Medical Management of Oral Submucous Fibrosis

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Contents

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Learning Goals

- Medical treatment has been shown to be of some benefit in the early stages of oral submucous fibrosis, while surgical treatment is reserved for advanced cases. The various medical therapeutic agents, their route of administration, and the current understanding of their effectiveness are discussed in this chapter.

16.1 Introduction

Oral submucous fibrosis (OSF) is an insidious, chronic, progressive, and debilitating disease characterized by fibrotic changes in the oral mucosa. The pathogenesis of oral submucous fibrosis (OSF) involves areca nut alkaloids causing disequilibrium in the regulation of matrix metalloproteinase and tissue inhibitors of matrix metalloproteinase resulting in the deposition of abnormal extracellular matrix (ECM) [1]. The cessation of areca nut habit is the most significant step in the management of OSF in areca nut users. In addition to habit cessation activities, various medical treatment modalities have been researched. These include dietary supplements (micronutrients, vitamins, and antioxidants), immunomodulatory/anti-inflammatory agents (corticosteroids), proteolytic agents (such as hyaluronidase and placental extracts), vasodilators, immunomodulators, and anticytokines. They have been administered orally, topically, or through submucosal injection. Herbal preparations containing substances like aloe vera, tulsi/basil, turmeric, and spirulina have also been used in the medical management of OSF [2–4]. Research related to oral submucous fibrosis that have been undertaken using these various agents are presented in Table 16.1.

The objectives of medical treatment are to eliminate the symptoms of burning sensation, to stabilize and improve mouth opening, and in the long term to prevent malignant transformation.

Surgery is reserved for patients in the advanced stages of the disease. Physical therapy acts synergistically with other treatment modalities. The complex nature of diseases and the lack of a universal treatment protocol makes the management of OSF a challenging process. We discuss here the results of different agents reported in the literature for the treatment of OSF and their limitations.

This chapter aims

1. To comprehensively present and discuss the medical interventions reported in the literature in the management of OSF.
2. To understand the mechanism of action of medicinal agents used.
3. To emphasize the applications and side effects of each of the medicinal regimens used to alleviate the signs and symptoms in OSF.

16.1.1 Medical Management of OSF

16.1.1.1 Pharmaceutical Agents

1. Systemic agents

- Levamisole (capsules; Immunomodulator).
- Antioxidant (capsules; Immunomodulator).
- Betamethasone (intralesional injections; corticosteroids).
- Hydrocortisone (intralesional injections; corticosteroids).
- Triamcinolone (intralesional injections; corticosteroids).
- Methylprednisolone (intralesional injections; corticosteroids).
- Hyaluronidase (intralesional injections; fibrinolytic enzyme).
- Placental extract (intralesional injections; biogenic stimulation).
- Vitamin E (capsules; Vitamins).
- Micronutrient supplements (capsules; vitamins, minerals, and omega-3 fatty acids).
- Pentoxifylline (tablets; vasodilator).
- Isoxsuprine (tablets; vasodilator).
- Lycopene (capsules; antioxidant).

2. Topical agents

- Triamcinolone acetonide (oromucosal pastes; corticosteroids).
- Clobetasol propionate (oromucosal pastes; corticosteroids).

16.1.1.2 Herbal Remedies

1. Systemic agents

- Curcumin (tablets/lozenges; anti-inflammatory and antioxidant).
- Oxitard (capsules; immunomodulation, anti-inflammatory, anti-anxiety, anti-convulsive, and anti-arthritic properties).
- Spirulina (tablets; antioxidant).
- Colchicine (tablets; anti-inflammatory).

2. Topical agents

- Aloe vera (gel; antioxidant, antibacterial, and provides hydration).
- Curcumin (gel; anti-inflammatory and antioxidant).

Table 16.1 Research studies on oral submucous fibrosis using various medical therapies

Authors	Type of study[a]	Sample	Intervention	Duration of treatment/ Follow-up	Mouth opening assessment (Measured with vernier caliper) B: baseline; A: after intervention; F: after follow-up	Burning sensation assessment (Measured with visual analog scale, VAS) B: baseline; A: after the intervention; F: after follow-up	Observations reported by authors
Immunomodulators: Levamisole							
Jirge et al. [12]	Randomized, single-blind study Levamisole Antioxidant Levamisole + Antioxidant	45 OSF patients Counseled to quit areca nut practice	**Group I:** (n = 15) Levamisole 50 mg tablets (Vermisol)—one tablet three times daily, for three consecutive days in a week for three alternate weeks **Group II:** (n = 15) Antioxidant capsules (ANTOXID) one capsule two times daily for 6 weeks **Group III:** (n = 15) Combination of group I and II treatments	6 weeks of treatment Post-treatment follow-up for 2 months	**Group I:** Levamisole B: 2.8 ± 0.6 cm A: 3.0 ± 0.7 cm **Group II:** Antioxidant B: 3.0 ± 1.1 cm A: 3.2 ± 1.0 cm **Group III:** Combination B: 2.5 ± 1.0 cm A: 2.7 ± 1.0 cm	**Group I:** Levamisole B: 51.7 ± 19.9 A: 1.0 ± 2.8 **Group II:** Antioxidant B: 58.0 ± 29.7 A: 10.1 ± 13.8 **Group III:** Combination B: 39.3 ± 16.9 A: 2.7 ± 6.8	Authors inferred that treatment of OSF with levamisole, antoxid, and the combination produced statistically significant improvement in mouth opening and reduction in burning sensation. Overall, a better response was seen to levamisole alone, than to antoxid and combination therapy.
Shinge et al. [13]	Randomized control trial Levamisole Antioxidant Levamisole + Antioxidant	60 OSF subjects Divided into four groups according to OSF stages, then randomly subdivided into three groups based on treatments.	**Group A:** (n = 30) Levamisole 150 mg (Tab. Vermisol) once a day for 3 consecutive days in a week for the following 3 alternate weeks **Group B:** (n = 20) Antioxidant capsules (Antoxid) 2 times daily for 6 weeks **Group C:** (n = 20) Combination of levamisole 150 mg + antioxidant capsules	60 days	Improvement in mouth opening (%) **Group A:** Levamisole Stage 1: 10% Stage 2: 22% Stage 3: 18% Stage 4: 7% **Group B:** Antoxid Stage 1: 10% Stage 2: 16% Stage 3: 18% Stage 4: 12.5% **Group C:** Combination Stage 1: 20% Stage 2: 22% Stage 3: 20% Stage 4: 5%	Evaluation of reduction (%) **Group A:** Levamisole Stage 1: 54% Stage 2: 64% Stage 3: 54% Stage 4: 20% **Group B:** Antoxid Stage 1: 32% Stage 2: 34% Stage 3: 32% Stage 4: 15% **Group C:** Combination Stage 1: 66% Stage 2: 66% Stage 3:54% Stage 4: 17%	Combination drugs fared better than individual treatment groups. Further, being economical, non-invasive, safe and efficacious, levamisole and antioxidants can be considered an effective treatment protocol.

