ORIGINAL RESEARCH

Effectiveness of Fenugreek as an Adjuvant in the Management of Oral Potentially Malignant Disorders: A Randomized Controlled Trial

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Received on: 03 October 2024; *Accepted on:* 28 November 2024; *Published on:* 13 January 2025

Abstract

Aim: This study aimed to evaluate the effectiveness of fenugreek as an adjuvant in managing oral potentially malignant disorders (OPMDs), specifically leukoplakia, lichen planus, and oral submucous fibrosis (OSMF).

Materials and methods: Twenty-one participants prediagnosed with OPMDs were randomly divided into a study group (SG) and a control group (CG), with 10 participants in SG and 11 in CG, respectively. The SG received 2 gm of fenugreek as an adjuvant with standard systemic treatments tailored to the respective lesions: intralesional injection of vitamin A 1,00,000 IU (Aquasol A) and topical application of triamcinolone acetonide 0.1% (Kenacort) for 2 months for leukoplakia. Subjects with oral lichen planus were administered prednisolone 5 mg/day (Wysolone), chlorhexidine mouthwash 0.2% (Peridex), and Zincovit once daily for 8 weeks. For subjects with OSMF, one capsule of SM Fibro once daily for 12 weeks along with dexamethasone 1.5 mL (Decadron) was given, and hyaluronidase 1,500 IU (Hynidase) with 0.5 mL lignocaine HCL (Xylocaine) was injected intralesionally biweekly and mouth exercise was advised for 2 months; control group received only the standard treatment. Sociodemographic data were collected, and clinical assessments, evaluating size and shape for leukoplakia, erythema, and burning sensation for oral lichen planus, and mouth opening, cheek flexibility, and burning sensation for OSMF were assessed from baseline through 2 months. Data collected were organized in Excel and analyzed using Statistical Package for the Social Sciences version 21.0.

Results: The SG and CG had 10 and 11 participants, with 4 in each group for leukoplakia, 2 participants in SG and 3 in CG for lichen planus, and 4 participants for OSMF in each group, respectively. Most participants presented with leukoplakia under 2 cm on the buccal mucosa bilaterally, with no significant changes in size or shape postintervention. For lichen planus, mild erythema and burning sensation were noted, but there were no significant differences within or between groups postintervention. A mild burning sensation, a statistically significant improvement in mouth opening was observed in SG ($p < 0.051$) when compared with CG after 8 weeks postintervention in OSMF. Also, significant improvement in cheek flexibility was noted from baseline to the fourth follow-up in SG post intervention. However, there were no differences between groups during the follow-up period.

Conclusion: The findings from this trial suggest that SG showed significant improvement in OSMF than CG, whereas the improvements in leukoplakia and lichen planus remained same in both groups.

Clinical significance: Fenugreek, being a cost-effective and affordable agent known for its anticancer, anti-inflammatory, antioxidant, and antiulcerative properties, could be used as an adjuvant for its management in OPMDs.

Keywords: Adjuvant, Fenugreek, Leukoplakia, Lichen planus, OPMDs, OSMF, Trigonella.

The Journal of Contemporary Dental Practice (2024): 10.5005/jp-journals-10024-3773

Introduction

Oral cancer accounts for about 3% of all malignancies, posing a major global public health threat, with the highest incidence, mortality, and disability-adjusted life year, among cancers.[1,2] It often results in poor quality of life and increased health expenditures. Oral potentially malignant disorders (OPMD) are chronic conditions that precede oral cancer, with lesions in the oral mucosa at increased risk of malignant transformation (1.4–7%).[3] Common OPMDs include leukoplakia, oral lichen planus (OLP), and oral submucous fibrosis (OSMF).

Leukoplakia is defined as a predominantly white plaque of questionable risk, excluding other known diseases.[4] The global prevalence of leukoplakia is 2%, and in India, it ranges from 0.2 to 5.2%, with a malignant transformation rate of 0.13 to 10%.[5,6] The OLP is a chronic inflammatory disease with a global prevalence of 1.01% and 2.6% in India, with an annual malignant transformation rate below 1%.[7,8] The OSMF is a chronic disease affecting the lamina propria of the oral mucosa, progressing to deeper tissues, commonly found in regions with a culture of betel nut chewing.[9] The global prevalence of OSMF is 15%, and 6.42% in India, with a malignant transformation rate of 2–8%.[10]

Routine treatment for OPMDs includes pharmacotherapy, surgery, and radiotherapy, with recent additions of lasers and cryosurgery.[11] Management often involves cessation of tobacco

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How to cite this article: Balasundaram N, Narayanan MBA, Arul Antony LS, *et al*. Effectiveness of Fenugreek as an Adjuvant in the Management of Oral Potentially Malignant Disorders: A Randomized Controlled Trial. J Contemp Dent Pract 2024;25(10):921–929.

Source of support: Nil

Conflict of interest: None

and alcohol use. Leukoplakia can be treated with vitamin A, topical bleomycin, and systemic 13-*cis* retinoic acid.[12] The OLP treatment aims to reduce symptomatic outbreaks using topical and systemic corticosteroids like prednisone, along with oral hygiene measures.[13] The OSMF treatment includes intralesional dexamethasone injections and topical triamcinolone acetonide.[14,15]

Natural therapies are becoming popular for treating various diseases due to their limited side effects and potential for improving quality of life.[16] Medicinal plants and natural products like tulsi, curcumin, lycopene, chamomile, aloe vera, green tea, colchicine, spirulina, and raspberry extracts are used for managing potentially malignant oral diseases due to their immunomodulatory and antioxidant properties.[17–21] Fenugreek (*Trigonella foenum-graecum* Linn.) has attracted attention for managing various systemic diseases. Traditionally used in Indian medicine for digestive and mucosal conditions, fenugreek exhibits antidiabetic, antifertility, anticancer, antimicrobial, and antiparasitic effects, with radical scavenging activity reported from its extracts. Fenugreek seeds have shown potential in stimulating insulin secretion, improving glycemic control, and enhancing periodontal health, but scientific evidence for their role in oral cancer prevention remains limited.[22,23]

Hence, this study determined to evaluate the effectiveness of fenugreek as an adjuvant in managing OPMDs namely leukoplakia, lichen planus, and OSMF. The objective was to assess fenugreek's effectiveness clinically and photographically in OPMD management. The hypothesis was that fenugreek in its natural form, used alongside standardized treatment protocols, may influence OPMD resolution.

