

RESEARCH ARTICLE

Efficacy of curcumin gel and tulsi gel in oral submucous fibrosis

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ABSTRACT

Background: Oral submucous fibrosis (OSMF) is a chronic condition which has characteristics of inflammation and fibrosis in the oral cavity which is progressive in nature. Steroids are the standard treatment of OSMF, but considering their side effect profile, we thought of taking herbal preparations as these have minimal side effects. **Aims and Objectives:** This study aims to compare the efficacy of curcumin and tulsi gels in OSMF. **Materials and Methods:** This is a prospective, randomized study conducted in ENT OPD on 60 patients who were diagnosed on the basis of clinical criteria of OSMF. Patients were divided into two groups, one group was given tulsi gel and other group curcumin gel and each group was given topical steroids along with the test drugs. Follow-up was done for 6 weeks and patients were assessed on the basis of improvement in interincisal distance, burning sensation, and tongue protrusion at 2, 4, and 6 weeks. **Results:** There was an improvement in all the three parameters at subsequent visits, but the curcumin gel showed better improvement than tulsi gel in burning sensation after 6 weeks of treatment which was highly statistically significant $P < 0.01$. **Conclusion:** Curcumin gel and tulsi gel are effective in improving OSMF symptoms, but curcumin gel is more efficacious without any side effects. Hence, we can advocate these drugs as adjuvant treatment in addition to the recommended treatment.

KEY WORDS: Curcumin Gel; Tulsi Gel; Burning Sensation; Interincisal Distance; Oral Submucous Fibrosis

INTRODUCTION


Oral submucous fibrosis (OSMF) is a chronic state of the oral cavity characterized by epithelial inflammatory reaction and progressive fibrosis of the submucosal tissues.^[1,2] As the disease progresses, the jaw becomes rigid and the person is unable to open the mouth. "Atrophica idiopathica" was the term coined by Schwartz in 1952. Later, in 1953, Joshi coined the term OSMF.^[3]

OSMF classification according to Pindborg staging is the most widely accepted clinical criteria.

It is classified as follows:

- Stage 1: Stomatitis includes erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation, and mucosal petechia.
- Stage 2: Fibrosis occurs in ruptured vesicles and ulcers when they heal, which is the hallmark of this stage.
- Stage 3: Sequelae of OSMF are as follows: Leukoplakia is found in >25% of individuals with OSMF. Speech and hearing deficits due to the involvement of the tongue and the eustachian tubes.

OSMF is predominant in males between 20 and 40 years of age.^[4] Various etiological agents are chewing of areca nut, chilies, iron deficiency, Vitamin B deficiency, autoimmunity, genetic, and other environmental factors. The use of areca nut is thought to be the most important causative factor. Areca nut consists of alkaloids such as arecaidine, arecoline, and guvacoline apart from flavonoids, tannins, catechin, and

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copper. The alkaloids stimulate the fibroblasts to produce more collagen.^[5,6]

The early features of OSMF include burning sensation, xerostomia, and mucosal blanching with a characteristic marble-like appearance. Late features of OSMF include restricted tongue movements, swallowing difficulty, defects in speech and hearing, and also defective gustatory sensation.

Treatment of OSMF

Glucocorticoids are the first line of drugs used in the treatment of OSMF in the form of topical ointments (triamcinolone acetate) or intralesional injections (triamcinolone acetate and dexamethasone), due to their anti-inflammatory properties. They inhibit inflammatory factors' production and also accelerate the programmed cell death of inflammatory cells.^[7,8]

Other available treatment options are lycopene, curcumin, tulsi, hyaluronidase, aloe vera gel, and spirulina.

The treatment of OSMF is still a debatable issue with no proven available cure and there is still a gap in our knowledge to fully understand its pathophysiology. There is also sparsity of safer therapeutic options available for the management of OSMF, and the natural products have high safety profile as compared to the steroids which have many side effects. Hence, we have chosen the herbal modalities, i.e., curcumin and tulsi as our test drugs.

Turmeric (common name for *Curcuma longa*) is an Indian spice derived from the rhizomes of the plant and is used in Ayurvedic medicine to treat inflammatory conditions.

The primary active constituent of turmeric is "diferuloylmethane" which had been identified in 1910. Since then, it is widely used.

The medicinal activity of curcumin had been attributed to its various pharmacological activities including the antioxidant, antimicrobial, proapoptotic, and anti-inflammatory effects.^[9]

Tulsi (*Ocimum sanctum* Linn.) plant has many medicinal values. Tulsi is used in ayurvedic medicine as various immunity and metabolic functions enhancing formulations. It also reduces inflammation by causing their enzyme inhibition. The credit of the medicinal value of tulsi has been given to its antioxidant and anti-inflammatory properties.^[10]

Taking into account the anti-inflammatory and also antioxidant properties of tulsi and curcumin, we have tried to explore the beneficial effects of these herbal remedies in OSMF.

