



Research Article

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EVALUATION OF EFFICACY OF HERBAL PREPARATION IN THE MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS: A STUDY

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ABSTRACT

Oral submucous fibrosis is a chronic debilitating disease and a well-recognized potentially premalignant condition of the oral cavity, various medical and surgical modalities have been used but results are not satisfactory owing to recurrence, adverse effects and some worsening condition. Our study comprised of 30 patients attending the department of Oral and Maxillofacial surgery, King George's Medical University, Lucknow, India. It was open-label randomized clinical trial 30 patients of clinically diagnosed cases of oral submucous fibrosis. The herbal preparation was made and given to the patients for oral rinse and gargle for 3-5 minutes twice a day for 4 months. Clinical evaluation was done every 15 days. Pre and post-interventional evaluation of biochemical parameters, serum antioxidant, Malondialdehyde, Superoxide dismutase and Glutathione peroxidase were done. There was a marked improvement in clinical as well as biochemical parameters. The herbal preparation is effective in reducing burning sensation, intolerance to spicy food, pain in mouth opening, bringing change in the colour of mucosa from white to red, reduction of blackening of oral mucosa.

Keywords: Burning sensation, *Sphaeranthus indicus*, mouth opening, *Ocimum sanctum*, oral sub-mucous fibrosis, Tulsi, honey

INTRODUCTION

Oral submucous fibrosis is an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx. Oral submucous fibrosis (OSMF) has also been previously described as idiopathic scleroderma of mouth, idiopathic palatal fibrosis, sclerosing stomatitis and juxta-epithelial fibrosis¹. The hallmark of the disease is submucosal fibrosis that affects most parts of the oral cavity, progressive trismus of cheeks, pharynx and upper third of the oesophagus leading to dysphagia².

The disease is mainly seen in Asian countries and the prevalence is more in India. Schwartz (1952)³ first reported OSMF while examining five Indian women from Kenya, which he called as "*Atrophica idiopathica (tropica) mucosae oris*". Joshi (1953)⁴ from Mumbai re-designated the condition as OSMF, implying predominantly its histological nature⁴. Paymaster (1956)⁵ first reported its precancerous potential. Rao (1962)^{5,6} suggested that OSMF is a localized condition of collagen disease.

The chief differential diagnosis of OSMF is oral manifestations of scleroderma, a connective tissue disorder in which there is fibrosis of the skin, blood vessels and visceral organs.

The etiopathogenesis of oral submucous fibrosis is mainly due to chewing areca nut in different forms. One of the chemical released from areca nut chewing is alkaloids, causes constant irritation and subsequent inflammatory response along with an increase in collagen production and a decrease in collagen degradation which leads to the formation of insoluble cross linked collagen fibres leading to fibrosis, which is difficult to degrade.

The clinicians and researchers have been baffled with nature of the disease. It is posing a serious problem to our population due to its potential of transforming into malignancy, leading to dysphasia and restricted mouth opening, which in turn results into serious consequences like poor oral hygiene, loosening of teeth, foul odour and many more systemic diseases. With the advent of newer drugs, more understanding of its etiopathogenesis, screening and awareness programmes by the Governments, the disease has been controlled up to some extent but it still needs augmentation of social awareness, public screening, early

diagnosis and tobacco cessation clinics and programmes. Management is within the habit control and management of local symptoms. Moreover, the high recurrence rate of the disease demands multiple modalities of treatment which becomes a major challenge for an oral physician/oral surgeon.

This warrants the need for a single alternative therapy, the treatment outcome of which is comparable to that of the existing modalities of treatment for the disease. Herbal medicines are of great significance in improving the local environment and modulating the disease.

The condition was first described in ancient Indian Manuscripts by Sushruta in Sushruta Samhita describing it as “VEDARI” where he describes patients suffering from narrowing of mouth, burning sensation and pain. As the disease OSMF cannot exactly be equated with any Mukharoga in *Ayurvedic* classics, it can be considered as Anukta Vyadhi (unexplained disease) and can be managed according to methodology given by Acharya Charaka.

On-going through the *Ayurveda* texts as well as recent studies, numerous description of herbs like *Tulsi* (*Ocimum sanctum* Linn) and *Curcuma longa* (Turmeric) can be found which is effective in treating this condition. Various studies have also demonstrated the wound healing properties of honey in treating OSMF with significant improvement in burning sensation and mouth opening⁷.