Materials and Methods

The study was designed as a randomized controlled clinical trial, conducted in accordance with the Consolidated Standards of Reporting Trials guidelines. It was carried out at a public teaching Dental Institution in Tamil Nadu, India, from January to September 2021 on the individuals reporting to out-patient department. The study protocol was reviewed and approved by the Institutional Review Board (IRB reference number: 4/IRB/2019). The trial was registered in the clinical trial registry of India (CTRI/2020/02/040893). The sample size required for the trial was calculated using G*Power software and was found to be 28. Hence, the sample size required per group was 14 participants.

Adults diagnosed with leukoplakia, lichen planus, and OSMF were included in the trial, while those with systemic illnesses, participating in other trials, or having hypersensitivity to fenugreek (such as nasal congestion, coughing, wheezing, facial swelling, or allergic reactions) were excluded. The purpose of the study was clearly explained to the participants. During a 9-month recruitment period, 40 subjects were assessed for potentially malignant oral disorders. After excluding 19 participants for various reasons, 21 subjects were included in the final study (Fig. 1). Allocation concealment was achieved using the sequentially numbered opaque sealed envelope technique. Subjects prediagnosed with OPMD in the Oral Medicine and Radiology Outpatient Department were randomly assigned to either the study group (SG) or the control group (CG) using computer-generated numbers. The final study population consisted of 10 participants in the SG and 11 in the CG. The sequence generation and randomization were conducted by a co-investigator using numbered envelopes. Written informed consent was obtained from participants, with information provided in either Tamil or English.

The demographic data and medical history of the subjects were recorded at the initial visit. Clinical and photographical assessment of the lesion was carried out every 15 days up to the follow-up period of 2 months in both groups. Clinical assessments of leukoplakia included measuring the lesion's size in centimeters

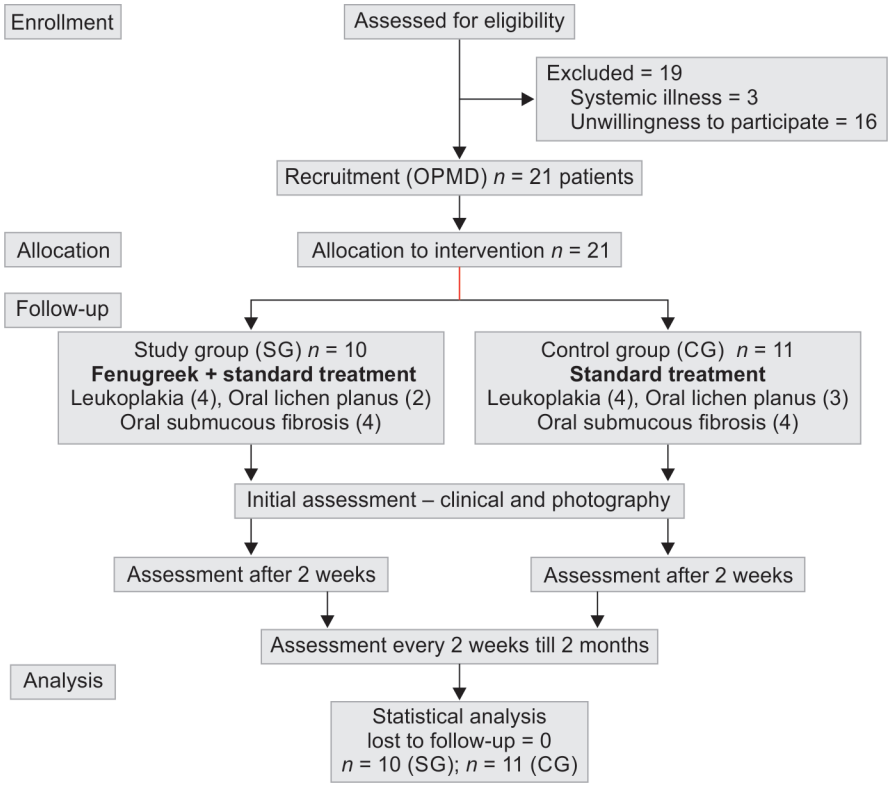

Fig. 1: Consolidated standards of reporting trials flowchart

with a metal divider and millimeter ruler, following Van der Wal's 2001 criteria. The shape of the lesion was categorized as linear, circular, or elliptical. Consistency was classified as soft, medium, or hard. Induration and ulceration were noted simply as present or absent. Clinical evaluations for OLP included checking for erythema, ulceration, and burning sensation. Erythema and ulceration were rated using a semi-quantitative scale, the Modified Oral Mucositis Index.[24,25] The burning sensation was measured on a visual analog scale from 0 (minimum) to 10 (maximum). Clinical assessments for OSMF included evaluating the burning sensation on a visual analog scale from 0 to 10, measuring mouth opening with a metal divider as per Mishra and Ranganathan criteria, and recording the presence or absence of blanching in the oral mucosa. Cheek flexibility was assessed by measuring the distance from the maxillary incisal midline to the cheek retractor during retraction, graded according to Patil et al. standards.[26,27]

Trial drugs were dispensed in paper bags by an uninvolved assistant, and the co-investigator ensured that participants followed proper drug intake instructions. The chief investigator was blinded to the intervention details. Along with the trial drug–fenugreek in its natural form, standardized treatment protocol for three lesions was followed for SG, whereas those in the CG were administered only the standard treatment as per protocol guidelines. Since no previous studies were undertaken with fenugreek, advice for administration of fenugreek was sought from Siddha and Ayurvedha experts as well as from World Health Organization monograph on herbal medicine.[28] As per their guidance, the dosage for administration of fenugreek was fixed as 2 gm/day bid. This trial drug was weighed using a standardized digital apparatus (Selves Enterprises and B06XMZV7RH), pocketed in small sachet of 28 sachets and was dispensed to the SG group subjects. They were instructed to swallow fenugreek after food by 8 a.m. in the morning and 8 p.m. at night at 12 hours interval for 2 weeks to be repeated till 8 weeks of the trial period.