The objective of this study is to compare the efficacy of curcumin and tulsi gels in OSMF.

MATERIALS AND METHODS

Study Design

It is a prospective, randomized study which was carried out in our hospital over a period of 6 months in the Department of ENT. The study was conducted after obtaining informed consent from all the participants and institutional ethical committee clearance approval no: ELMC/R Cell/EC/2018/110. Patient selection was based on Pindborg staging of the classification of OSMF.

New patients of OSMF in conformity with Pindborg staging and old patients of OSMF who have left treatment 6 weeks before were included in the study. Patients with chronic diseases such as TB, DM, AIDS, and any other oral mucosal lesions along with OSMF, pregnant patients, and lactating mothers were excluded from the study.

Triamcinolone gel and Curcumin gel were procured from Abbott Pharmaceuticals and Tulsi gel from MAQS Herbs, Haridwar, (Uttarakhand).

Study Groups

Patients of OSMF who satisfied the inclusion criteria were registered in the study.

Patients were divided into two groups by randomization using computer software.

- Group 1 - Patients were given 5 mg of curcumin gel and 5 mg triamcinolone acetate gel, each for local application twice a day.
- Group 2 - Patients were given 5 mg of tulsi gel and 5 mg triamcinolone acetate gel, each for local application twice a day.

The patients were explained how to apply the ointments and were cautioned not to swallow them.

Efficacy endpoint

Patients were assessed at 0, 2, 4, and 6 weeks for the following parameters.

Burning sensation

Patients were explained how to note their burning sensation on the visual analog scale.

Interincisal distance (IID)

IID was measured with the help of Vernier calipers as the distance between upper and lower jaw central incisors on maximum opening of mouth.

Tongue protrusion (TP)

TP was measured with the help of Vernier calipers as the distance of movement of the tongue beyond the incisal tips of the lower incisors.

Statistical Analysis

Statistical analysis was done by GraphPad Prism version 6.

IID and TP were compared using Student’s *t*-test and burning sensation was assessed using Mann–Whitney *U*-test.

P < 0.05 which was considered statistically significant and *P* < 0.01 which was considered highly statistically significant.

RESULTS

this study was done for the duration of 6 months on 60 patients who met the inclusion and exclusion criteria and were not lost to follow ups. They were given triamcinolone gel as standard treatment in addition to tulsi and curcumin gels in their respective groups. The burning sensation, TP, and IID were measured at baseline, 2nd, 4th, and 6th weeks. No side effects were reported with any of the drugs given during the course of the treatment [Figure 1].

In this study, the mean age of patients was almost similar in the two groups being 40.4 years for tulsi group and 37.4 years in the curcumin group. The male population predominated in both groups. Majority of the population was found to be from the rural area [Table 1].

Table 1: Demographic profile

Age distribution	Tulsi	Curcumin	
Mean age±SD (years)	40.4±10.03	37.4±10.2	
Gender distribution	Tulsi	Curcumin	Total
Males	22	22	44
Females	8	8	16
Locality	Tulsi	Curcumin	Total
Rural	17	19	36
Urban	13	11	24

Table 2: Comparison of improvement in IID

Iid	Tulsi	Curcumin	Unpaired <i>t</i> -test
Visits	Mean±SD	Mean±SD	<i>P</i> -value
Day 0	24.9±5.03	23.9±5.18	0.436
2 weeks	26.4±4.95	26.1±4.42	0.784
4 weeks	27.3±4.52	27.4±4.07	0.881
6 weeks	28.2±4.43	28.9±3.58*	0.503
ANOVA	F=2.62	F=7.23	
	<i>P</i> -value=0.0634	<i>P</i> -value=0.0002*	

**P*<0.01 highly significant, IID: Interincisal distance

There was clinical improvement in IID with both tulsi and curcumin at subsequent visits. On doing intergroup comparison by unpaired *t*-test comparing tulsi with curcumin, the results showed that there was no statistically significant difference in the IID at 0, 2, 4, and 6 weeks in both the groups, thus showing that both groups are comparable to each other in terms of IID. On doing intragroup comparison, there was increment in IID with tulsi which was not significant, but there is increment in IID with curcumin which was significant [Table 2].