Our present study includes a preparation which combines the properties of *Tulsi* (*Ocimum sanctum* Linn) and honey with the addition of *Gorakhmundi* (*Sphaeranthus indicus* Linn), a common flowering plant found in the terrains of India which has been in use in *Ayurvedic* medicine since time immemorial for various local and systemic disorders.

In current years many researchers have elicited and worked upon, the existing aetiology/pathophysiology concerned to OSMF. Until date, no efficient treatment is accessible for this progressively disabling condition with elevated malignant potential. Management of OSMF thus postulates major challenge for an oral physician/oral surgeon. Various types of treatment modalities include conservative methods, medical management and invasive methods like surgical elimination of the fibrotic bands and combined therapy.

On looking at the *Ayurvedic* classics, some scattered description of symptoms related to OSMF such as Krichchen Vivrinoti Mukham (difficulty in opening the mouth), Mukhadaha, Ushna (burning sensation in mouth), (Tikshna Asaha) (intolerance to spicy food), Mukhashosha (dryness of mouth), Arasagyata, Alparasagyata, or Virasagyata (defective gustatory sensation), Mukhantargata Vrana (ulceration of the oral mucosa) and Vranavastu, Durudha Vrana (fibrosis) can be found.

Hence, analysing this condition, OSMF can be considered as Vata Pitta dominant Tridoshaja chronic Sarvasara Mukharoga (disease involving the entire oral cavity) and it needs to be addressed at local as well as systemic level.

Gorakhmundi (*Sphaeranthus indicus*) reduces vatadosha (vatadosha nashaka), *Tulsi* (*Ocimum sanctum*) is tridosha nashaka (vata, pitta, kapha) and honey is also considered tridosha nashaka and hence, they are used in this study to effectively treat this condition.

Gorakhmundi

Gorakhmundi is also known as: Mundi and quote; in Hindi, it is a flowering plant of the genus *Sphaeranthus*. In Sanskrit, it is recognized by many names like “Tapaswini”, “Mahamundi Aruna”, “Nilak Dambika”, etc⁸. Scientifically *Gorakhmundi* is called as *Sphaeranthus indicus* Linn. and in English, it is known as and quote; East Indian globe thistle and quote; *Gorakhmundi* is an aromatic herb that is found throughout India, but in Southern India, it is found in abundant. According to *Ayurveda*, all parts through the plant have medicinal properties. They are used in vitiated conditions of jaundice, hemicranias, cough, leucoderma, hepatopathy, hernia, gastropathy, urinary discharges, indigestion, helminthiasis, asthma, looseness of the breasts, dysentery, haemorrhoids, spleen diseases, pain over the uterus and vagina, pain in the rectum, vomiting, skin diseases and dyspepsia. The external application *Gorakhmundi* plant pastes are used in treating oedema, pruritus, filariasis, arthritis and gout and cervical adenopathy⁹.

Tulsi

Tulsi enhances immunity and improves metabolic functions. Their extract has been found to reduce inflammation by inhibiting enzymes. It also lowers the stress and has antioxidant properties. *Tulsi* is rich in antioxidants and renowned for its restorative powers, it has several benefits: relieves stress/adaptogen, bolsters immunity, enhances stamina and promotes healthy metabolism and a natural immunomodulator. Some of the main chemical constituents of *Tulsi* are: oleanolic acid, ursolic acid, rosmarinic acid, eugenol, carvacrol, linalool, β caryophyllene (about 8%), β -elemene (c.11.0%) and germacrene D (about 2%).¹⁰ The proposed mechanism of action of this medicament in OSMF is anti-inflammatory, antioxidant, anti-stress, analgesics and others¹¹.

Honey

Bee’s honey is one of the most cherished natural substances known to mankind. Honey known as “Madhu” in *Ayurvedic* scriptures is one of the most important medicines used in *Ayurveda*. In *Ayurveda*, honey is used for both internal and external applications. According to *Ayurveda*, there are eight different types of honey-Pouttika, Bhamara, Kshoudra, Makshika, Chatra, Arghya, Oudalaka, Dala¹². Topical application of honey can be used for the management of radiation-induced oral mucositis and chemotherapy induced oral stomatitis⁷.

The antioxidants that occur naturally in honey are flavonoids, phenolic acids, enzymes (e.g., glucose oxidase, catalase), ascorbic acid, carotenoid-like substances, organic acids, Maillard reaction products, amino acids and proteins.