The intervention for the CG included intralesional injection of vitamin A 1,00,000 IU (Aquasol A) and topical application of triamcinolone acetonide 0.1% (Kenacort) for 2 months for leukoplakia. Subjects with oral lichen planus were administered prednisolone 5 mg/day (Wysolone), chlorhexidine mouthwash 0.2% (Peridex), and Zincovit once daily for 8 weeks. For subjects with OSMF, one capsule of SM Fibro once daily for 12 weeks along with dexamethasone 1.5 mL (Decadron) was given, and hyaluronidase 1,500 IU (Hynidase) with 0.5 mL lignocaine HCL (Xylocaine) was injected intralesionally biweekly and mouth exercise was advised as intervention for 2 months. Subjects in both the groups were instructed to adhere to the intervention protocol for a period of 2 weeks and to return after 2 weeks for outcome assessment till 8 weeks.

Compliance and attrition were secondary outcomes. Subjects in both groups were asked to return leftover medicine at subsequent visits. A co-investigator collected these and classified subjects as compliant or noncompliant based on whether they used at least 80% of the medicine (no more than one packet remaining). Compliance rates were calculated for each group separately. Lesion evaluations and photographic assessments (Figs 2 to 4) were conducted from baseline to 8 weeks. Subjects were reminded of follow-up appointments by phone and written instructions on their outpatient cards. At each visit, lesions were examined, and decisions about continuing treatment were made by the investigator.

Data were tabulated in Microsoft Excel and analyzed using IBM Statistical Package for the Social Sciences (Version 21.0). Descriptive statistics reported sociodemographic data. The Fisher exact Chi-square test assessed differences in lesion size, shape, and erythema between groups. The Friedman test and Mann–Whitney *U*-test compared the mean values of burning sensation, mouth opening, and cheek flexibility within and between groups, respectively. Significant within-group differences were further analyzed using the Wilcoxon signed-rank test post-Friedman test.

Results

Out of 21 participants, 8 participants had leukoplakia; 5 had lichen planus, and 8 had OSMF. All participants were aged between 25 and 57 years, with a mean age of 42.59 ± 8.418 years (Table 1). Overall, male participants outnumbered females, except in the case of lichen planus, where females were more prevalent (Table 1).

Most participants presented with leukoplakia of the buccal mucosa (75%), typically bilateral with lesion sizes of less than 2 cm (Table 2). The lesions varied in shape, including linear, circular, elliptical, or combinations thereof. Postintervention analysis revealed no significant differences in parameters such as size and shape of leukoplakia between the groups during each follow-up (Table 3). Intragroup comparisons of size and shape also showed no significant differences between baseline measurements and each follow-up (Table 3).

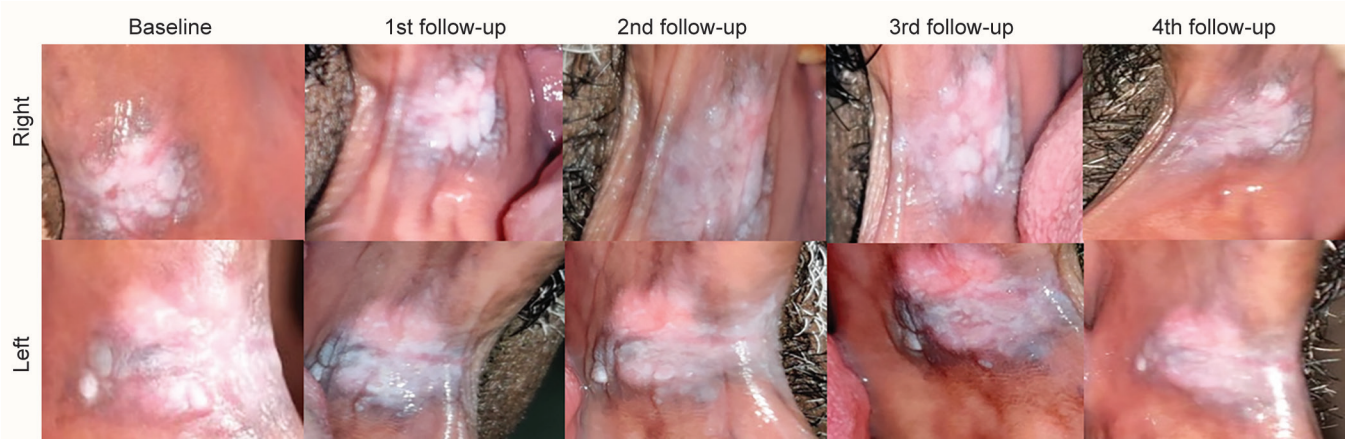

Fig. 2: Photographic assessment of leukoplakia on the right and left side of the buccal mucosa

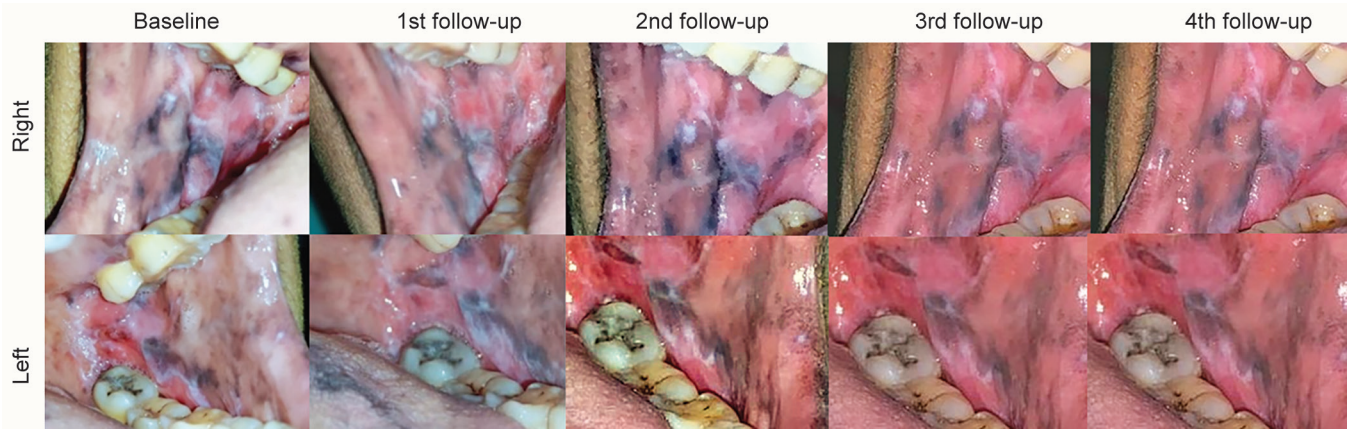

Fig. 3: Photographic assessment of lichen planus on the right and left side of the buccal mucosa

