

Turmeric in the management of oral submucous fibrosis – A systematic review and meta-analysis

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ABSTRACT

Objectives: Oral submucous fibrosis (OSMF), a premalignant condition, is frequently occur in the buccal mucosa and is associated with betel nut chewing. Various treatment modalities are tested to treat this condition. An effective intervention is needed, which is cost effective, safe, and efficient, considering the disease burden in high incident countries. Turmeric has promising results in the management of OSMF because of its potent anti-inflammatory and anti-oxidant pharmacological actions. The objectives of the study were to analyze the efficacy of turmeric in managing OSMF based on the available literature.

Methods: The articles were searched from Medline/PubMed and Journal of web, which were published from 2000 to 2019 and reviewed for the determined outcomes.

Results: The review showed a positive response for turmeric usage in managing OSMF, in terms of improved mouth opening and decreased burning sensation.

Conclusion: Multicenter studies in high incidence countries with long-term follow-up are recommended to better understand the curative aspect of curcumin in OSMF.

Keywords: Curcumin, mouth opening, oral submucous fibrosis, premalignant condition, turmeric

Introduction

Oral Submucous fibrosis (OSMF), a premalignant oral condition, was first described by Schwartz (1952)^[1] which frequently affects the buccal mucosa. Clinical features of this disease include restricted mouth opening, burning sensation, tongue protrusion, and decreased cheek flexibility. Limited mouth opening further leads to restricted food consumption, oral hygiene maintenance issues, and also speech impairment. The disease has a multifactorial pathogenesis, ranging from areca nut chewing, chilli ingestion, genetic and immunologic processes, and nutritional deficiencies.^[2] It is widely prevalent in South Asian countries^[3] and has a malignant transformation rate of 5–15 %.^[4,5]

The increasing trend of consuming areca nut with tobacco has greatly increased OSMF frequency.^[6]

Various medical interventional therapies are reported in literature ranging from nutritional supplements, antioxidants, immunomodulators, biogenic stimulators, enzymes, fibrinolytic agents, and vasodilators in systemic, topical, and intralesional forms.^[7] Advanced lesions are treated surgically. The penultimate goal of treatment must be to maintain oral functioning and to stop the progression towards malignant

transformation. Considering the fact that the disease is widely prevalent in socio-economically backward strata, a cost-effective treatment modality must be designed.

Various herbs are used in medicine due to their anti-oxidant effect, of which polyphenols are the most common. Curcumin is a polyphenol compound extracted from the plant *Curcuma longa*, usually seen in South Asia, occurring as a yellow pigment. It possesses various therapeutic and medicinal effects such as anti-inflammatory, anti-oxidant, and anti-cancer properties.^[8-11]

Curcumin has been used by many researchers to treat OSMF as a non-invasive adjunct to conventional therapy. This review was hence done to assess the bioefficacy of turmeric in the management of OSMF.

Methods

Literature search was carried out using search engines such as PubMed, Scopus, and Journal on web databases. All relevant articles published only in the English language were searched for by the authors. The search terms used by the authors were: “OSMF” OR “turmeric” OR “management” OR “curcumin.” No limitation on the year of publication was set. In addition,

search strategies such as hand search of reference lists and contacting the authors when the full text was not available were also employed. To remove duplicates for the same type of article in more than one database, the endnote software was used.

Inclusion and exclusion criteria

Only papers which were a primary study conducted on patients affected with OSMF and treated with turmeric were included in the study. Unpublished conference proceedings and state of the art reports were excluded as they could not be easily accessed.

Data extraction

All the titles and the extracts were independently screened by the reviewer. The full texts of those articles considered to be eligible were acquired which was subsequently screened for their eligibility. Data extraction included variables such as author, year of study, intervention and control group information, duration, sample size, and outcome.

Quality assessment

The selected articles were reviewed for the quality as per the quality assessment tool designed by Effective Public Health Practice Project^[12] consisting of six components such as selection bias, study design, confounders, blinding, data collection method, withdrawal, and dropouts. A rating of weak, moderate, and strong criterion was set for each component.

Outcome assessed

The primary outcome of burning sensation, mouth opening, cheek flexibility, and tongue protrusion was assessed.

Data synthesis

For the meta-analysis, only burning sensation and mouth opening were evaluated. Effect size estimates were done as per Gene Glass's formula.

Results

Database and hand searches of the reference list yielded 276 articles. The study of abstracts excluded 174 studies. The review finally was done on nine articles after excluding 51 as they assessed different outcomes were letter to editor or review articles [Chart 1]. The characteristics of these articles are presented in Table 1.