Aims and objectives

- To evaluate the role of a herbal preparation (*Gorakhmundi*, *Tulsi* and Honey) in the early stages (Grade I and Grade II) of oral submucous fibrosis and its consequent improvement in trismus and mouth opening and reduction in burning sensation.
- To assess the changes in the levels of serum IL-6 and serum antioxidants after administration of the herbal preparation both topically and systemically

MATERIAL AND METHODS

The study comprised of minimum 30 patients having OSMF aged from 16 and up to 60 years attending the OPD of Department of Oral and Maxillofacial Surgery, Faculty of Dental Sciences, King George's Medical University, Lucknow.

The patients were enrolled in the study irrespective of sex, caste and creed. An informed consent was taken from the patient. It was an open-label randomized clinical trial comprising of holistic

Ayurvedic approach in which 30 patients of OSMF would be chosen for the treatment. Ethical clearance was obtained from the Ethical Approval Committee, Research Cell, King George's Medical University and Lucknow.

A solution of *Gorakmundi ark* (*Sphaeranthus indicus*) and *Tulsi ark* (*Ocimum sanctum*) and honey (30 ml, twice a day) was used for oral rinse and gargle for 3-5 minutes daily for 3 months and followed for 1 month. Ingredients of the solution and their proportions:

Name of Drug	Botanical/English name	Proportions
Gorakmundi	<i>Sphaeranthus indicus</i>	1
Tulsi	<i>Ocimum sanctum</i>	1
Madhu	Honey	2

Inclusion criteria

- Age group between 16 and 60 years
- The patients having clinical signs and symptoms of OSMF

Exclusion criteria

- Disease was most advanced with premalignant and malignant changes
- Generalized fibromatosis
- Oral manifestation of scleroderma
- Pale oral mucosa of anaemia mimicking blanching
- Chronic debilitating conditions such as DM, HT, HIV etc.
- Patients not willing to give up addiction habits of Gutkha, Pan-masala, tobacco, etc.
- If the patient was hypersensitive to any of the ingredients.

Criteria for assessment

A thesis form was filled up in the beginning

Subjective

All the signs and symptoms were given scoring depending on their severity.

Signs and Symptoms

Burning Sensation in mouth (Mukhadaha)

	Score
• Nil	0
• On taking spicy food	1
• On taking food	2
• Continuous	3

Intolerance to Spicy Food: Present/Absent

Pain in Mouth Opening: In VAS scale

Colour of Mucosa: Pink, redness, white, blackening

Consistency: Soft/Leathery/Hard

Objective

IID SCORING parameter was adopted to assess improvement in the opening of mouth and is measured by taking the distance between mesial angles of upper and lower central incisors with vernier callipers.

Fibrous Bands

- Labial mucosa: Present / Absent
- Buccal mucosa: Present/Absent
- Retromolar region: Present/Absent

	Interincisal distance (mm)	Score
1	41 or above considering normal	0
2	37-40	1
3	33-36	2
4	29-32	3
5	25-28	4
7	21-24	5
8	17-20	6
9	13-16	7
10	09-12	8
11	05-08	9
12	0-04	10

Pre and Post-interventional evaluation of biochemical parameters

- Serum levels of antioxidants
- MDA (Malondialdehyde) SOD (Superoxide dismutase),
- Glutathione peroxidase
- Beta carotene and vitamin A, Vitamin E, Serum IL-6

Statistical analysis

The results were analysed using descriptive statistics and making comparisons between pre and post observations. Discrete (categorical) data were summarized as in proportions and percentages (%) and Mean \pm SD (standard deviation).

The following statistics were calculated in the present analysis Mean and standard deviation (SD). The sample mean is the average and is computed as the sum of all the observed outcomes from the sample divided by the total number of events. We use \bar{x} as the symbol for the sample mean. In math terms, where 'n' are the sample size and the x correspond to the observed valued.

We define the variance to be and the standard deviation to be:

The Chi Square Test: This test is used to find association between categorical variables.

Paired t-test: Paired Sample T-Test

The paired sample t-test, sometimes called the dependent sample t-test, is a statistical procedure used to determine whether the mean difference between two sets of observations is zero. In a paired sample t-test, each subject or entity is measured twice, resulting in pairs of observations. The formula of paired t test is:

Where numerator of right side denotes mean of paired differences and denominator denotes the standard error.