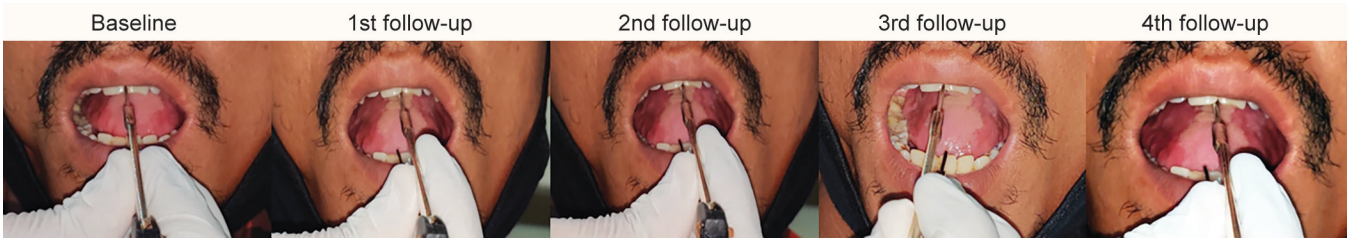

Fig. 4: Photographic assessment of mouth opening using stainless steel metal divider in oral submucous fibrosis

Table 1: Demographic characteristics of the participants in both groups

Groups	*Category*	*Mean age (42.59 ± 8.418)*	*Total participants, n (%)*	*Male, n (%)*	*Female, n (%)*
Study group	Leukoplakia	42 ± 12.83	4 (40)	4 (100)	0
	Lichen planus	32.5 ± 7.77	2 (20)	0	2 (100)
	OSMF	43.5 ± 7.04	4 (40)	2 (50)	2 (50)
Control group	Leukoplakia	46.5 ± 11.21	4 (36.4)	4 (100)	0
	Lichen planus	45.3 ± 2.08	3 (27.2)	2 (50)	1 (50)
	OSMF	39.50 ± 5.97	4 (36.4)	4 (100)	0

Table 2: Baseline assessment of both groups

Lesions	*Variables*	*Category*	*SG, n (%)*	*CG, n (%)*	*Total, n (%)*
Leukoplakia	Site	Bilateral buccal mucosa	3 (37.5)	3 (37.5)	6 (75)
		Bilateral buccal mucosa and palate	1 (12.5)	0	1 (12.5)
		Bilateral commissure of lips	1 (12.5)	0	1 (12.5)
	Size	<2 cm	3 (62.5)	3 (62.5)	6 (62.5)
		2–4 cm	1 (37.5)	1 (37.5)	2(37.5)
		>4 cm	0	0	0
	Shape	Linear	1 (50)	1 (50)	2 (100)
		Circular + elliptical	2 (100)	0	2 (100)
		Circular	0	2 (100)	2 (100)
		Elliptical	1 (50)	1 (50)	2 (100)
	Consistency	Hard	0	0	0
		Soft	4 (100)	4 (100)	8
	Induration	Present	0	0	0
		Absent	4 (100)	4 (100)	8

(Contd...)

Table 2: *(Contd...)*

Lesions	*Variables*	*Category*	*SG, n (%)*	*CG, n (%)*	*Total, n (%)*
Lichen planus	Erythema	Mild	1 (50)	1 (50)	2 (100)
		Moderate	1 (33.3)	2 (66.7)	3 (100)
		Severe	0	0	0
	Ulceration	Mild	0	0	0
		Moderate	0	0	0
		Severe	0	0	0
	Burning sensation (mean ± SD)		1.5 ± 0.707	1.67 ± 0.577	–
OSMF (mean ± SD)	Burning sensation		1.75 ± 2.217	0.50 ± 0.577	–
	Mouth opening		25 ± 7.165	27 ± 6.055	–
	Flexibility		21.5 ± 6.952	21.5 ± 5.745	–

SD, standard deviation

Table 3: Intra- and intergroup comparison of parameters in leukoplakia

Parameters	*Criteria*	*Time period*	*SG, n (%)*	*CG, n (%)*	*p-value*[a]
Size	<2 cm	Baseline	3 (62.5)	3 (62.5)	0.070
	2–4 cm		1 (37.5)	1 (37.5)	
	<2 cm	1st follow-up	3 (75)	4 (100)	0.070
	2–4 cm		1 (25)	0	
	<2 cm	2nd follow-up	4 (100)	4 (100)	1.000
	<2 cm	3rd follow-up	4 (100)	4 (100)	1.000
	<2 cm	4th follow-up	4 (100)	4 (100)	1.000
Intragroup comparison[b]			*p*-value = –1.000	*p*-value = –1.000	
Shape	Linear	Baseline	1 (50)	1 (50)	0.592
	Circular + elliptical		2 (100)	0	
	Circular		0	2 (100)	
	Elliptical		1 (50)	1 (50)	
	Linear	1st follow-up	1 (50)	1 (50)	0.592
	Circular + elliptical		2 (100)	0	
	Circular		0	2 (100)	
	Elliptical		1 (50)	1 (50)	
	Linear	2nd follow-up	4 (57.14)	3 (42.86)	0.814
	Elliptical		0	1 (100)	
	Linear	3rd follow-up	4 (100)	4 (100)	1.000
	Linear	4th follow-up	4 (100)	4 (100)	1.000
Intragroup comparison[b]			*p*-value = –0.351	*p*-value = –0.351	

[a]Fishers exact Chi-square test; [b]McNemar Chi-square test

Participants diagnosed with lichen planus presented with no ulceration but with mild to moderate erythema (Tables 2 and 4). Additionally, the majority reported a mild burning sensation, ranging from 0 to 5 on a scale of 0 to 10, observed in both groups (Table 4). There was no significant difference in erythema between the groups postintervention, at baseline, or during any follow-up visits (Table 4). Within-group comparisons showed no significant differences in burning sensation between follow-up visits (Table 5). Similarly, no significant difference in burning sensation was observed between the groups postintervention, at baseline, and at each follow-up visit (Table 5).