This review included nine articles, all of which were randomized, parallel design controlled trial used both for systematic review and meta-analysis. All studies included participants of both genders.

All the studies were single-center studies conducted in a hospital or institutional setup. The criteria of including patients were those who were clinically diagnosed, with only one study confirming the diagnosis histopathologically.^[20] Stratification of the study subjects was done in only one study^[20] based on the range of mouth opening in affected patients.

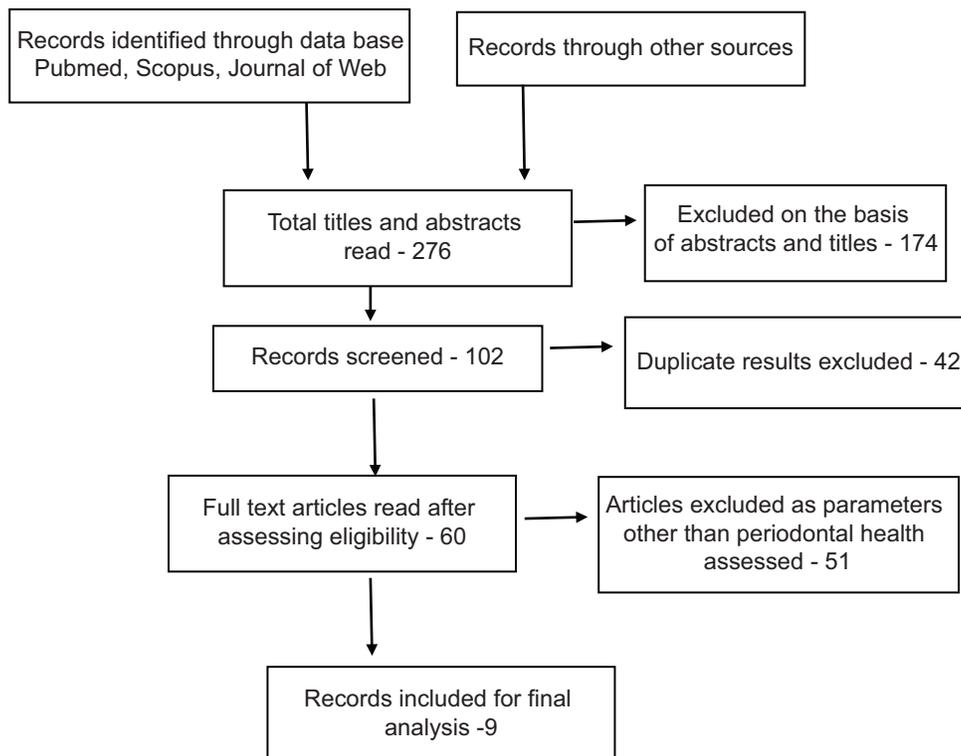


Chart 1: Flowchart depicting data extraction for systematic review

Table 1: Characteristics of studies assessed

Authors, study year	Sample size	Study duration	Groups	Side effects	Loss to follow-up	Results
Shah <i>et al.</i> , ^[13] 2018	120 patient	8 weeks	Group I – Curcumin Tablets (350 mg) Group II – Group III – Group IV –	None		Mean difference in tongue protrusion was highest in Curcumin capsule and Curcumin oil with 0.3 mm each followed by Curcumin tablets with 0.2 mm and controls with 0.1 mm
Srivastava <i>et al.</i> , ^[14] 2015	41	3 months	A single group treated with 1 g tulsi and 1 g turmeric mixed in glycerine base	None	4 patients	Mean mouth opening improved significantly at $P<0.001$ at the end of the study. (24.46+4.0 mm vs. 27.85+3.39 mm)
Aich <i>et al.</i> , ^[15] 2019	40	60 days	A single group intervened with 10 ml of turmeric, Triphala, and honey mouth wash	None	No dropouts	Mean mouth opening increased significantly at the end of trial at $P<0.001$ (25.22+7.17 mm vs. 28.58+6.95 mm)
Virani <i>et al.</i> , ^[16] 2018	30	3 months	Group using Tulsi and turmeric gel in carbopol base	None	None	No significant difference in mean mouth opening at the end of the study (23.00+6.29 vs. 23.66+6.45 mm)
Saran <i>et al.</i> , ^[17] 2018	60	3 months	Group A: 4 mg of lycopene Group B: 300 mg of curcumin capsules	None	None	Mean mouth opening difference in lycopene administered patients was slightly greater than curcumin group (0.35+0.01 vs. 0.20+0.01 mm)
Hazarey <i>et al.</i> , ^[18] 2015	30	9 months	Test group – curcumin lozenges Control group – Tenovate ointment	3 subjects reported yellowish staining on teeth	None	Test group exhibited 5.93+2.37 mm increase in mouth opening compared to 2.66+1.76 mm in control group
Sharma <i>et al.</i> , ^[19] 2017	42	30 days	A test group-administered tablet turmix mixed with honey	None	3 subjects	A significant decrease in VAS scale was noted (6.31+1.12 vs. 2.37+0.95)