Test of significance

P-value < 0.05 was considered to be significant.

RESULT

Before therapy among the 12 (40.0%) cases the burning sensation was continuous, 10 (33.3%) cases had burning sensation on taking food and 8 (26.7%) subjects had burning sensation on taking spicy food. After the treatment (post therapy) only one case (6.7%) found burning sensation on taking food and one case of continuous burning sensation. Among the 15 (55.6%) cases the burning sensation completely eliminated. So a highly significant treatment effect in removal of burning sensation was found among the study cases (chi sq = 31.8, $p < 0.001$)

Before therapy among the 28 (93.3%) cases the intolerance to spicy food was present. After the treatment (post therapy) the intolerance to spicy food was present in only 9 (30.0%) cases. So a highly significant treatment effect in removal of the intolerance to spicy food was found among the study cases (chi sq = 25.45, $p < 0.001$).

Before therapy among all the 30 (100%) cases the pain in mouth was present with VAS score 1. After the treatment (post therapy) the pain in mouth was present in only 16 (53.3%) cases. So a highly significant treatment effect in pain in mouth opening was found among the study cases (chi sq = 16.89, $p < 0.001$). Before therapy among the 11 (16.7%) cases the colour of mucosa was seen whitish and in remaining 19 (83.3%) cases the colour was seen red. After the treatment (post therapy) the whitish colour was seen in 7 (16.7%) cases and red in 23 (83.3%) cases. No significant treatment effect in change of the colour of mucosa was found among the study cases (chi sq = 1.27, $p = 0.260$). Before therapy among the 4 (13.3%) cases blackening was present. After the treatment (post therapy) blackening was not present in any case. A significant treatment effect in controlling of blackening was found among the study cases (chi sq = 4.286, $p = 0.038$)

Before therapy among the 22 (73.3%) cases the consistency was seen to be leathery and in remaining 8 (26.7%) cases the consistency was seen to be soft. After the treatment (post therapy) the leathery consistency was seen in only 9 (30.0%) cases and in remaining 21 (70.0%) cases the consistency was seen to be soft. A highly significant treatment effect in change of the consistency

was found among the study cases (chi sq = 11.28, $p < 0.001$). Before therapy among the 12 (40.0%) cases the ulceration was present and in remaining 18 (60.0%) cases the ulceration was absent. After the treatment (post therapy) ulceration was remarkably reduced and found in only one (3.3%) cases. A highly significant treatment effect in reduction of the ulceration was found among the study cases (chi sq = 11.88, $p < 0.001$). Before, therapy among the 17 (56.7%) cases the fibrous bands in labial mucosa was present and in remaining 13 (43.3%) cases the fibrous bands were absent. After the treatment (post therapy) the fibrous bands in labial mucosa were found in 13 (44.8%) cases. However, no significant treatment effect in change of proportion of fibrous bands in labial mucosa was found among the study cases (chi sq = 0.827, $p = 0.363$). Before, therapy among the 29 (96.7%) cases the fibrous bands in buccal mucosa was present and in remaining one (3.3%) case the fibrous band was absent. After the treatment (post therapy) the fibrous bands in buccal mucosa were found in 11 (36.7%) cases. Highly significant treatment effect in change of proportion of fibrous bands in the buccal mucosae was found among the study cases (chi sq = 24.3, $p < 0.001$)

Before therapy among the 19 (63.3%) cases the fibrous bands in retromolar region was present and in remaining 11 (36.7%) cases the fibrous bands were absent. After the treatment (post therapy) the same proportion of absence and presence of fibrous bands was seen. No treatment effect in change of proportion of fibrous bands in retromolar region was found (chi sq = 0.000, $p = 1.000$)

DISCUSSION

The considerable reduction in the burning sensation of mouth (Mukhadaha) post therapy in the present study is attributed to the anti-inflammatory property of Tulsi (*Ocimum sanctum*) and *Gorakhmundi* (*Sphaeranthus indicus* Linn). For normal epithelium to mature, enzyme cytochrome oxidase, which contains iron, is required. In iron deficiency, this enzyme level is low and resultant atrophy of epithelium results. This causes burning sensation and ulcerations of the oral cavities in areca nut chewers. Consumption of food becomes unpalatable for the patient with anaemia. A vicious cycle develops.