Anti-inflammatory: Corticosteroids							
Goel et al. [10]	Clinical longitudinal study Lycopene Betamethasone Control	270 OSF patients Two treatment groups and a control group (90 in each group) Counseled to quit areca nut practice. Patients of each treatment group were further subdivided into three clinical stages of OSF (Stages I, II, III:).	**Lycopene group:** (n = 90) 2 mg of capsule lycopene per day (Lycored™) twice daily **Betamethasone group:** (n = 90) Intralesional injection of betamethasone 4 mg/ml diluted in 1.0 ml of 2% xylocaine (Injection Betnesol) biweekly with half dose on each side **Control group:** (n = 90)	6 months of treatment 6 months of follow-up	Post-treatment average improvement **Lycopene group:** Stage I: 3.00 ± 1.11 mm Stage II: 6.07 ± 2.00 mm Stage III: 6.53 ± 1.45 mm **Betamethasone group:** Stage I: 3.30 ± 1.51 mm Stage II: 9.47 ± 2.47 mm Stage III: 3.27 ± 1.36 mm **Control group:** Stage I: 0.00 ± 0.00 mm Stage II- 0.00 ± 0.00 mm Stage III- 0.00 ± 0.00 mm	----------	A positive clinical response was seen in all three clinical stages in both the test groups when compared with the control group. Lycopene and betamethasone injection were seen to be efficacious, safe, and reliable drugs in the management of OSF.
Kisave et al. [95]	Prospective clinical study Placentrex Hydrocortisone	60 OSF patients Grade II and Grade III Counseled to quit the areca nut practice. Physiotherapy and multivitamins were advised.	**Group A:** (n = 30) 2 ml of placentrex, 2 injections per week **Group B:** (n = 30) 2 ml of hydrocortisone, 2 injections per week	3 months	**Group A:** Placentrex B: 24.81 ± 1.11 mm A: 30.00 ± 0.86 mm **Group B:** Hydrocrotisone B:23.14 ± 1.25 mm A: 34.83 ± 0.85 mm	**Group A:** Placentrex B: Mild-32.3%; moderate-35.5%; severe- 32.3% A: absent-32.3% mild- 29.0% **Group B:** Hydrocortisone B: mild-27.6%; moderate-34.5%, severe-37.9% A: absent-17.2% mild-48.3%	Overall, hydrocortisone seems to be a better regimen to improve mucosal health and increase mouth opening as compared to placentrex regimen. However, placentrex is better than hydrocortisone in reducing the burning sensation.
Antioxidant: Lycopene							
Chole et al. [17]	Randomized controlled trial Lycopene Lycopene + Triamcinolone Placebo	90 OSF patients Areca nut practice cessation was ascertained. Groups 1,2,3 (Khanna and Andrade's classification) were included; Group 4a and 4b were advised surgery.	**Group A:** (n = 25) 16 mg of lycopene (Cap Lycored) **Group B:** (n = 25) 16 mg of lycopene + topical triamcinolone acetonide 0.1% (Cap Lycored + Ointment Kenacort) **Group C:** (n = 25) Placebo	3 months	**Group A** showed 87% increase in mouth opening while **Group B** showed 93% and **Group C** showed 16% increase in mouth opening.	**Group A** showed 75%, **Group B** showed 94% and **Group C** showed 12% decrease in burning sensation in mouth	Lycopene was effective in improving mouth opening and alleviating pain and burning sensation when used in combination with triamcinolone acetonide 0.1%. No side effects or intolerance to lycopene were reported.

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Table 16.1 (continued)

Author	Type of study[a]	Sample	Intervention	Duration of treatment/ Follow-up	Mouth opening assessment (Measured with vernier caliper) B: baseline; A: after intervention; F: after follow-up	Burning sensation assessment (Measured with visual analog scale, VAS) B: baseline; A: after the intervention; F: after follow-up	Observations reported by authors
Karemore et al. [31]	Randomized controlled trial Lycopene Placebo	92 OSF patients	**Lycopene group:** (n = 46) 8 mg soft gel Lycored™ orally per day in two divided doses of 4 mg each **Placebo group:** (n = 46) soft gel placebo twice a day orally	3 months	**Lycopene group:** Improvement at exit: 32 (69.56%) No improvement at exit: 14 (30.63%) Mean diff. in MO: 4.46 ± 3.65 mm **Placebo group:** Improvement at exit: 6 (13.04%) No improvement at exit: 40 (86.95%) Mean diff. in MO: 1.13 ± 1.6 mm	**Lycopene group:** Baseline: Present 46, Absent 0, Reduced 0 Exit: Present 1, Absent 31, Reduced 14 **Placebo group:** Baseline: Present 46, Absent 0, Reduced 0 Exit: Present 1, Absent 7, Reduced 38	Lycopene appears to be a very promising drug in the management of OSF.
Selvam et al. [35]	Randomized controlled trial Lycopene + Dexamethasone + Hyaluronidase Antioxidant + Dexamethasone + Hyaluronidase Dexamethasone + Hyaluronidase	45 OSF patients	**Group A** (n = 15): Oral Lycopene capsules 16 mg (Lycostar®, Lycopene 5000 µg + micronutrients), one capsule/day along with biweekly intralesional injections of Dexamethasone 1.5 ml and Hyaluronidase 1500 IU mixed with lignocaine. **Group B** (n = 15) Oral antioxidant capsules (Multivitamin A–Z soft capsules), one capsule/day along with biweekly intralesional injections of Dexamethasone 1.5 ml and Hyaluronidase 1500 IU mixed with lignocaine. **Group C** (n = 15): Biweekly intralesional injections of Dexamethasone 1.5 ml and Hyaluronidase 1500 IU with lignocaine	6 weeks	Improvement in mouth opening between baseline and end of 6 weeks **Group A:** 4.9 ± 2.5 mm **Group B:** 4.3 ± 0.8 mm **Group C:** 3.4 ± 0.5 mm	**Group A:** B: 7.5 A: 0 **Group B:** B: 7.0 A: 0 **Group C:** B: 7.5 A: 0	Lycopene with intralesional steroids showed greater improvement in mouth opening than antioxidants with intralesional steroids. However, the results of both groups did not differ enough to be statistically significant ('p' > 0.05). Lycopene in combination with intralesional steroids and hyaluronidase is highly efficacious in improving mouth opening and reducing other symptoms.

Singh et al. [28]	Prospective, randomized, and blinded controlled study Lyocpene Betamethasone	44 OSF patients Oral prophylaxis advised. Counseled to quit the areca nut practice.	**Group I:** (n = 22) 10,000 mcg of lycopene (*Lyconex soft gels*) daily in two equally divided doses **Group II:** (n = 22) Intralesional injections of betamethasone (1 mL ampule of 4 mg each) twice weekly	Duration of treatment: 2 months Follow-up 2 months after completion of treatment; total duration 4 months	**Group I:** Lycopene B: 3.19 ± 0.55 mm A: 4.39 + 0.29 mm **Group II:** Betamethasone B: 3.00 ± 0.82 mm A: 3.39 ± 0.63 mm	**Group I:** Lycopene B: 51.82 ± 24.08. A: 94.5% reduction **Group II:** Betamethasone B: 49.55 ± 24.15. A: 54.1% reduction	Lycopene capsules (Lyconex; lycopene with vitamins) are better than intralesional betametha-sone injections in improving mouth opening and decreasing burning sensation.
Elizabeth et al. [36]	Randomized controlled trial Lycopene + Triamcinolone + Hyaluronidase Triamcinolone + Hyaluronidase	38 OSF patients Complete oral prophylaxis and counseling on improving oral hygiene and motivated to stop areca nut use.	**Group 1:** (n = 19): Oral Lycopene capsules 16 mg, one capsule/day along with intralesional injections of Triamcinolone (Kenacort) 40 mg/ml, 1 ml and Hyaluronidase 1500 IU mixed with 2% lignocaine once a week. **Group 2:** (n = 19): Intralesional Injections of Triamcinolone (Kenacort) 40 mg/ml, 1 ml, and Hyaluronidase 1500 IU mixed with 2% Lignocaine once a week.	Duration of treatment: 6 weeks Follow-up post-treatment: 6 months	**Group 1:** Lycopene + cor-ticosteroid injections B: 1.5 cm F: 4.5 ± 1.5 cm **Group 2:** Corticosteroid injections F: 3.5 ± 1.5 cm	--------	Lycopene in combination with intralesional steroids and hyaluronidase is highly efficacious in improving the mouth opening compared to intralesional steroid and hyaluronidase injections alone.
Subramaniam et al. [37]	Randomized controlled trial Lycopene Ultrasound + Muscle kneading exercises	30 OSF patients	**Group A** (n = 15): 16 mg of lycopene (Lycored) daily in 2 equally divided doses (8 mg each) **Group B** (n = 15): 15 consecutive sittings of therapeutic ultrasound of 5 min to left and right cheek each for 15 consecutive days, with permissible 1 day off each week. (Frequency of 3 MHz and Intensity 0.8 to 1.5 W/cm^2). Muscle kneading exercises: buccinator stretch, finger kneading and TMJ mobilization (anterior capsule stretch, TMJ joint mobility exercises) were given.	Duration of treatment: 6 weeks Followed up until 3 months	Mean improvement in mouth opening (mm) **Group A:** Lycopene F: 5.10 mm **Group B:** Ultrasound F: 6.20 mm	Mean improvement in burning sensation **Group A:** Lycopene F: 2.73 **Group B:** Ultrasound F: 1.4	The mean improvement in tongue protrusion and burning sensation is significantly better with lycopene compared to therapeutic ultrasound. The mean improvement in mouth opening is better in ultrasound group but the difference is not statistically significant. The authors suggest that lycopene in isolation can be used as the initial treatment modality of OSF to relieve burning sensation, but if used in conjunction with therapeutic ultrasound will improve mouth opening.

