulty in mouth opening, intolerance to spicy food, difficulty in swallowing, signs like shrunken uvula, hockey stick appearance of uvula and objective parameters like blanching, sites of fibrosis, burning sensation, pain, IID, tongue protrusion and cheek flexibility was done between group 1 and Group 2 patients from baseline to 6th month showed statistically significant changes in group 2 (curcumin) with $p<0.001$.

All the patients in the study tolerated the treatment regimens well. None of the patients reported any allergic or abnormal reaction nor did elicit any signs and symptoms of toxicity to the treatment modality. It is evident from the study that curcumin holds good promise in the treatment of OSMF.

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