Most participants diagnosed with OSMF experienced a mild burning sensation, with mean values of (1.5 ± 0.707) and (1.67 ± 0.577) in the SG and CG after 2 months, respectively (Table 2). The mean mouth opening was 25 ± 7.165 mm in the SG and 27 ± 6.055 mm in the CG, while the mean flexibility was 21.5 ± 6.952 mm in SG and 21.5 ± 5.745 mm in CG after 2 months (Table 2). However, within-group analysis showed significant differences in burning sensation between baseline and the 4th follow-up in OSMF ($p = 0.034$) (Table 6). Similarly, significant differences were observed within groups in mouth opening ($p = 0.016$) and flexibility ($p = 0.027$) between baseline and the 4th follow-up, respectively (Table 6). There were no significant differences between the groups in terms of burning sensation, mouth opening, and flexibility in OSMF during any follow-up visits (Table 6). Though the measured parameters after trail intervention remained stable in leukoplakia and lichen

Table 4: Outcome assessment of erythema in lichen planus

Time period	*Category*	*SG, n (%)*	*CG, n (%)*	*Total, n (%)*	*p-value**
Baseline	Mild	1 (66.7)	1 (33.3)	2 (100)	1.000
	Moderate	1 (33.3)	2 (66.7)	3 (100)	
1st follow-up	Mild	2 (50)	2 (50)	4 (100)	1.000
	Moderate	0	1 (100)	1 (100)	
2nd follow-up	Mild	2 (100)	3 (100)	5 (100)	1.000
3rd follow-up	Mild	2 (100)	3 (100)	5 (100)	1.000
	Moderate	0	0	0	
4th follow-up	Mild	2 (100)	3 (100)	5 (100)	1.000

*Chi-square test

Table 5: Intra- and intergroup comparison of burning sensation in lichen planus

Intragroup comparison[a]						
Groups (Mean ± SD)	Baseline	1st follow-up	2nd follow-up	3rd follow-up	4th follow-up	*p*-value[a]
SG	1.5 ± 0.707	1.5 ± 0.707	1.5 ± 0.707	1.5 ± 0.707	1.5 ± 0.707	1.000
CG	1.67 ± 0.577	1.67 ± 0.577	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	0.167
Intergroup comparison[b]						
Time period	SG			CG		*p*-value[b]
Baseline	1.5 ± 0.707			1.67 ± 0.577		1.000
1st follow-up	1.5 ± 0.707			1.67 ± 0.577		1.000
2nd follow-up	1.5 ± 0.707			1.00 ± 0.00		0.400
3rd follow-up	1.5 ± 0.707			1.00 ± 0.00		0.400
4th follow-up	1.5 ± 0.707			1.00 ± 0.00		0.400

SD, standard deviation; [a]Friedman test; [b]Mann–Whitney *U*-test

Table 6: Intragroup comparison of burning sensation, mouth opening, and cheek flexibility in OSMF

Intergroup comparison[a]									
	Burning sensation			*Mouth opening*			*Cheek flexibility*		
Time period	*SG*	*CG*	*p*-value[a]	*SG*	*CG*	*p*-value[a]	*SG*	*CG*	*p*-value[a]
Baseline	1.75 ± 2.217	0.50 ± 0.577		25 ± 7.165	27 ± 6.055		21.5 ± 6.957	2.25 ± 0.957	
1st follow-up	1.5 ± 1.732	0.50 ± 0.577	0.657	26.25 ± 7.411	27.5 ± 5.686	0.372	22.75 ± 5.909	1.75 ± 0.500	0.661
2nd follow-up	0.25 ± 0.500	0.50 ± 0.577	0.657	27.75 ± 6.185	28.25 ± 5.188	0.372	23.75 ± 4.924	1.75 ± 0.500	0.462
3rd follow-up	0.25 ± 0.500	0	1.000	28 ± 6.000	28.5 ± 5.066	0.442	24.5 ± 4.359	1.75 ± 0.500	0.234
4th follow-up	0.25 ± 0.500	0	1.000	28.25±5.852	28.5 ± 4.924	0.552	24.5 ± 4.359	1.75 ± 0.500	0.234
Intragroup comparison (*p*-value)[b]	0.023*	0.092		0.009*	0.025*		0.029*	0.034*	
Post hoc *z*-value	4th follow-up–baseline −2.121			4th follow-up–baseline −2.410			4th follow-up–baseline −2.214		
p-value[c]	0.034*			0.016*			0.027*		

[a]Mann–Whitney *U*-test; [b]Friedman test; [c]Wilcoxon signed rank test; *Statistically significant *p*-value; *p* values are statistically significant.

planus, OSMF showed positive changes in burning sensation, mouth opening, and cheek flexibility in SG after 2 months.

Discussion

Oral cancer represents about 3% of all malignancies, with many cases arising from OPMDs. The prevalence of OPMDs is 10.54%, with specific disorders such as leukoplakia, lichen planus, and OSMF ranging from 0.2 to 5.2%, 1 to 4%, and 0.2 to 2.3%, respectively. Leukoplakia, lichen planus, and OSMF have been identified as the most common OPMDs among the South Asian population.[7, 29–32] Therefore, our trial specifically targeted these lesions.

To address the malignant transformation and reduce the mortality due to cancer, early detection, correct diagnosis, and timely treatment of OPMDs was required. This included regular dental examination and removal of implicated environmental and behavioral risk factors.[1,13] While various treatment protocols exist, natural products, due to their beneficial biological properties, offer

advantages over conventional treatments, including overcoming chemoresistance, reducing cytotoxicity to healthy cells, and being cost-effective. These natural compounds show promise as adjuvant, neoadjuvant, and chemoprevention agents for OPMDs. Recent studies have explored the widespread use and beneficial properties of fenugreek, particularly its potential applications for various disorders.[33]