Sphaeranthus indicus (*Gorakhmundi*) is expected to significantly increase the antioxidant levels in blood. In an *in vitro* study (2006), ethanolic extract of *S. indicus* (1000 μ g/mL) showed maximum scavenging of the radical 2,2-azinobis-(3-ethylbenzothiazoline-6-sulfonate) (ABTS), 1,1-diphenyl, 2-picryl hydrazyl (DPPH), superoxide and nitric oxide radical¹⁵. The extract also showed moderate scavenging activity of iron chelation.¹⁶

So in the study, due to the antioxidant effect and iron chelation by *Sphaeranthus*, there has been a consequent re-epithelisation of mucosa and reduced ulcerations and burning sensation.

According to the Central Drug Research Institute, Lucknow, India, *Tulsi* (*O. sanctum*) can help in maintaining normal levels of the stress hormone – cortisol in the body¹³. It can ward off harmful effects of free radicals. In addition it is loaded with phytonutrients, essential oils, Vitamin A and C. The anti-inflammatory action of *Tulsi*, which has been observed in both acute and chronic inflammatory models in animals, is attributed to *Tulsi*'s eugenol and linoleic acid content and the inhibition of both the cyclooxygenase and the lipoxygenase pathways of arachidonic acid metabolism. This enables *Tulsi* to exert anti-inflammatory effects comparable to non-steroidal anti-inflammatory drugs such as phenylbutazone, ibuprofen, naproxen, aspirin and indomethacin.¹⁷ Some animal studies have

shown that *O. sanctum* also maintains the balance of cortisol hormone in the body. So it can be concluded that this herbal preparation which was used in this study with *Tulsi* as a chief ingredient will decrease burning sensation and fibrotic bands because of the effect of cortisol:

The prime mechanism of action of corticosteroids (cortisol) is immune modulation. It suppresses inflammation and resulting fibrosis and furthermore it up regulates immune mediated fibrolytic pathways.

Many studies have shown that intra lesional steroid therapy due to its anti-inflammatory property is useful in controlling burning sensation.

The results of the study conducted by Srivastav *et al* (2015)¹⁷ showed that the synergistic action of *Tulsi* and turmeric herbs results in higher efficacy and highly potent anti-OSMF treatment. The findings in our study is concordant with the findings of Srivastav *et al.* (2015)¹⁷ although turmeric was not used in our study.

Also the topical effect of Honey debrides wounds rapidly, replacing sloughs with granulation tissue. It also promotes rapid epithelialization and absorption of oedema from around the ulcer margins. So the reduction in burning sensation and ulceration is the combined result of all the three constituents of the herbal preparation used in the study.

According to *Ayurveda*, OSMF is a vata, pitta vyadhi (disease) Since *Gorakhmundi* is pitta, krimirog, kushtha nashaka rasayana (rejuvenating drug), vata nashaka and moreover, a type of volatile oil and an alkaloid named speranthine is released from this plant which is seen to be very beneficial in inflammation, it is used here¹⁴.

A statistically significant improvement in intolerance to spicy food and in general food items post therapy can be described by anti-inflammatory properties of *Sphaeranthus indicus* (*Gorakhmundi*), *Ocimum sanctum* (*Tulsi*) and soothing effect of honey. Honey has long been known to have a soothing action on mucus membranes and recommended for the management of oral mucositis⁷.

Palliation from burning sensation due to decrease in inflammation in significant number of cases in our study can also be attributed to properties of honey as described by V. Singh (2017)⁷. According to *Ayurveda* when pitta dosha increases in the body it leads to burning sensation in the oral cavity and subsequent intolerance to spicy food. *Sphaeranthus* decreases vatadosha, *Tulsi* is tridosha nashaka (vata, pitta, kapha) and honey is tridosha nashaka. There has been a significant reduction in the pain during mouth opening in our study. The chloroform and ethanol extracts of the *Sphaeranthus indicus* (*Gorakhmundi*) has also shown to exhibit potential antipyretic and analgesic activity comparable with that of paracetamol¹⁸. The aqueous extract obtained from the root of *S. indicus* was found to be moderately active in down-regulating *P. acnes* induced TNF- α and IL-8 production¹⁹. So the significant reduction in pain post herbal therapy can be justified again by the soothing effect produced by honey and the analgesic effect of *Gorakhmundi*.