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Table 16.1 (continued)

Author	Type of study[a]	Sample	Intervention	Duration of treatment/ Follow-up	Mouth opening assessment (Measured with vernier caliper) B: baseline; A: after intervention; F: after follow-up	Burning sensation assessment (Measured with visual analog scale, VAS) B: baseline; A: after the intervention; F: after follow-up	Observations reported by authors
Arshad et al. [39]	Randomized controlled trial Methylprednisolone Lycopene Methylprednisolone + Lycopene	45 OSF patients	**Group A** (n = 15): Methylprednisolone 20 mg/0.5 ml preparation was injected every month, at a single site on the buccal mucosa, bilaterally (40 mg in total) **Group B** (n = 15): Lycopene 10 mg soft gels **Group C** (n = 15): Intralesional methylprednisolone and lycopene capsules	Duration of treatment: 6 months Follow-up post-treatment: 6 months	**Group A:** B: 15.67 ± 6.46 mm A: 19.13 ± 6.79 mm **Group B:** B: 17.07 + 4.2 mm A: 19.53 ± 4.54 mm **Group C:** B: 17.87 ± 5.23 mm A: 24.87 + 5.9 mm	----------	The most favorable response in terms of clinical efficacy was derived from the combination of intralesional steroid and oral antioxidant therapy in patients abstaining from areca nut habit and indulging in rigorous physiotherapy.
Kopuri et al. [44]	Randomized controlled trial Lycopene Curcumin	30 OSF patients	**Group A** (n = 15): Lycopene capsules Lycored 8 mg/day in 2 divided doses (Lycopene (2000 mcg), zinc (7.5 mg), and selenium (35 mcg)). **Group B** (n = 15): Curcumin Haridra 800 mg/day in 2 divided doses (Curcuma longa 400 mg)	3 months	**Group A:** Lycopene B: 24.26 ± 1.53 mm A: 30.07 ± 1.1 mm **Group B:** Curcumin B: 26.07 ± 2.66 mm A: 29 ± 2.27 mm	**Group A:** Lycopene B: Mild 0, Moderate 11, Severe 4 A: Mild 8, Moderate 7, Severe 0 **Group B:** Curcumin B: Mild 0, Moderate 13, Severe 2 A: Mild 13, Moderate 15, Severe 0	Lycopene has produced better improvement in mouth opening and reduction in fibrous bands than curcumin. Curcumin has produced better improvement in burning sensation and blanching. Overall, a better response was seen to lycopene, than to curcumin.
Saran et al. [34]	Randomized clinical trial Lycopene Curcumin	60 OSF patients Counseled to quit the areca nut practice.	**Group A:** (n = 30) lycopene capsules (Cap Lycored; lycopene: 4 mg, zinc: 7.5 mg, selenium: 35 mg) orally given per day in two divided doses **Group B:** (n = 30) curcumin tablets (Turmix; curcuma longa extract: 300 mg and piper nigrum: 5 mg) one tablet thrice daily per day	3 months	**Group A:** Lycopene B: 3.17 ± 0.08 cm A: 3.52 ± 0.07 cm **Group B:** Curcumin B: 3.32 ± 0.07 cm A: 3.52 ± 0.08 cm	**Group A:** Lycopene B: 65.83 ± 3.98 A: 0.00 ± 0.00 **Group B:** Curcumin B: 62.33 ± 5.22 A: 0.00 ± 0.00	Lycopene showed better results than curcumin in improving mouth opening; both drugs were equally effective in decreasing burning sensation in OSF patients. Lycopene and curcumin were safe, nontoxic, and effective alternatives to conventional drugs.

Johny et al. [33]	Nonrandomized controlled trial Lycopene Lycopene + hyaluronidase	45 OSF patients (with Grade 2 OSF)	**Group A:** (n = 15): LycoRed™, containing 100% natural lycopene, with zinc, selenium, and phytonutrients) 16 mg daily **Group B:** (n = 15): LycoRed™ along with hyaluronidase (Hynidase) intralesional injection 1500 IU twice weekly **Group C:** (n = 15): Placebo capsules	6 months	% in improvement **Group A:** Lycopene 100% complete response **Group B:** Lycopene with hyaluronidase 100% complete response **Group C:** Placebo 46.2%	% in improvement **Group A:** Lycopene 100% partial response **Group B:** Lycopene with hyaluronidase 7.2% complete response and remaining partial response **Group C:** Placebo 38.5%—partial response, 30.8% stable, 30.8% showed progression	Hyaluronidase with lycopene when compared with lycopene only showed better results but it was not statistically significant. The authors suggest that lycopene appears to be a very promising antioxidant in the management of oral submucous fibrosis, both in clinical and symptomatic improvement.
Bhowmick et al. [40]	Clinical prospective study Lycopene Lycopene + Hyaluronidase	50 OSF patients Counseled to quit the areca nut practice. Mouth exercises advised.	**Group A:** (n = 25) Lycopene (Cap Lycored™) 8 mg daily in two equally divided dose **Group B:** (n = 25) Lycopene (Cap Lycored™) 8 mg daily in two equally divided doses + intralesional injections of 1500 IU of Hyaluronidase (Hynidase) weekly	3 months	**Group A:** Lycopene B: 25.20 ± 3.01 mm A: 29.36 ± 3.17 mm **Group B:** Lycopene + Hyaluronidase B: 24.58 ± 3.90 mm A: 32.41 ± 3.22 mm	**Group A:** Lycopene B: 7.16 ± 0.96 A: 0.88 ± 0.72 **Group B:** Lycopene + Hyaluronidase B: 6.47 ± 1.10 A: 0.20 ± 0.12	Combination therapy of lycopene with intralesional corticosteroids was comparatively more effective in relieving clinical symptoms.
Antioxidant: Curcumin							
Hazarey et al. [53]	Randomized clinical trial Curcumin Clobetasol propionate	30 OSF patients with mouth opening 15–30 mm Counseled to quit the areca nut practice Physiotherapy for both groups using a mouth exercise device (MED). The patients were instructed to exercise for 20 min (10 min on each side) with the help of the MED three times a day for 3 months.	**Test group:** (n = 15) 400 mg curcumin (Longvida lozenges) 2 g of daily dosage **Control group:** (n = 15) Topical clobetasol propionate (Tenovate™) 3 times daily	3 months	**Test group:** Curcumin B: 21.13 ± 4.54 mm A:27.06 ± 4.80 mm **Control group:** clobetasol propionate B: 23.93 ± 2.98 mm A:26.6 ± 4.06 mm	**Test group:** Curcumin B: 64 (42–73) A: 7 (3–24) **Control group:** clobetasol propionate B: 34 (14.5–64.5) A: 8 (3.5–37)	Curcumin was effective and the results achieved were sustained through a follow-up span of 9 months. A combination strategy comprising curcumin treatment + physiotherapy + areca nut cessation provides favorable outcome.