Several studies have shown that fenugreek seeds exhibit anticancer properties across various cancer types. Research by Raju et al.,[34] Verma et al.,[35] and Khalil et al.,[36] demonstrated antiproliferative and cytotoxic effects against gastrointestinal cancers. Shabbeer et al.,[37] Alshatwi et al.,[38] and Alsemari et al.[39] found similar effects on breast cancer. Additionally, studies on hematological cancers and lung cancer[39–41] revealed inhibition of cell growth and tumor reduction. Azari et al. found out that fenugreek seed extract protected the gastric mucosa from injury, reducing the gastric erosion and ulceration against experimentally induced gastric ulcers in rats.[42] The varied effects of fenugreek in humans were noted by Tavakoly et al.[43] for its anti-inflammatory and antioxidant effects in type 2 diabetes; Emtiazy et al.[44] identified fenugreek's flavonoids effect on lipid peroxidation, thereby protecting against oxidative stress, with improvements in respiratory function. Bordia et al. found that a 2.5 gm dose twice daily significantly reduced cholesterol and triglycerides in coronary artery disease patients with non-insulin dependent diabetes mellitus.[45]

Also, fenugreek in its naturally occurring form (seed) was found to exhibit anti-inflammatory, hypocholesterolemic, hypoglycemic, antioxidant, and antiulcer properties.[46,47] The seed proteins are reported to be responsible for the high antioxidant activity of fenugreek with an excellent amino acid profile (high amount of Glu, Asp, Lue, Thr, and Arg).[48] It has been successively administered for various cancers due to several important components such as trigonelline, diosgenin, and protodioscin. An important component of fenugreek, diosgenin, was a steroid saponin and has been reported to inhibit cell growth and induce apoptosis. The mechanism of action of diosgenin was proposed to be induction of apoptosis in HT-29 cells partially by inhibition of bcl-2 and by induction of caspase-3 protein expression.[33,34] A study by Jagadeesan et al. showed that diosgenin exhibits anticarcinogenic activity via reducing peroxidation reaction and marker enzymes by enhancing the intrinsic antioxidant defense system.[49]

One of the main causes for the development of OPMDs was the increase in levels of oxidative enzyme and relatively increased oxidative stress. Fenugreek exerts its antioxidant activity by increasing the levels of antioxidants. In addition to the above stated advantages of using the fenugreek seeds, some of the other properties of fenugreek could have been masked on various forms of its formulation. Hence fenugreek in its natural form was used to evaluate its effectiveness on OPMDs in the present study. The systemic use of fenugreek employed in the present clinical trial was according to the World Health Organization Monograph on herbal medicinal plants.[28] To the best of our knowledge, no previous studies have been done to study the effectiveness of fenugreek in the management of OPMDs and hence, this is the first of the kind in administering fenugreek as an adjuvant for the management of OPMDs.

Leukoplakia was common in men over 40 years, with prevalence increasing with age. In this study, all participants with leukoplakia were above 50 years of age and were predominantly male. A significant reduction in lesion size and shape were observed postintervention. This could be attributed by fenugreek's saponins and proteins with antioxidant and anticancer properties, promoting apoptotic cell death and preventing malignant transformation. The OLP was found to be mostly affecting middle-aged women, which was in accordance with previous studies. It showed no significant reduction in erythema or burning sensation postintervention, indicating a need for more extensive studies to fully evaluate fenugreek's effectiveness on this condition. It is evident from few studies that flavonoids possess anti-inflammatory action that helps reduce the severity of the lesion.[50]

In this study, fenugreek as an adjuvant significantly reduced burning sensation, mouth opening, and cheek flexibility in OSMF within groups during follow-ups predominantly in males. These findings suggest the potential benefits of fenugreek in managing OSMF, likely due to its anti-inflammatory and antinociceptive properties, anticarcinogenic activity exhibited by diosgenin via reduction of peroxidation reaction and marker enzymes.[42] Also, this regression of symptoms could have been due to the anti-inflammatory and antinociceptive activity of alkaloid and flavonoid fractions of fenugreek seeds as well as due to the antioxidant effect exerted by fenugreek seeds, which is evident through its action in inhibiting superoxide generation and preventing tumor promotion.[5,51,52] However, no significant intergroup differences were noted, highlighting the need for longer follow-ups to determine efficacy.

The study observed good compliance with the fenugreek treatment and no attrition, indicating good participant engagement and adherence to the trial protocol. Thus, the study highlighted that fenugreek could be used as an adjuvant for managing OPMDs. The strengths of the present study were that the noninvasive, simple, and economical nature of the intervention along with its easy availability, accessibility, affordability, and acceptance by the community led to high cooperation and compliance from the subjects. However, the study's follow-up duration was only 2 months, insufficient for observing complete regression of lesions that often have a lengthy clinical course. Recruitment during the COVID-19 pandemic's second wave limited the sample size, affecting the generalizability of the results. The effective dose of fenugreek was not specifically calculated. Also, the effect of fenugreek on different grades/stages of OPMD's were not specifically studied in the present trial. Hence, future research should explore fenugreek as a therapeutic agent, with well-controlled clinical trials featuring larger samples, emphasizing on different stages/grades of the lesion with longer follow-ups to fully establish its effectiveness in managing OPMDs.

Conclusion

The OPMDs can lead to oral cancer, necessitating early intervention. Fenugreek, known for its anticancer, anti-inflammatory, antioxidant, and antiulcerative properties, was used as an adjuvant in this study. It was found to reduce lesion severity in OSMF, showing significant progress during follow-ups. However, its effects were limited in leukoplakia and oral lichen planus cases. While fenugreek appears to be an adjuvant, more extensive clinical trials are necessary to understand its full potential and mechanisms in managing these disorders.