The development of a post-inflammatory pigmentation includes two processes: an increase in melanin production and an abnormal distribution of the pigment. The first one is related to a direct stimulation of melanocytes by inflammatory mediators. The second step of the development of post inflammatory hyper pigmentation is an abnormal distribution of melanin pigment²⁰.

The reduction of blackening of involved mucosa can be solely attributed to the anti-inflammatory action of both *Ocimum* and *Sphaeranthus indicus* as well as the wound healing properties of honey and *Sphaeranthus*. *Sphaeranthus* is known to enhance the rate of wound contraction and the period of epithelialization and this effect was comparable to neomycin²¹

According to *Ayurveda*; Bhrajaka pitta, one of the 5 types of pitta, is responsible for skin colour. Increase in Bhrajaka pitta causes hyper pigmentation and decrease in the same causes hypo pigmentation. *Sphaeranthus indicus* is known to cause balancing this pitta as well as vata²². So, in the present study, *S. indicus* is responsible for the above findings in reduction of blackening of mucosa.

The change in consistency of mucosa after the herbal treatment can be explained by the anti-fibrotic activity, exhibited by *Ocimum sanctum* (*Tulsi*) as it effect cortisol release and balancing of its levels in the body.

In *in-vivo* studies, the glucocorticoid steroids inhibit fibroblast growth and the production of specific cell products such as collagen and mucopolysaccharide²³.

Moreover, *Sphaeranthus* increases blood circulation in local as well as systemic level and hence causes increased healing and rapid epithelization²¹.

Topical application of the herbal preparation used in this study reduces fibrosis in buccal mucosa where it is easily in contact for maximum amount of time. Access to the retromolar bands and thin labial mucosa bands is comparatively lesser and hence no significant change or decrease in fibrosis is seen in these regions in the study. So the anti-fibrotic activity of *Ocimum* has reported in literature is concordant with the findings in our study.

A statistically significant increase in interincisal distance was noted post therapy. A possible explanation to this is the significant reduction of buccal mucosa bands, although more increase in mouth opening would've been seen if retromolar bands had also reduced.

There is no significant change in the overall serum level of IL-6 in the pre and post therapy condition (out of 30 samples). But in some of the cases, IL-6 levels were decreased after administration of the herbal preparation which is indicative of the anti-inflammatory property of the extract. IL-6 levels can also be increased in case of obesity, depression and stress which cannot be ruled out and are considered confounding factors as far as the study is concerned. For further study we need a larger sample size for the significant variation of the levels of IL-6 and its variation. According to Haque MF *et al.* (2000)²⁴ it has been postulated that external stimuli such as areca nut may cause OSMF by increasing the levels of inflammatory cytokines in the lamina propria and also by up regulating their production by the peripheral mononuclear cells. Up regulation of pro inflammatory cytokines i.e. IL-6 and IL-8 has been seen. It may be due to the T-cell activation; which occurs secondary to the chronic inflammation. Also an up regulation of certain fibrogenic cytokines such as TNF- α , TGF- β , platelet-derived growth factor, basic fibroblast growth factors is seen in OSMF. An under expression of anti-fibrotic cytokine interferon-gamma may also contribute to increased fibrosis. The above features are suggestive of an altered immune response in circulating monocytes along with an increase in number of local antigen presenting cells and lymphocytes in OSMF patients. This increases the genetic susceptibility of these patients and thus causes the penetration of arecoline and arecadine into the oral mucosa. The reduction in post therapy

burning sensation scores and reduction in blackening of mucosa strongly suggest considerable decrease in inflammation. Although the serum pro-inflammatory cytokine levels of IL-6 before and after the herbal treatment are comparable and do not suggest a significant decline in the degree of inflammation, the scores are none the less reduced in post therapy phase, if not found statistically significant.

There is no significant change in the overall serum level of IL-6 in the pre and post therapy condition (out of 30 samples). But in some of the cases, IL-6 levels were decreased after administration of the herbal preparation which is indicative of the anti-inflammatory property of the extract. IL-6 levels can also be increased in case of obesity, depression and stress which cannot be ruled out and are considered confounding factors as far as the study is concerned. Moreover, the reduction in inflammation is more appreciable at the local level, as seen clinically, in comparison to its systemic effects as seen from the pre and post treatment serum IL-6 levels. So it can be postulated based on the above findings that the herbal preparation has a better topical effect in contrast to its systemic effect. For further study we need a larger sample size for the significant variation of the levels of IL-6 and its variation.