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Table 16.1 (continued)

Author	Type of study[a]	Sample	Intervention	Duration of treatment/ Follow-up	Mouth opening assessment (Measured with vernier caliper) B: baseline; A: after intervention; F: after follow-up	Burning sensation assessment (Measured with visual analog scale, VAS) B: baseline; A: after the intervention; F: after follow-up	Observations reported by authors
Piyush et al. [52]	Randomized placebo-controlled parallel clinical study Curcumin Lycopene Placebo	90 OSF patients	**Group A:** (n = 30) curcumin (300 mg) twice daily **Group B:** (n = 30) Lycopene capsules (8 mg) twice daily **Group C:** (n = 30) Placebo capsules once daily	Active treatment:6 months Clinical evaluation: 9 months	**Group A:** Curcumin B:25.40 ± 7.2 mm A:29.35 ± 8.8 mm **Group B:** Lycopene B:24.43 ± 6.6 mm A: 28.57 ± 7.2 mm **Group C:** Placebo B:28.97 ± 9.7 mm A:30.37 ± 10.7 mm	**Group A:** Curcumin B: 6.03 ± 3.1 A: 1.17 ± 1.2 **Group B:** Lycopene B:6.80 ± 2.2 A: 1.77 ± 1.5 **Group C:** Placebo B:5.80 ± 2.4 A:4.23 ± 2.2	The therapeutic efficacy of curcumin and lycopene therapeutic were found to be almost equal.
Antioxidant: Aloe vera							
Patil et al. [63]	Prospective study Lycopene Aloe vera	120 OSF patients Counseled to quit the areca nut practice.	**Group A:** (n = 60) 8 mg lycopene (Lycored™) in two divided doses of 4 mg **Group B:** (n = 60) 5 mg aloe vera gel topically thrice daily	3 months	**Group A:** Lycopene B: 18.2 ± 2.1 mm A: 25.9 ± 2.3 mm **Group B:** Aloe vera B: 17.7 ± 2.2 mm A: 22.1 ± 1.9 mm	**Group A:** Lycopene B: present: 60 A: present:7, absent:32, reduced:21 **Group B:** Aloe vera B: present: 60 A: present:9, absent:29, reduced:22	Lycopene comparatively showed better improvements than aloe vera. Though few patients reported nausea with lycopene, it was well tolerated.
Nerkar Rajbhoj et al. [54]	Randomized clinical trial Curcumin Aloe vera	60 OSF patients Counseled to quit the areca nut practice.	**Group A:** (n = 30) 5 mg curcumin gel (Curenext oral gel) 1 mg applied 3–4 times a day to achieve a total of 5 mg per day **Group B:** (n = 30) 5 mg Aloe Vera gel (1 mg of gel 3–4 times a day)	6 months	**Group A:** Curcumin gel B: 30.5 ± 6.30 mm A: 32.23 ± 6.25 mm **Group B:** Aloe Vera gel B: 31.500 ± 6.74 mm A: 32.867 ± 6.66 mm	**Group A:** Curcumin B: 7.50 ± 1.55 A: 4.43 ± 1.81 **Group B:** Aloe Vera B: 7.33 ± 1.47 A: 2.83 ± 1.66	Reduction in burning sensation was statistically significant in the aloe vera group when compared to the curcumin group. Both can be an effective alternative to conventional treatment.
Antioxidant: Spirulina							
Shetty et al. [66]	Intervention study Spirulina + Betamethasone Placebo + Betamethasone	40 OSF patients Counseled to quit the areca nut practice.	**Group A:** (n = 20) Spirulina 500 mg orally twice daily **Group B:** (n = 20) placebo capsules orally twice daily Inj. Betamethasone 4 mg/ml biweekly for both groups	3 months	**Group A**: Spirulina B: 31.05 mm A: 36.8 mm **Group B**: Placebo B: 32.95 mm A: 35.8 mm	**Group A:** Spirulina B: 5.8 A:4.6 **Group B:** Placebo B:5.3 A:2.65	Comparatively better improvement in clinical symptoms was observed in Spirulina group.

Mulk et al. [65]	Randomized clinical trial Pentoxifylline Spirulina	40 OSF patients 20 min of mouth exercise was advised.	**Group 1:** (n = 20) Oral pentoxifylline 400 mg twice daily **Group 2:** (n = 20) Oral spirulina capsules 0.5 g twice daily	4 months	**Group 1:** Pentoxifylline B:2.63 ± 0.78 mm A:2.93 ± 0.77 mm **Group 2:** Spirulina B:3.38 ± 1.29 mm A:3.73 ± 1.26 mm	**Group 1:** Pentoxifylline B:6.05 ± 1.67 A:1.60 ± 0.94 **Group 2:** Spirulina B:6.95 ± 1.00 A:1.55 ± 1.32	Spirulina fared better in reducing burning sensation while statistically nonsignificant results were recorded with mouth opening. The authors state that spirulina is relatively safe over pentoxifylline as it is known to cause adverse effects.
Patil et al. [64]	Randomized clinical trial Spirulina Aloe vera	42 OSF patients Counseled to quit the areca nut practice.	**Group A:** (n = 21) 500 mg spirulina in two divided doses **Group B:** (n = 21) Aloe vera gel 5 mg topically thrice daily	3 months	**Group A:** Spirulina B: 19.9 ± 2.1 mm A: 25.8 ± 2.5 mm **Group B:** Aloe vera B: 19.1 ± 2.7 mm A: 23.9 ± 1.9 mm	**Group A:** Spirulina B: present:21 A: present:3, absent:12, reduced:6 **Group B:** Aloe vera B: present:21 A: present:5, absent:9, reduced: 7	Though similar reduction in burning sensation was noted, spirulina fared better in improving mouth opening.
Vasodilators: Pentoxifylline (PTX)							
Mehrotra et al. [75]	Randomized controlled trial Placebo (Multivitamin) Pentoxifylline	62 OSF patients Counseled to quit the areca nut practice.	**Group A:** (n = 30) placebo (multivitamin) therapy **Group B:** (n = 32) Tab. Pentoxifylline 400 mg for 7 months (inductive regime for the initial 30 days at a reduced dosage of 2 tablets daily followed by 3 tablets daily for 6 more months)	Treatment duration: 7 months Clinical follow-up: 18 months	Mouth opening improved by 15.4% in placebo group and 35.7% in PTX	Burning sensation improved by 39.4% in placebo group and 86.6% in PTX.	Authors reported a statistically significant improvement in PTX group. No local or systemic side effect were found in the placebo treatment group. However, side effects were observed with the use of PTX. The most frequent side effects were dyspepsia and nausea, which were observed in 24% of the patients. Bloating and flatus were the complaints of 18% of patients and headache, vomiting, anxiety, and tremors were observed in 2% of patients. These symptoms were relatively mild in nature, lasted for 1–2 weeks, and settled on their own without cessation of drug or requiring medication.