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References

1. Mortazavi H, Baharvand M, Mehdipour M. Oral potentially malignant disorders: An overview of more than 20 entities. J Dent Res Dent Clin Dent Prospects 2014;8(1):6–14. DOI: 10.5681/joddd.2014.002.
2. Ren ZH, Hu CY, He HR, et al. Global and regional burdens of oral cancer from 1990 to 2017: Results from the global burden of disease study. Cancer Commun 2020;40(2–3):81–92. DOI: 10.1002/cac2.12009.
3. Yardimci G, Kutlubay Z, Engin B, et al. Precancerous lesions of oral mucosa. World J Clin Cases 2014;2(12):866–872. DOI: 10.12998/wjcc.v2.i12.866.
4. Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, et al. Oral potentially malignant disorders: A consensus report from an international seminar on nomenclature and classification, convened by the WHO Collaborating Centre for Oral Cancer. Oral Dis 2021;27(8):1862–1880. DOI: 10.1111/odi.13704.
5. Masthan KM, Babu NA, Sankari SL, et al. Leukoplakia: A short review on malignant potential. J Pharm Bioallied Sci 2015;7(Suppl 1):S165–S166. DOI: 10.4103/0975-7406.155890.
6. Sridharan G. Epidemiology, control and prevention of tobacco induced oral mucosal lesions in India. Indian J Cancer 2014;51(1):80–85. DOI: 10.4103/0019-509X.134651.
7. González-Moles MÁ, Warnakulasuriya S, González-Ruiz I, et al. Worldwide prevalence of oral lichen planus: A systematic review and meta-analysis. Oral Dis 2021;27(4):813–828. DOI: 10.1111/odi.13323.
8. Varghese SS, George GB, Sarojini SB, et al. Epidemiology of oral lichen planus in a cohort of South Indian population: A retrospective study. J Cancer Prev 2016;21(1):55–59. DOI: 10.15430/JCP.2016.21.1.55.
9. Kerr AR, Warnakulasuriya S, Mighell AJ, et al. A systematic review of medical interventions for oral submucous fibrosis and future research opportunities. Oral Dis 2011;17:42–57. DOI: 10.1111/j.1601-0825.2011.01791.x.
10. Ganesh D, Sreenivasan P, Öhman J, et al. Potentially malignant oral disorders and cancer transformation. Anticancer Res 2018;38(6):3223–3229. DOI: 10.21873/anticanres.12587.
11. Lorini L, Bescós Atín C, Thavaraj S, et al. Overview of oral potentially malignant disorders: From risk factors to specific therapies. Cancers 2021;13(15):3696. DOI: 10.3390/cancers13153696.
12. Lodi G, Franchini R, Warnakulasuriya S, et al. Interventions for treating oral leukoplakia to prevent oral cancer. Cochrane Database Syst Rev 2016;7(7):CD001829. DOI: 10.1002/14651858.CD001829.pub4.
13. Alrashdan MS, Cirillo N, McCullough M. Oral lichen planus: A literature review and update. Arch Dermatol Res 2016;308(8):539–551. DOI: 10.1007/s00403-016-1667-2.
14. Aara A, Satishkumar GP, Vani C, et al. Comparative study of intralesional dexamethasone, hyaluronidase and oral pentoxifylline in patients with oral submucous fibrosis. Glob J Med Res 2012;12(7):1–4. DOI:10.13140/RG.2.2.19209.88162.
15. Shen YW, Shih YH, Fuh LJ, et al. Oral submucous fibrosis: A review on biomarkers, pathogenic mechanisms, and treatments. Int J Mol Sci 2020;21(19):7231. DOI: 10.3390/ijms21197231.
16. Danaraddi S, Koneru A, Hunasgi S, et al. Natural ways to prevent and treat oral cancer. J Oral Res Rev 2014;6(1):34–39. DOI: 10.4103/2249-4987.140213.
17. Chakravarthy PK, Smriti K, Yeturu SK. Role of herbal and natural products in the management of potentially malignant oral disorders. Nat Oral Care Dental Therapy 2020;30:61–79. DOI: 10.1002/9781119618973.ch4.
18. Salehi B, Lopez-Jornet P, López E, et al. Plant-derived bioactives in oral mucosal lesions: A key emphasis to curcumin, lycopene, chamomile, aloe vera, green tea and coffee properties. Biomolecules 2019;9(3):106. DOI: 10.3390/biom9030106.
19. Daga D, Singh RK, Pal US, et al. Efficacy of oral colchicine with intralesional hyaluronidase or triamcinolone acetonide in the Grade II oral submucous fibrosis. Natl J Maxillofac Surg 2017;8(1):50–54. DOI: 10.4103/njms.NJMS_5_17.
20. Desai KM, Hallikermath S, Kale A. Spirulina: An emerging treatment modality for the management of oral submucous fibrosis. Int J Oral Care Res 2011;5:328–331. DOI: 10.5005/jp-journals-10051-0125.
21. Warner BM, Casto BC, Knobloch TJ, et al. Chemoprevention of oral cancer by topical application of black raspberries on high at-risk mucosa. Oral Surg Oral Med Oral Pathol Oral Radiol 2014;118(6):674–683. DOI: 10.1016/j.oooo.2014.09.005.
22. Yadav UC, Baquer NZ. Pharmacological effects of *Trigonella foenum-graecum* L. in health and disease. Pharm Biol 2014;52(2):243–254. DOI: 10.3109/13880209.2013.826247.
23. Sundaram G, Ramakrishnan T, Parthasarathy H, et al. Fenugreek, diabetes, and periodontal disease: A cross-link of sorts! J Indian Soc Periodontol 2018;22(2):122–126. DOI: 10.4103/jisp.jisp_322_17.
24. Van der Waal I, Schepman KP, Van der Meij EH. A modified classification and staging system for oral leukoplakia. Oral Oncol 2000;36(3):264–266. DOI: 10.1016/s1368-8375(99)00092-5.
25. Chainani-Wu N, Silverman Jr S, Reingold A, et al. Validation of instruments to measure the symptoms and signs of oral lichen planus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105(1):51–58. DOI: 10.1016/j.tripleo.2007.06.022.
26. Mishra G, Ranganathan K. An overview of classification schemes for oral submucous fibrosis. J Oral Maxillofac Pathol 2006;10:55–58.
27. Patil S, Maheshwari S. Proposed new grading of oral submucous fibrosis based on cheek flexibility. J Clin Exp Dent 2014;6(3):e255–e258. DOI: 10.4317/jced.51378.
28. World Health Organization. WHO monographs on selected medicinal plants. WHO consultation on selected medicinal plants, WHO consultation on selected medicinal plants (2nd: 1999: Ravello-Salerno, Italy), WHO consultation on selected medicinal plants (3rd: 2001: Ottawa, Ont) & WHO consultation on selected medicinal plants (4th: 2005: Salerno-Paestum, Italy) [Internet]. World Health Organization. 2006. Available from: https://iris.who.int/handle/10665/42052.
29. Richards D. Prevalence of oral potentially malignant disorders. Evid Based Dent 2018;19(4):120–121. DOI: 10.1038/sj.ebd.6401348.
30. Mohammed F, Fairozekhan AT. Oral leukoplakia. Treasure Island, FL: StatPearls Publishing; 2020.
31. Rao NR, Villa A, More CB, et al. Oral submucous fibrosis: A contemporary narrative review with a proposed inter-professional approach for an early diagnosis and clinical management. J Otolaryngol Head Neck Surg 2020;49(1):3. DOI: 10.1186/s40463-020-0399-7.
32. El-Naggar AK, Chan JK, Takata T, et al. The fourth edition of the head and neck World Health Organization blue book: Editors' perspectives. Hum Pathol 2017;66:10–12. DOI: 10.1016/j.humpath.2017.05.014.
33. Tewari D, Jóźwik A, Łysek-Gładysińska M, et al. Fenugreek (*Trigonella foenum-graecum* L.) seeds dietary supplementation regulates liver antioxidant defense systems in aging mice. Nutrients 2020;12(9):2552. DOI: 10.3390/nu12092552.
34. Raju J, Patlolla JM, Swamy MV, et al. Diosgenin, a steroid saponin of *Trigonella foenum-graecum* (fenugreek), inhibits azoxymethane-induced aberrant crypt foci formation in F344 rats and induces apoptosis in HT-29 human colon cancer cells. Cancer Epidemiol Biomarkers Prev 2004;13(8):1392–1398. PMID: 15298963.
35. Verma SK, Singh SK, Mathur A. In vitro cytotoxicity of *Calotropis procera* and *Trigonella foenum-graecum* against human cancer cell lines. J Chem Pharm Res 2010;2:861–865.
36. Khalil MI, Ibrahim MM, El-Gaaly GA, et al. *Trigonella foenum* (fenugreek) induced apoptosis in hepatocellular carcinoma cell line, HepG2, mediated by upregulation of p53 and proliferating cell nuclear antigen. Biomed Res Int 2015;2015:914645. DOI: 10.1155/2015/914645.
37. Shabbeer S, Sobolewski M, Anchoori RK, et al. Fenugreek: A naturally occurring edible spice as an anticancer agent. Cancer Biol Ther 2009;8(3):272–278. DOI: 10.4161/cbt.8.3.7443.