There is an increase in serum antioxidant level in the post therapy phase in comparison with the pre therapy phase which indicates that the levels were increased to neutralize the reactive oxygen species (ROS). From the above result, it can be concluded that the preparation is effective in increasing the level of antioxidants in the body and consequently at the local site in the oral cavity the levels of which are usually diminished due to OSMF. In an *in vivo* study by Tiwari Bk, Khosa R L (2009)²⁵, methanolic extract of *S. indicus* exhibited a significant antioxidant effect showing increasing levels of superoxide dismutase, catalase, and glutathione peroxides by reducing malondialdehyde levels in rats. Thus it can be postulated that *Sphaeranthus indicus* is the contributory agent to the marginal increase in the levels of serum antioxidants in the cases.

Also, the long term storage of samples (more than one and half year's app.) might have led to inadequate readings in some cases. In future, immediate storage and evaluation will be the goal for more promising results.

The immunomodulatory effect of *Gorakhmundi* (*Sphaeranthus indicus*) used in our study also counteracts the autoimmune basis of the disease.

Van Wyk CW *et al* (1994)²⁶ postulated the presence of HLA A10 and DR3, DR7 antigens in OSMF patients. Also increased auto antibodies directed toward the gastric parietal cells, thyroid gland, antinuclear antibodies and anti-smooth muscle antibodies has been seen in OSMF. Humoral immunity may also play a role as increased circulating immune complexes and increased serum levels of IgG and IgA have been found in OSMF patients. Brandtzaeg P, Tolo K (1977)²⁷ had stated that serum-derived antibodies provide a further basis for an increase in mucosal permeability and accentuate the already existing pathologic condition.

The immunomodulatory activity of *S. indicus* was explored by evaluating its effect on antibody titre, delayed type hypersensitivity response, phagocytic function and cyclophosphamide-induced myelo-suppression in mice²⁸.

Wang CC *et al.* (2007)²⁹ holds Arecoline responsible for suppression of T cell activity which in turn decreases the cell mediated immunity and thus results in decreased phagocytic activity of the cells.

Eudesmanolide type of sesquiterpene from *S. indicus* was reported to have immunostimulating activity which might be useful in prophylactic treatment of the disease³⁰ Hence correlating with literature, it can be postulated that *Sphaeranthus indicus* is an active immunomodulatory agent that can be used prophylactically in this condition to arrest the disease at an early stage.

Another aspect which needs to be considered is the viral aetiology of OSMF. According to Pillai R *et al.* (1992)³¹ An important link between OSMF and decreased immune response may be the suggested viral origin of the disease (HSV, HPV). Viral lesions show similar immune derangements such as abnormal CD4/CD8 cell ratio as seen in OSMF. Also viral antigen can elicit specific suppressor T-cell response. The resulting immunosuppression allows the spread of viral antigen and associated transformation of epithelium. Again according to Pillai R *et al* (1992)³¹ a defect in target cell or viral cell lysis are seen by NK cells in OSMF. Methanol extract of *S. indicus* (*Gorakhmundi*) showed inhibitory activity against mouse corona virus and herpes simplex virus at a concentration as low as 0.4 µg/mL³², an avenue which might be unexplored and the scope of future research as well.

Table 1: Comparison of Pre and Post Therapy Burning Sensations among the Cases

Burning Sensation in the Mouth (<i>Mukhadaha</i>)	Pre Therapy		Post Therapy		chi sq	p-value
	No.	%	No.	%		
Nil	0	0	15	55.6	31.8	<0.001
Spicy Food	8	26.7	10	37.0		
On taking food	10	33.3	2	6.7		
Continuous	12	40.0	3	10.0		
Total	30	100.0	30	100.0		

Table 2: Comparison of Pre and Post Therapy Intolerance to Spicy Food among the Cases

Intolerance to spicy food	Pre Therapy		Post Therapy		chi sq	p-value
	No.	%	No.	%		
Absent	2	6.7	21	70.0	25.45	<0.001
Present	28	93.3	9	30.0		
Total	30	100.0	30	100.0		

Table 3: Comparison of Pre and Post Therapy Pain in Mouth Opening among the Cases in VAS scale

Pain in mouth opening	Pre Therapy		Post Therapy		chi sq	p-value
	No.	%	No.	%		
VAS score 0	0	0	14	46.7	16.89	<0.001
VAS score 1	30	100.0	16	53.3		
Total	30	100.0	30	100.0		