(continued)

Table 16.1 (continued)

Author	Type of study[a]	Sample	Intervention	Duration of treatment/ Follow-up	Mouth opening assessment (Measured with vernier caliper) B: baseline; A: after intervention; F: after follow-up	Burning sensation assessment (Measured with visual analog scale, VAS) B: baseline; A: after the intervention; F: after follow-up	Observations reported by authors
Patil et al. [85]	Prospective study Pentoxifylline Placebo (Multivitamin)	106 OSF patient	**Group A:** (n = 53) 400 mg pentoxifylline twice daily **Group B:** (n = 53) Placebo (Multivitamins)	3 months	**Group A:** PTX B: 20.2 ± 2.1 mm A: 27.1 ± 2.3 mm **Group B:** Placebo B: 20.9 ± 2.1 mm A: 24.9 ± 2.1 mm	**Group A:** PTX B: present 53, absent 0, reduced 0 A: present 16, absent 23, reduced 14 **Group B:** Placebo B: present 53, absent 0, reduced 0 A: present 27, absent 17, reduced 9	The patients in PTX group showed significant improvement in all the parameters measured, mouth opening, tongue protrusion, pain associated with the condition, burning sensation, and difficulty in speech and swallowing. However, few patients from PTX complained of bloating, nausea, anxiety, and dyspepsia.
Prabhu et al. [83]	Randomized clinical trial Pentoxifylline + Conventional therapy Conventional therapy	30 OSF patients	**Interventional group:** (n = 15) PTX initial 15 days of 2 tablets daily followed by 3 tablets daily + Conventional therapy (intralesional corticosteroid, hyaluronidase, and placentrix injections + local heat therapy and mouth stretching exercises) **Control group:** (n = 15) conventional therapy alone	4 months	**Interventional group:** PTX B: 19.93 ± 3.13 mm A:21.00 ± 4.12 mm **Control group:** Conventional therapies B:22.93 ± 3.56 mm A:23.80 ± 2.91 mm	**Interventional group:** PTX B: 0.93 ± 0.88 A:0.40 ± 0.51 **Control group:** Conventional therapies B:1.00 ± 0.85 A:0.33 ± 0.49	PTX presented vasodilatation at the histological level; however clinical improvement is at par with other drugs. Its use is questionable given the long duration of treatment and its response.

Sadaksharam et al. [86]	Single-blinded randomized clinical trial Pentoxifylline Dexamethasone + Hyaluronidase	30 OSF patients Counseled to quit the areca nut practice.	**Group A:** (n = 15) Oral pentoxifylline 400 mg thrice daily after meals for 3 months **Group B:** (n = 15) 0.5 ml of local anesthesia with 2 ml of dexamethasone + 1500 I.U of hyaluronidase biweekly for 6 weeks	Clinical follow-up: 6 months	**Group A:** PTX B: 25.66 ± 5.33 mm A: 30.20 ± 6.03 mm **Group B:** Dexamethasone + Hyaluronidase B: 27.20 ± 5.70 mm A: 29.93 ± 5.80 mm	**Group A:** PTX B: 6.66 ± 2.58 A: 0.00 ± 0.00 **Group B:** Dexamethasone + Hyaluronidase B: 6.53 ± 2.26 A: 0.13 ± 0.35	Both groups reported satisfactory improvement. A highly significant reduction in burning sensation, improvement in mouth opening, and changes in submucosal thickness were noticed in both groups, and significant improvement in echogenicity in both groups was noticed. However, the pentoxifylline group showed marginally better improvement than the dexamethasone group. PTX being well tolerated, noninvasive, and cost-effective could be considered as an alternative where intralesional steroids or hyaluronidase is contraindicated.
Bhambal et al. [87]	Prospective case-control clinical study Pentoxifylline Multivitamin	80 OSF patients Counseled to quit the areca nut practice.	**Experimental drug group (EDX):** (n = 40) Pentoxifylline (Trental) 200 mg thrice daily for the first 30 days followed by 400 mg thrice daily for 2 more months **Standard drug group (SDX):** (n = 40) Multivitamin capsules (B-complex one capsule before sleep daily)	3 months	**EDX:** Pentoxifylline B:26.79 ± 7.8 mm A:29.13 ± 7.87 mm **SDX:** Multivitamin B:25.75 ± 7.93 mm A:26.96 ± 7.33 mm	**EDX:** Pentoxifylline Mean ranks B:33.97 A:26.94 **SDX:** Multivitamin B:31.03 A:38.06	Pentoxifylline was found to be a superior drug to the multivitamin drug. Hence it is suggested as an additional therapy in the routine management of OSF.
Bishnoi et al. [89]	Randomized clinical trial Pentoxifylline Multivitamin	40 OSF patients Counseled to quit the areca nut practice.	**Study Group:** (n = 20) Pentoxifylline extended-release tablets, 400 mg twice daily **Control group:** (n = 20) Multivitamin capsule twice daily after food	3 months	**Study group:** Pentoxifylline B: 26.32 ± 4.34 mm A: 30.48 ± 4.28 mm **Control group:** Multivitamin B: 25.57 ± 3.97 mm A: 26.17 ± 3.61 mm	**Study group:** Pentoxifylline B: 4.1 ± 1.34 A: 2.3 ± 1.31 **Control group:** Multivitamin B: 4.3 ± 1.53 A: 3.9 ± 1.95	Pentoxifylline showed a significant increase in mouth opening, decrease in burning sensation, and pain as compared with multivitamin capsules. However, occasional gastrointestinal disturbances reported may lead to poor patient compliance. Pentoxifylline can be safer and better alternative treatment for oral submucous fibrosis.

(continued)

Table 16.1 (continued)

Author	Type of study[a]	Sample	Intervention	Duration of treatment/ Follow-up	Mouth opening assessment (Measured with vernier caliper) B: baseline; A: after intervention; F: after follow-up	Burning sensation assessment (Measured with visual analog scale, VAS) B: baseline; A: after the intervention; F: after follow-up	Observations reported by authors
Vasodilators: Isoxsuprine							
Bhadage et al. [91]	Randomized controlled trial Isoxsuprine Dexamethasone + Hyaluronidase Placebo (fine sugar)	40 OSF patients Counseled to quit the areca nut practice. Physiotherapy was advised.	**Group A:** (n = 15) Oral 10 mg isoxsuprine tablets (Tablet Duvadilan) 4 times a day **Group B:** (n = 15) intralesional injections of 2 ml dexamethasone (Injection Dexona) + 1500 IU hyaluronidase (Injection Hyalase) twice a week bilaterally **Group C:** (n = 10) orally placebo capsules containing fine sugar	Duration of treatment: 6 weeks Follow-up: 4 months	**Group A:** Isoxsuprine B: 26.5 ± 8.5 mm A: 29.2 ± 8.9 mm F: 29.5 ± 8.9 mm Average improvement: 4 mm **Group B:** Dexamethasone + Hyaluronidase B: 22.9 ± 3.5 mm A: 26.7 ± 3.1 mm F: 26.9 ± 3.1 mm Average improvement: 3 mm **Group C:** Placebo B: 28.3 ± 6.7 mm A: 28.5 ± 6.8 mm F: 29.0 ± 7.1 mm	**Group A:** Isoxsuprine B: 5.53 ± 3.13 A: 0.53 ± 1.41 F: 0.67 ± 1.80 **Group B:** Dexamethasone + Hyaluronidase B: 5.80 ± 2.93 A: 0.00 ± 0.00 F: 0.00 ± 0.00 **Group C:** Placebo B: 5.80 ± 1.03 A: 5.20 ± 1.62 F: 0.00 ± 0.00	Though dexamethasone and hyaluronidase injections alleviate pain at a faster pace, the benefit of isoxsuprine is that it does not require frequent visits to the clinic. Oral isoxsuprine, as well as dexamethasone with hyaluronidase injections combined with physiotherapy, alleviate symptoms of oral submucous fibrosis. significantly more efficiently than physiotherapy alone. They suggest that dexamethasone and hyaluronidase may hold a risk of tissue atrophy and injury while isoxsuprine may present with systemic effects with large doses of administration.
Biogenic stimulation: Placental extract							
Katharia et al. [94]	Prospective study Placental extract	22 OSF patients	2 ml of Inj. Placental extract (Inj.Placentrex) was given locally in predetermined areas once a week	1 month	Based on mouth opening scores B: 5.13 ± 0.29 mm A: 3.68 ± 0.25 mm	B: 2.81 ± 0 10 A: 1.68 ± 0.13	Maximum improvement (40.21%) was observed in burning sensation followed by 38.55% in mucosal color; 30.59% in fibrous bands; 28.26% in mouth opening and 18.46% in protrusion of the tongue. Statistically significant changes were observed with improvement in mouth opening, change in color, and reduction in fibrous band.