38. Alshatwi AA, Shafi G, Hasan TN, et al. Fenugreek induced apoptosis in breast cancer MCF-7 cells mediated independently by fas receptor change. Asian Pac J Cancer Prev 2013;14(10):5783–5788. DOI: 10.7314/apjcp.2013.14.10.5783.
39. Alsemari A, Alkhodairy F, Aldakan A, et al. The selective cytotoxic anti-cancer properties and proteomic analysis of *Trigonella foenum-graecum*. BMC Complement Altern Med 2014;14(1):1–9. DOI: 10.1186/1472-6882-14-114.
40. Hibasami H, Moteki H, Ishikawa K, et al. Protodioscin isolated from fenugreek (*Trigonella foenum-graecum* L.) induces cell death and morphological change indicative of apoptosis in leukemic cell line H-60, but not in gastric cancer cell line KATO III. Int J Mol Med 2003;11:23–26. PMID: 12469212.
41. Al-Daghri NM, Alokail MS, Alkharfy KM, et al. Fenugreek extract as an inducer of cellular death via autophagy in human T lymphoma Jurkat cells. BMC Complement Altern Med 2012;12(1):1–8. DOI: 10.1186/1472-6882-12-202.
42. Azari O, Kheirandish R, Shojaeepour S. Protective effect of fenugreek seeds (*Trigonella foenum-graecum*) extract against experimental gastric ulcer in rats. Comp Clin Pathol 2014;23:1743–1748. DOI: 10.1007/s00580-014-1980-0.
43. Tavakoly R, Maracy MR, Karimifar M, et al. Does fenugreek (*Trigonella foenum-graecum*) seed improve inflammation, and oxidative stress in patients with Type 2 diabetes mellitus? A parallel group randomized clinical trial. Eur J Integr Med 2018;18:13–17. DOI: 10.1016/j.eujim.2018.01.005.
44. Emtiazy M, Oveidzadeh L, Habibi M, et al. Investigating the effectiveness of the *Trigonella foenum-graecum* L. (fenugreek) seeds in mild asthma: A randomized controlled trial. Allergy Asthma Clin Immunol 2018;14:1–8. DOI: 10.1186/s13223-018-0238-9.
45. Bordia A, Verma SK, Srivastava KC. Effect of ginger (*Zingiber officinale* Rosc.) and fenugreek (*Trigonella foenum-graecum* L.) on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. Prostaglandins Leukot Essent Fatty Acids 1997;56(5):379–384. DOI: 10.1016/s0952-3278(97)90587-1.
46. Srivastava A, Singh Z, Verma V, Choedon T. Potential health benefits of fenugreek with multiple pharmacological properties. In: Information Resources Management Association, editor. Research Anthology on Recent Advancements in Ethnopharmacology and Nutraceuticals. Hershey (PA): IGI Global; 2022. pp. 672–687.
47. Setti K, Kachouri F, Hamdi M. Improvement of the antioxidant activity of fenugreek protein isolates by *Lactococcus lactis* fermentation. Int J Pept Res Ther 2018;24(4):499–509. DOI: 10.1007/s10989-017-9636-y.
48. Ruwali M. *Trigonella foenum-graecum* (fenugreek) as a potential cancer chemo-preventive agent. Austin J Biotechnol Bioeng 2014;1(6):2.
49. Jagadeesan J, Nandakumar N, Rengarajan T, et al. Diosgenin, a steroidal saponin, exhibits anticancer activity by attenuating lipid peroxidation via enhancing antioxidant defense system during NMU-induced breast carcinoma. J Environ Pathol Toxicol Oncol 2012;31(2):121–129. DOI: 10.1615/jenvironpatholtoxicoloncol.v31.i2.40.
50. Goyal S, Gupta N, Chatterjee S. Investigating therapeutic potential of *Trigonella foenum-graecum* L. as our defense mechanism against several human diseases. J Toxicol 2016;2016:1250387. DOI: 10.1155/2016/1250387.
51. Amudhan A, Aishwarya V, Amudhan A. Management of oral submucous fibrosis – An update. Eur J Mol Clin Med 2020;7(5):1380–1392.
52. Ahmad A, Alghamdi SS, Mahmood K, et al. Fenugreek a multipurpose crop: Potentialities and improvements. Saudi J Biol Sci 2016;23(2):300–310. DOI: 10.1016/j.sjbs.2015.09.015.