Table 4: Comparison of Pre and Post Therapy Color of Mucosa among the Cases

Color of Mucosa	Pre Therapy		Post Therapy		chi sq	p-value
	No.	%	No.	%		
RED	19	83.3	23	83.3	1.27	0.26
WHITE	11	16.7	7	16.7		
Total	30	100.0	30	100.0		

Table 5: Comparison of Pre and Post Therapy Blackening among the Cases

Blackening	Pre Therapy		Post Therapy		chi sq	p-value
	No.	%	No.	%		
Absent	26	86.7	30	100.0	4.286	0.038
Present	4	13.3	0	0		
Total	30	100.0	30	100.0		

Table 6: Comparison of Pre and Post Therapy Consistency among the Cases

Consistency	Pre Therapy		Post Therapy		chi sq	p-value
	No.	%	No.	%		
Leathery	22	73.3	9	30.0	11.28	<0.001
Soft	8	26.7	21	70.0		
Total	30	100.0	30	100.0		

Table 7: Comparison of Pre and Post Therapy Ulceration among the Cases

Ulceration	Pre Therapy		Post Therapy		chi sq	p-value
	No.	%	No.	%		
Absent	18	60.0	29	96.7	11.88	<0.001
Present	12	40.0	1	3.3		
Total	30	100.0	30	100.0		

Table 8: Comparison of Pre and Post Therapy Labial Mucosa in Fibrous Bands among the Cases

Fibrous Bands-Labial Mucosa	Pre Therapy		Post Therapy		chi sq	p-value
	No.	%	No.	%		
Absent	13	43.3	16	55.2	0.827	0.363
Present	17	56.7	14	44.8		
Total	30	100.0	30	100.0		

Table 9: Comparison of Pre and Post Therapy Buccal Mucosa in Fibrous Bands among the Cases

Fibrous Bands-Buccal Mucosa	Pre Therapy		Post Therapy		chi sq	p-value
	No.	%	No.	%		
Absent	1	3.3	19	63.3	24.3	<0.001
Present	29	96.7	11	36.7		
Total	30	100.0	30	100.0		

Table 10: Comparison of Pre and Post Therapy Retromolar Region in Fibrous Bands among the Cases

Fibrous Bands-Retromolar Region	Pre Therapy		Post Therapy		Chi Sq	P-Value
	No.	%	No.	%		
Absent	11	36.7	11	36.7	0.00	1.00
Present	19	63.3	19	63.3		
Total	30	100.0	30	100.0		

Table 11: Comparison of Pre and Post Therapy Interincisal Distance among the Cases

Parameter	Pre Therapy		Post Therapy	
	Mean	SD	Mean	SD
INTERINCISAL DISTANCE (mm)	5.70	1.055	3.57	1.040
t-value	10.877			
p-value	<0.001			

Table 12: Comparison of Pre and Post Therapy Interleukin-6 level among the Cases

Parameter	Pre Therapy		Post Therapy	
	Mean	SD	Mean	SD
Interleukin -6 level	54.24	31.63	52.77	35.56
t-value	0.316			
p-value	0.754			

Table 13: Comparison of Pre and Post Therapy Serum antioxidant level among the Cases

Parameter	Pre Therapy		Post Therapy	
	Mean	SD	Mean	SD
Serum Antioxidant level	2.48	0.588	2.53	0.704
t-value	0.601			
p-value	0.551			

CONCLUSION

The herbal preparation (*Gorakmundi*, *Tulsi* and honey) used in this study is an effective alternative to the pre-existing conservative methods of management of early stage OSMF, a vata pitta dominant tridoshaja.

Considerable improvement in the hallmark clinical symptoms of OSMF like burning sensation, intolerance to spicy food, pain in mouth opening, ulceration, reduction in interincisal distance, fibrotic bands, blackening can be appreciated in the post therapeutic period of the herbal therapy. So based on the observations of this study it can be concluded that the herbal preparation:

- Is effective in reducing burning sensation to a considerable extent.
- Is conducive to reducing the intolerance to spicy food.
- Is effective in reducing pain in mouth opening to a considerable extent.
- Is efficacious in bringing change in the colour of mucosa from white to red suggesting a reduction in the disease severity.
- Is effective in reduction of blackening which is suggestive of accelerated oral mucosal healing.

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