Naik et al. [97]	Comparative case series analysis Triamcinolone + Hyaluronidase Placental extract	60 OSF patients	**Group A:** (n = 30) Triamcinolone acetonide (10 mg/ml) + hyaluronidase (1500 IU) at weekly intervals **Group B:** (n = 30) 2 ml of placentrex injection intralesionally at weekly interval	8 weeks	**Group A:** Corticosteroid B: 16.27 mm A: 35.9 mm **Group B:** Placentrex B: 15.83 mm A: 33.8 mm	**Group A:** Corticosteroid B:2.36 A: 0.96 **Group B:** Placentrex B:2.56 A: 0.86	A combination of triamcinolone acetonide and intralesional hyaluronidase was more effective than intral-esional placental extract in the treatment of OSF. However, placental extract injections are cost-effective. No side effects were seen in both study groups.
Raj et al. [98]	Longitudinal study Placental extract	24 OSF patients	**Group A:** (n = 12) patients with inter-incisal mouth opening (MO) of less than 25 mm (moderately advanced OSF). **Group B:** (n = 12) patients with inter-incisal mouth opening between 26 and 30 mm (moderate OSF). Patients of both groups received 2 ml of placental extract submucosal injection alternatively on right and left buccal mucosa once a week.	10 weeks	**Group A:** MO < 25 mm B: 22.5 mm A: 27.08 mm Avg.increase:4.58 mm **Group B:** MO 26–30 mm B: 27.5 mm A: 33.67 mm Avg.increase: 6.16 mm	All the patients had moderate to severe burning sensations during their first visit. After treatment, there was reduction in the severity of the burning sensation; with occurrence of mild burning sensation while having spicy food.	The authors conclude that the treatment of OSF with placental extract injection is more effective in moderate fibrosis compared to moderately advanced fibrosis. The placental extract is also helpful in reducing the burning sensation in OSF patients.
Dinesh et al. [99]	Prospective study Placental extract	30 OSF patients	2 ml of Inj. Placentrex (0.1–0.8 gm, % nitrogen/ml) is given submucosally using a 2 ml syringe with a 24-gauge needle retromolar trigone once a week	4 weeks	Mean inter-incisal distance (Mean ± SD) B: 2.13 ± 0.74 cm A: 2.74 ± 0.78 cm Improvement (%): 28.63%	B: 2.2 ± 0.71 A: 0.9 ± 0.88 Improvement (%): 51%	Significant improvement in mouth opening, color of the mucosa, tongue protrusion, and reduction in burning sensation is observed with the use of the placental extract. The authors conclude that placental extract produces long-standing effects and can be used in the early stages of oral submucous fibrosis with good results.
Shah et al. [101]	Retrospective study Placental extract + Dexamethasone Hyaluronidase + Dexamethasone	25 OSF patients (Stage III OSF)	**Group A:** (n = 15) placental extract (2 ml) + dexamethasone (4 mg/ml) **Group B:** (n = 10) hyaluronidase (1500 IU) + dexamethasone (4 mg/ml)	8 weeks	**Group A:** B: 26.5 ± 6.52 mm A: 30.03 ± 6.42 mm **Group B:** B: 21.7 ± 6.29 mm A: 25.35 ± 7.11 mm	**Group A:** B: 6.67 ± 0.97 A: 1.53 ± 0.99 **Group B:** B: 6.40 ± 1.17 A: 1.50 ± 1.71	The pre- and post-treatment differences were found to be statistically significant for both groups (p < 0.05). Both the treatment regimens studied were equally effective in the treatment of OSF.

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Table 16.1 (continued)

Author	Type of study[a]	Sample	Intervention	Duration of treatment/ Follow-up	Mouth opening assessment (Measured with vernier caliper) B: baseline; A: after intervention; F: after follow-up	Burning sensation assessment (Measured with visual analog scale, VAS) B: baseline; A: after the intervention; F: after follow-up	Observations reported by authors
Priyankar et al. [100]	Randomized single-blinded comparative study Placental extract Dexamethasone Hyaluronidase	30 OSF patients (stage II)	**Group A:** (n = 10) 2 ml intralesional placental extract (Placentrex) mixed with 2 ml of 2% lignocaine HCL weekly **Group B:** (n = 10) Intralesional injection of dexamethasone 1.5 ml, mixed with 2 ml of 2% lignocaine HCL weekly. **Group C:** (n = 10) Intralesional hyaluronidase 1500 IU mixed with 2 ml of 2% lignocaine HCL weekly. Patients were advised to do mouth opening exercises for 30 min daily without any dropout	2 months	**Group A:** Placentrex B: 18.49 ± 2.75 mm A: 26.51 ± 4.10 mm Avg. improvement: 8.02 mm **Group B:** Dexamethasone B: 17.11 ± 3.15 mm A: 24.39 ± 4.43 mm Avg. improvement: 7.28 mm **Group C:** Hyaluronidase B: 16.94 ± 2.45 mm A: 26.14 ± 3.05 mm Avg. improvement: 9.20 mm	**Group A:** Placentrex B: 8.00 ± 0.65 A: 3.10 ± 1.05 **Group B:** Dexamethasone B: 8.70 ± 1.05 A: 2.00 ± 0.35 **Group C:** Hyaluronidase B: 8.70 ± 0.65 A: 5.50 ± 1.01	Improvement in mouth opening was observed maximum with intralesional injection of hyaluronidase followed by placental extract and then dexamethasone. Improvement in burning sensation was observed maximum with intralesional injection of dexamethasone followed by placental extract and comparatively less improvement was seen with hyaluronidase.
Shinde et al. [102]	Prospective randomized single-blinded study Placental extract Triamcinolone acetonide	40 OSF patients Counseled to quit the areca nut practice.	**Group P:** (n = 20) intralesional injections of 2 ml aqueous placental extract bilaterally at weekly intervals **Group T:** (n = 20) triamcinolone acetonide (40 mg/ml; 1 ml) bilaterally at weekly intervals	10 weeks	**Group P:** Placental extract B:21.25 mm A:25.15 mm **Group T:** Triamcinolone B:21.50 mm A:25.20 mm	**Group P:** Placental extract B: 67.50 A: 35.50 **Group T:** Triamcinolone B:66.50 A:25.50	Intralesional triamcinolone acetonide was found to be a superior intralesional drug when compared to placental extract.
Kale et al. [103]	Randomized clinical trial Triamcinolone + Hyaluronidase Placental extract	60 cases diagnosed with OSF with mild to moderately restricted mouth opening	**Group A:** (n = 30) Intralesional regimen of injection triamcinolone 40 mg and hyaluronidase 1500 IU **Group B:** (n = 30) 2 ml injection of placental extract alone Both the groups were treated with oral antioxidants and physiotherapy simultaneously along with intralesional injections.	6 weeks Follow-up: 3 months	Improvement in mouth opening (mm) **Group A**: Corticosteroid—10 mm **Group B**: Placental extract—7 mm	**Group A:** Corticosteroid 21 patients showed 75% improvement and 7 patients between 50 and 75% **Group B:** Placental extract—14 patients showed 75% improvement and 11 patients between 50 and 75%	Improvement in mouth opening and reduction in burning sensation was better with the use of corticosteroid than placental extract. However, no significant difference was observed between the two drug regimens. The authors suggest that intralesional injection can give symptomatic relief and in addition, cessation of habits, antioxidants oral hygiene helps in the improvement of OSF.