On comparing the tulsi group with curcumin group by Mann–Whitney *U*-test, they were comparable in terms of improvement in burning sensation at the 2nd and 4th weeks. The curcumin group showed better improvement in burning sensation after 6 weeks of treatment which was highly statistically significant [Table 3].

There was clinical improvement in TP with both tulsi and curcumin at subsequent visits. On doing intergroup comparison by unpaired *t*-test comparing tulsi with curcumin, the results showed that there was no statistically significant difference in the TP at 0, 2, 4, and 6 weeks, thereby showing the groups are comparable to each other in terms of TP. On doing intragroup comparison, there was improvement in TP with tulsi and curcumin which was significant [Table 4].

DISCUSSION

OSMF is a precancerous condition that is usually associated with chewing of areca nut. Till date, there is no ideal treatment available for OSMF. The important advantages claimed for

Table 3: Comparison of improvement in BS

BS	Tulsi	Curcumin	Mann–Whitney <i>U</i> -test
Visits	Mean±SD	Mean±SD	<i>P</i> -value
Day 0	5.4±1.33	5.8±1.54	0.121
2 weeks	3.97±1.13	3.8±1.45	0.853
4 weeks	3.37±1.1	2.8±1.1	0.083
6 weeks	2.9±0.923	2±1.08	0.0009*

**P*<0.01 highly significant when compared to day 0, BS: Burning sensation

Table 4: Comparison of improvement in TP

TP	Tulsi	Curcumin	Unpaired <i>t</i> -test
Visits	Mean±SD	Mean±SD	<i>P</i> -value
Day 0	23.9±4.93	23.1±5.36	0.549
2 weeks	25.6±4.78	25.6±4.77	0.9785
4 weeks	26.3±4.6	26.9±4.15	0.639
6 weeks	27.4±4.8*	27.8±3.63 [#]	0.717
ANOVA	F=2.95	F=6.24	
	<i>P</i> -value=0.0355*	<i>P</i> -value=0.0006 [#]	

**P*<0.05 significant compared to day 0, [#]*P*<0.01 highly significant compared to day 0, TP: Tongue protrusion

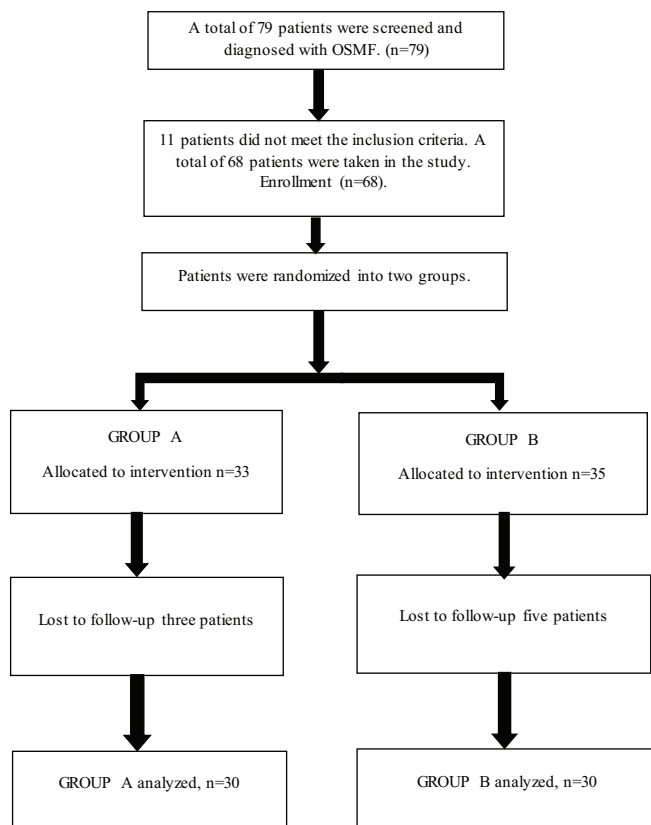


Figure 1: The flow diagram of the study participants

the therapeutic use of herbal plants in various ailments are their safety profile and easy availability.^[11] Therefore, in this study, we have evaluated the role of curcumin and tulsi gel in correcting the symptoms of the disease. In clinical practice, there are a number of treatments for OSMF. Often, combination strategies are used.

Patients that were included in the study had almost similar baseline demographic profiles between the groups. Both tulsi and curcumin showed better clinical results in IID, and the difference between the two groups was not found to be statistically significant, hence, showing that both the groups gave comparable results. On doing intragroup comparison, there was significant improvement in IID in curcumin group.