Agarwal <i>et al.</i> , ^[20] 2014	30	30 days	A single group divided into 4 categories based on mouth opening; all administered curcumin tablets. Group A – 35 mm Group B – between 30 and 35 mm Group C – 20–30 mm Group D – <20 mm	None	None	An increase in mouth opening of 4.1%, 1.52%, 0.77%, and 5.16% was seen in Group A, B, C, and D, respectively
Piyush <i>et al.</i> , ^[21] 2018	90 patients	90 days	Group A – Curcumin 300 mg tablets Group B – Lycopene tablets Group C – placebo capsules	None	None	Curcumin exhibited an improvement of 3.9+4.9 mm for mean mouth opening in curcumin group while it was 4.1+4.2 mm for lycopene group

A study done by Hazarey *et al.*^[18] employed physiotherapy by mouth exercise device. None of studies had a separate group to test the effectiveness of habit control alone. Outcomes evaluated by the studies were mouth opening and burning sensation in all studies. Tongue protrusion and cheek flexibility parameters were assessed in the study of Hazarey *et al.*^[18] Other subjective outcomes such as altered taste sensation, dryness of mouth, and difficulty in chewing or swallowing were not assessed due to the lack of a validated index.

Quality assessment of the included studies is presented in Table 2. All studies were assessed for risk of selection bias, bias in study design, confounding, blinding, data collection, and withdrawal risk. Overall, all studies had strong quality. The confounder bias was ticked high in studies of Srivastava *et al.*,^[14] Aich *et al.*,^[15] and Virani *et al.*^[16] as their tested formulation of turmeric was used in combination. Srivastava

et al.^[14] used a paste made out of tulsi and turmeric, Aich *et al.*^[15] used mouthwash in the combination of Triphala, turmeric, and honey while Virani *et al.*^[16] used capsules of turmeric and tulsi together.

Meta-analysis

The overall weighted mean effect size was 0.32 and the meta-analytic r was 0.336 [Table 3].

Discussion

OSMF, a premalignant condition of oral cavity was first described by Schwartz in 1952 as “An insidious chronic disease characterized by the deposition of fibrous tissue in the submucosal layer of pharynx, palate, fauces, cheeks, and esophagus and in the underlying muscles of mastication.”^[22]

Table 2: Quality of risk assessment

Study	Overall quality assessment	Selection bias	Study design	Confounders	Blinding	Data collection	Withdrawal and drop out
Shah <i>et al.</i> ^[13]	+	++	+	+++	+	+	+
Srivastava <i>et al.</i> ^[14]	+	+	+	+++	+	+	+
Aich <i>et al.</i> ^[15]	+	+	+	+++	+	+	+
Virani <i>et al.</i> ^[16]	+	+	+	+++	+	+	+
Saran <i>et al.</i> ^[17]	+	+	+	+	+	+	+
Hazarey <i>et al.</i> ^[18]	+	+	+	+	+	+	+
Mamata Sharma <i>et al.</i> ^[19]	+	+	+	+++	+	+	+
Piyush <i>et al.</i> ^[21]	+	+	+	+	+	+	+