Vitamins and micronutrients							
Thakur et al. [109]	Prospective clinical study Micronutrient supplements + Physiotherapy exercises Physiotherapy exercises Micronutrient supplements	64 OSF patients Counseled to quit the areca nut practice.	**Group I:** (n = 24) micronutrient supplement (vitamins, minerals, and omega-three fatty acid) in the form of capsule MMO3 + physiotherapy exercises four times per day at an interval of 2–3 h **Group II:** (n = 24): physiotherapy exercises four times per day at an interval of 2–3 h **Group III:** (n = 24): micronutrients supplements alone	6 weeks	Maximum improvement in group I followed by III and then group II.	Groups I and III showed improvement within the first week of intervention	Micronutrients along with physiotherapy substantially improved the mouth opening.
Nallapu et al. [106]	Comparative study Dexamethasone + Hyaluronidase + Lignocaine Dexamethasone + Hyaluronidase + Lignocaine + Vitamin E	20 OSF patients	**Group A:** (n = 10) Intralesional bilateral injections of dexamethasone 2 ml (2 mg/ml), hyaluronidase (1500 IU), and 0.2 cc lignocaine (2%) weekly once **Group B:** (n = 10) Intralesional injections of dexamethasone + hyaluronidase + lignocaine + oral vitamin E capsules of 400 IU once daily	8 weeks	**Group A:** Dexamethasone + Hyaluronidase + Lignocaine Post-treatment: 5-moderate, 4-mild,1-no improvement **Group B:** Dexamethasone + Hyaluronidase + Lignocaine + Vitamin E Post-treatment: 2-excellent, 5-moderate, 3-mild	**Group A:** Dexamethasone + Hyaluronidase + Lignocaine B: Absent-0; Present-10 A: Absent-9; Present-1 **Group B:** Dexamethasone + Hyaluronidase + Lignocaine + Vitamin E B: Absent-0; present-10 A: Absent-10; present-0	Vitamin E with conventional therapy presented better results.
Nayak et al. [108]	Clinical prospective study Lycopene Lycopene + Vitamin E Placebo	72 OSF patients Counseled to quit the areca nut practice.	**Group A:** (n = 24) 8 mg of lycopene soft gels (Lycored TM) in two equally divided doses **Group B:** (n = 24) 8 mg of lycopene + vitamin E (400 I.U.) + selenium (200 mcg) in two equally divided doses (LYC-O-MATO soft gels) **Group C:** Placebo capsules once daily	Treatment period: 3 months Clinical follow-up: 2 months	**Group A:** Lycopene B: 24.80 mm A: 32.60 mm **Group B:** Lycopene + Vitamin E B: 24.60 mm A: 33.60 mm **Group C:** Placebo B: 25.10 mm A: 27.10 mm	**Group A:** Lycopene A: present-4; Absent-20 **Group B:** Lycopene + Vitamin E A: present-2; absent-22 **Group C:** Placebo A: present- 8; absent −16	Lycopene when combined with vitamin E presented with better efficacy suggesting noninvasive management yielding significant improvement.

(continued)

Table 16.1 (continued)

Author	Type of study[a]	Sample	Intervention	Duration of treatment/ Follow-up	Mouth opening assessment (Measured with vernier caliper) B: baseline; A: after intervention; F: after follow-up	Burning sensation assessment (Measured with visual analog scale, VAS) B: baseline; A: after the intervention; F: after follow up	Observations reported by authors
Raizada et al. [110]	An open-labeled randomized controlled trial Placebo Omega 3	48 clinically confirmed OSF patients	**Group A:** (n = 24) placebo (lactose capsule) for 3 months **Group B:** (n = 24) 1gm of omega 3 (flaxseed oil) three times daily Both the groups received biweekly intralesional injections of dexamethasone 1.5 ml and hyaluronidase 1500 IU mixed with lignocaine for 6 weeks	3 months	Mean interincisal distance (Mean ± SD) **Group A:** Placebo: 24.46 ± 5.43 mm **Group B:** Omega 3: 25.46 ± 4.3 mm	Scoring with VAS **Group A:** Placebo: 8.54 ± 1.53 **Group B:** Omega 3: 8.58 ± 1.5	Statistically significant improvement in inter-incisal distance, burning sensation, tongue protrusion, and cheek flexibility was observed in patients receiving omega 3 when compared to those receiving placebo. Omega 3 in conjunction with intralesional injections is an effective therapy when compared to intralesional injections alone in treatment of patients with OSF (grade II and III) with no side effects.
Novel therapies: Oxitard, a herbal antioxidant that contains the extracts of *Mangifera indica, Withania somnifera, Daucus carota, Glycyrrhiza glabra, Vitis vinifera,* powders of *Emblica officinalis* and *Yashada bhasma*, and oils of *Triticum sativum.*							
Patil et al. [117]	Prospective, randomized, and single-blind study Oxitard Aloe vera	120 OSF patients Counseled to quit the areca nut practice.	**Group A:** (n = 60) 2 oxitard capsules twice daily **Group B:** (n = 60) 5 mg aloe vera gel topically thrice daily	Medical management: 3 months Clinical follow-up: 2 months	**Group A:** Oxitard B: 19.1 ± 2.4 mm A: 31.5 ± 2.9 mm **Group B:** Aloe vera B: 17.7 ± 2.2 mm A: 22.1 ± 1.9 mm	Reported no significant improvement in burning sensation [p = 0.002] among both the groups.	Significant improvement in mouth opening, burning sensation, tongue protrusion, difficulty in swallowing and speech, and pain associated with the lesion was reported in oxitard group compared to the aloe vera group. However, the authors reported that 8 patients in oxitard group experienced mild abdominal discomfort. No other side effects were reported.

Patil et al. [116]	Prospective study Oxitard Placebo	120 OSF patients Counseled to quit the areca nut practice.	**Group A:** (n = 60) 2 oxitard capsules twice daily **Group B:** (n = 60) placebo tablets twice daily	3 months	**Group A:** Oxitard B: 19.1 ± 2.4 mm A: 31.5 ± 2.9 mm **Group B:** Placebo B: 20.1 ± 2.1 mm A: 23.1 ± 1.9 mm	**Group A:** Oxitard B: present:60, absent-0, reduced −0 A: present:3, absent-43, reduced −14 **Group B:** Placebo B: present:60, absent-0, reduced −0 A: present:24, absent-20, reduced −16	Oxitard capsules can bring about significant clinical improvements in the symptoms like mouth-opening, tongue protrusion, burning sensation, difficulty in swallowing and speech, and pain associated with the lesion thereby improving the quality of life of the affected individuals. Changes in the severity of burning sensation, difficulty in swallowing and speech, and pain were noted but were poorly defined in the absence of a recognized and validated pain scale.
Novel therapies: Colchicine							
Krishnamoorthy et al. [19]	Randomized controlled trial Colchicine + Hyaluronidase Hyaluronidase + Hydrocortisone acetate	50 OSF patients	**Group 1:** Tablet colchicine orally, 0.5 mg twice daily and 0.5 ml intralesional injection Hyaluronidase 1500 IU into each buccal mucosa once a week. **Group 2:** 0.5 ml intralesional injection Hyaluronidase 1500 IU and 0.5 ml intralesional injection Hydrocortisone acetate 25 mg/ml in each buccal mucosa once a week alternatively.	12 weeks	----------	Thirty-three percent in group 1 got relief from burning sensation in the second week	Intergroup comparisons of increase in mouth opening and reduction in histological parameters indicated that patients who received colchicine with steroids responded better than patients who received corticosteroid injections alone.
Daga et al. [125]	Comparative study Colchicine + Hyaluronidase Colchicine + Triamcinolone acetonide	30 OSF (Grade II) patients Counseled to quit the areca nut practice.	**Group A:** (n = 15) Tablet colchicine 0.5 mg twice daily + intralesional injection of hyaluronidase 1500 IU weekly interval for 12 weeks **Group B:** (n = 15) Tablet colchicine 0.5 mg twice daily + intralesional injection of triamcinolone acetonide 10 mg/ml at weekly intervals for 12 weeks.	Duration of treatment: 12 weeks Outcome assessment was done at intervals of 3 weeks, 6 weeks, 3 months, and 6 months.	**Group A:** increase of about 8 mm after 6 months of follow-up **Group B:** increase of about 5 mm after 6 months of follow-up	**Group A:** Significant reduction except in 2 patients **Group B:** Persisted in 6 patients	The use of injection hyaluronidase with oral colchicine yielded better results in terms of increase in mouth opening and improvement in burning sensation without notable side effects.