On comparing burning sensation in tulsi with curcumin, they were comparable at the 2nd and 4th weeks. The curcumin group showed better results in burning sensation after 6 weeks of treatment which was found to be statistically highly significant. Both tulsi and curcumin showed clinical improvement in TP, but the results were not statistically significant when evaluated using unpaired *t*-test. On doing intragroup comparison, there is improvement in TP with tulsi and curcumin which was significant.

Agarwal *et al.*, in 2011,^[12] evaluated the therapeutic potential of turmeric in the management of OSMF, and the results showed that curcumin is effective in improving the symptoms of OSMF by decreasing the burning sensation

and improvement in mouth opening. The results of our study were in concordance with this study. Other studies conducted by Singh *et al.*, 2017,^[13] and Yadav *et al.*, 2014,^[14] showed similar results.

Srivastava *et al.*^[15] have seen the role of tulsi and turmeric in the management of OSMF, and the results demonstrated that turmeric and tulsi produced statistically significant improvement in mouth opening and burning sensation, and it was also associated with less side effects. Similar results of the potential of tulsi in OSMF by improving burning sensation and TP were also observed in a study conducted by Madhulatha *et al.*, 2017.^[16]

In the present study, curcumin and tulsi showed improvement in IID and TP and a significant reduction in burning sensation which is in concordance with the above studies.

Therefore, the difference in the parameters observed among the groups at the last of the study may be considered as direct effect of the respective treatment given to them.

OSMF is associated with increase in the release and production of inflammatory mediators and the possible mechanisms contributing to this are increased fibrosis through alteration in collagen metabolism.^[17]

Arecoline is a component of areca nut which when get exposed to the buccal mucosal fibroblast results in the accumulation of collagen. Reduced collagenase activity and increased cross-linking of the fibers result in decreased degeneration of collagen. This suggests that OSMF may be considered a collagen-metabolic disorder resulting from chewing of areca nut.^[17]

Curcumin is a natural product, non-toxic and is extremely safe even at higher doses. Curcumin supplementation in OSMF patients shows positive result due to its anti-inflammatory potential. Curcumin modulates the inflammatory response by inhibiting the tumor necrosis factor-alpha (TNF-alpha), inflammatory cytokines, interleukin 1, 2, 6, 8, and 12, and migration inhibitory protein and works by downregulating lipoxygenase, cyclooxygenase, and inducible nitric oxide synthase enzymes.^[18]

In our study, the forwarded mechanism of the action of curcumin is by inhibiting the release of inflammatory mediators.

Akram *et al.*^[19] in their study evaluated the efficacy of curcumin and proposed the mechanism of action of curcumin as above. The study by Lawande^[20] showed similar mechanism of action which is in concordance with the present study.

Tulsi is a natural product, non-toxic and is extremely safe even at higher doses. It is rich in antioxidant and renowned for its salutary powers, it has several benefits, it helps in relieving stress, reinforce immunity, intensify stamina, and boost healthy metabolism and works as a natural immunomodulator.^[21] Some of the main chemical constituents of tulsi are oleanolic acid, rosmarinic acid, ursolic acid, carvacrol, eugenol, β -caryophyllene linalool, β -elemene, and germacrene D.^[22]

The proposed mechanism of the action of tulsi in OSMF is anti-inflammatory action which inhibits enzymes such as calcitonin gene-related peptide and substance *P* which contribute to pain, and it also has antioxidant, antistress, and analgesic action. Madhulatha *et al.* had proposed that tulsi has ursolic acid and a pentacyclic triterpene acid. It acts by inhibiting NF-kb activation that is induced by various carcinogens including TNF. It obstructs degeneration and phosphorylation of Ikba, p65 nuclear translocation, and NF-k β -dependent receptor gene expression.^[23-25] Tulsi contains polyphenol rosmarinic acid which acts as a powerful antioxidant. This attribute of tulsi is implemented in treating conditions like OSMF.

Srivastava *et al.* also proposed similar action. Tulsi is effective in reducing burning sensation and improving mouth opening in OSMF which is in concordance to the present study.

Thus, all of the above studies reinforce the fact that in near future, there will be availability of a promising herbal treatment for OSMF with minimal or no side effects.

The limitations of this study are the small population size and need of longer duration of the therapy, so as to understand its course along with the therapeutic changes.

CONCLUSION

The present study reveals that both the test drugs are effective in reducing the symptoms of OSMF, but curcumin was found to be more effective in the reduction of the symptoms, more effectively the burning sensation. Curcumin and tulsi are considered safe, non-toxic, and effective alternatives for many conventional drugs due to their varied therapeutic properties and multiple effects on various systems of the body. As this was a short-term study, further research is needed with a larger sample size over long term to achieve more definite results.

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