*Low: +, Moderate: ++, High: +++

Table 3: Meta-analysis of selected articles

Author	Intervention mean	Control mean	Duration	N	R	EsZr	W	W ² ES
Shah <i>et al.</i>	4.2+0.6	3.9+0.6	8 weeks	120	-0.5	-0.54	117	-63.18
Srivastava <i>et al.</i>	27.85+3.39	24.46+4.0	90 days	41	-0.84	-1.22	38	-46.36
Aich <i>et al.</i>	28.58+6.95	25.22+7.17	60 days	40	-0.46	-0.04	37	-1.48
Virani <i>et al.</i>	23.66+6.45	23.00 + 6.29		30	-0.1	-0.1	27	-2.7
Saran <i>et al.</i>	3.52+0.080	3.52+0.007	90 days	60	0	0	57	0
Hazarey <i>et al.</i>	26.53+4.85	24.16+3.25	9 months	30	-0.72	-0.9	27	-24.3
Sharma <i>et al.</i>	2.37+0.95	2.31+1.123	30 days	30	0.19	0.19	27	5.7
Piyush <i>et al.</i>	29.35+8.8	28.57+7.2	9 months	120	-0.1	-0.1	117	-11.7
Total							447	144.52
								Weighted mean ES
								0.32
								SE mean ES
								0.044
Meta-analytic r								0.3316

The pathogenesis of this chronic debilitating disease is not established confirmatively. A strong association of betel quid habit with OSMF is documented.^[23]

The treatment strategy for OSMF varies on the degree of clinical involvement. If identified at an early stage, cessation of habit will suffice. Medical intervention is predominantly symptomatic, focussing on enhancing mouth opening and tongue movements. Medicinal therapy aims at anti-fibrotic, anti-inflammatory, and antioxygen radical mechanisms. Surgical therapy will be required if trismus ensues. The fact to be noted is that healing is possible with all available treatments only when accompanied by primary prevention (cessation of habit).^[24]

All the studies included were parallel design randomized controlled trial. Five studies had only one group enrolled. The baseline scores of the test group served as the control group. The remaining studies used lycopene as a positive control.

Subjective outcome of burning sensation was evaluated using the Visual analog score employed consistently in all studies. The cultural differences in pain perception and tolerance must be considered and the existing validated instruments must be

modified according to the population chosen. Mouth opening as measured by inter incisal mouth opening is both reliable and reproducible as the objective measure of OSMF.^[25]

Of the nine articles reviewed, six studies proved the efficacy of curcumin in treating OSMF. One study found a significant difference. Two studies reported lycopene to have a slight edge over curcumin in improving mouth opening. Three subjects in the study of Hazarey *et al.*^[18] complained of yellowish stains on the teeth which were removed by prophylaxis. Dietary history was not elicited in any of the studies. Only nine articles fulfilled the eligibility criteria for review and eight for analysis, highlighting the lacunae for scientific evidence of curcumin in managing OSMF.

The weighted mean effect size was 0.32 demonstrating a small effect size, suggesting a trivial difference between groups' means.

Curcumin has been studied by various researchers for its anti-inflammatory action. It lowers inflammation by reducing histamine levels and, in turn, increasing natural cortisone production by adrenal glands. The mechanism of action by which curcumin exhibits anti-inflammatory effect is by

accentuating the inflammatory response of tumor necrosis factor- α motivated human endothelial cells by interfering with nuclear factor (NF)- κ B. Furthermore, it can prevent the platelet-derived growth factor (PDGF).^[26,27]

It exhibits antioxidant properties by scavenging superoxide radicals, hydrogen peroxide, and nitric oxide from activated macrophages, reducing iron complex and inhibiting lipid peroxidation. It can scavenge several reactive oxygen species produced by macrophages (including superoxide anions, hydrogen peroxide, and nitrite radicals) both *in vitro* as well as *in vivo*.^[28]

NF- κ B and signal transducer and activator of transcription 3 (STAT 3) have a key role in anticarcinogenic mechanism of action of curcumin. (NF)- κ B, a ubiquitous transcription factor, controls several genes involved in growth regulation, inflammation, and apoptosis. Literature evidence has shown that constitutive activation of (NF)- κ B leads to suppression of chemotherapy-induced apoptosis in cancer affected cells.

STAT3, a member of the STAT family of transcription factors, gets activated by tyrosine phosphorylation through upstream receptors such as epidermal growth factor, PDGF, and cytokines, such as interleukin-6. STAT 3 is a major mediator of carcinogenesis and its implication is by their effects on parameters such as apoptosis, cell proliferation, angiogenesis, and immune system evasion. Hence, the principal mechanism of anticarcinogenic activity of curcumin is by apoptosis induction and suppression of cellular signaling pathways.^[29]

Studies designed with long-term follow-up of patients are important to assess relapse or the premalignant condition transforming to malignant lesions.

Conclusion

The review results proved to be inconclusive, though curcumin was promising in treating OSMF effectively. Clinical trials designed with long-term follow-up and larger sample size is recommended to substantiate the effectiveness of curcumin after the trial.

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