[a] Type of study: as described by the author

16.2 Anti-inflammatory Agents

16.2.1 Corticosteroids

OSF is characterized by an initial phase of inflammation that progresses to fibrosis in the advanced stages. A systematic review of the medical interventions of OSF conducted by More et al. [4] shows that among all the interventions, corticosteroids have been widely used to reduce the burning sensation and pain symptoms. Kerr et al. [2] reviewed a total of 21 studies that used immunomodulatory agents to reduce the inflammatory component: 16 of these used injectable corticosteroids and 19 studies included the use of proteolytic enzymes to reduce fibrosis of which seven studies used hyaluronidases [2]. In Indian studies, steroids are the most commonly adopted medical treatment for OSF. Steroids have immunosuppressive and anti-inflammatory properties. They inhibit the action of soluble factors released by sensitized lymphocytes following activation by specific antigens and facilitate apoptosis of inflammatory cells. They reduce profibrotic inflammation and enhance profibrolytic immune-mediated pathways.

Several corticosteroids such as short-acting (hydrocortisone), intermediate-acting (triamcinolone), and long-acting (betamethasone and dexamethasone) have been utilized for the treatment of oral submucous fibrosis [5]. Most authors report their use in the early stages when a patient presents with a burning sensation. The topical corticosteroids commonly used are triamcinolone acetonide (0.1%), or Betamethasone (0.5%) applied locally for 3 months. In the advanced stage of the disease when palpable fibrous bands appear, submucosal injection of dexamethasone—4 mg/ml or triamcinolone diacetate—10 mg/ml, is given at multiple sites of the fibrosis, twice a week for 3 months. Hydrocortisone and methylprednisolone (20 mg/0.5 ml) have also been used as submucosal injections [3, 6].

Hyaluronidase degrades hyaluronic acid and lowers the thickness of intercellular cemental substances. Combination of corticosteroid and hyaluronidase shows better results in OSF due to deeper penetration of the steroid [3, 7]. Veedu et al. compared the effects of two conventional therapies, namely, submucosal injections of hyaluronidase (1500 I.U), dexamethasone (8 mg), or a combination of both (750 I.U and 4 mg), for a duration of 5 weeks. The authors concluded that hyaluronidase provided relief of the symptoms more rapidly [8]. Panigrahi et al. in their prospective study found that submucosal injection of a combination of triamcinolone acetonide and hyaluronidase is superior to triamcinolone alone, with respect to improvement in symptoms and patient convenience [9]. Goel et al. performed a hospital-based longitudinal study, on 270 OSF patients for a duration of 2 years. They proposed that both submucosal betamethasone and oral lycopene resulted in a significant enhancement in mouth opening. In stage II OSF patients, they found that the betamethasone group showed greater improvement in mouth opening of 9.47 ± 2.47 mm than the lycopene group where the average improvement of mouth opening was 6.07 ± 2.00 mm ($p < 0.0001$). In stage III, the lycopene group had a significant average improvement of mouth opening of 6.53 ± 1.45 mm compared to injection betamethasone group patients who showed an average improvement in mouth opening of 3.27 ± 1.36 mm ($p < 0.0001$). In both test groups capsule lycopene showed better results compared to injection betamethasone [10]. Intralesional injections of dexamethasone, hyaluronidase, and chymotrypsin independently or in combinations show better outcomes than using a single drug regimen [5].

The limitation of injecting corticosteroids include pain, scar formation due to needle prick, and greater chances of relapse once the treatment is withdrawn. Topical formulations are not effective in the long-term. One study reported hypertrichosis from repeated triamcinolone injection [11].

16.3 Immunomodulators

16.3.1 Levamisole

Levamisole is an anthelmintic drug with a wide range of immunomodulatory actions which influence both humoral and cellular immunity. It has been reported to be beneficial in the early stages of OSF.

A randomized, single-blind clinical trial conducted by Jirge et al. compared 50 mg of oral levamisole, three times daily, for 3 consecutive days a week for 3 alternate weeks with an oral antioxidant [ANTOXID—containing beta carotene, selenium oxide, zinc sulfate, manganese, and copper]. The 45 participants included in this study were divided equally between three study groups: oral levamisole (group I), ANTOXID (group II), or a combination of oral levamisole with ANTOXID (group III). At the end of the intervention period of 15 weeks, there was an improvement in mouth opening by 7.1%, 6.7%, and 8.0% in groups I, II, and III, respectively. These gains were maintained on further evaluation 2 months later. There was also a significant reduction in burning sensations in all study groups. The levamisole group showed a significant reduction in burning sensation and improvement in mouth opening and also an improvement in serum IgA, IgM, and IgG levels [12]. Shinge et al. evaluated the efficacy of levamisole and

antioxidants in 60 OSF patients as single and combined regimens. They found that the combined use of levamisole and antioxidant was more effective than use of levamisole or antioxidant alone [13].

16.3.2 Probiotic Agents

The use of probiotic agents, such as immunized cow's milk prepared by immunization of cows with human intestinal bacteria, has been proposed as a method of immunomodulation. Immunized milk contains vitamins such as vitamins A, C, B1, B2, B6, B12, nicotinic acid, pantothenic acid, folic acid, and elements iron, copper, and zinc. It suppresses inflammation and modulates cytokine production. 45 g of immunized milk powder twice a day for 3 months resulted in a significant improvement in the symptoms of OSF patients. The authors reported an increase of greater than 3 mm in mouth opening in 69% of their treated patients [6, 14–16].

16.4 Proteolytic/Fibrolytic Enzymes

Proteolytic enzymes are known to break down the cross-linking of collagen, which contributes to connective tissue fibrosis.

16.4.1 Hyaluronidase

Hyaluronidase degrades ECM hyaluronic acid, promotes the lysis of fibrin-formed coagulum, decreases the viscosity of intercellular cement substances, and decreases collagen synthesis. It is effective in reducing OSF symptoms and is often used in combination with steroids. It has been used as the first-line medical treatment in moderate grade of OSF [17, 18].

Krishnamoorthy et al. enrolled 50 patients and randomized them into two groups. Group 1 received intralesional injections of 1500 IU hyaluronidase mixed in 1 ml lignocaine (0.5 ml) injected submucosally into the buccal mucosa along with colchicine 0.5 mg twice daily and group 2 was given intralesional 0.5 ml of hydrocortisone acetate 25 mg/ml in addition to the hyaluronidase once a week for 12 weeks. Both groups received habit intervention. Thirty-three percent of patients in Group 1 had relief from the burning sensation in the second week. Group 1 patients responded better than Group 2 with an increase in mouth opening and improvement of histological parameters [19].

Cox and Zoellner compared the efficacy of physiotherapy and submucosal injections of a combination of hyaluronidase and corticosteroids in 54 Nepalese subjects. After 4 months, subjective and objective measures were compared with baseline. The physiotherapy group showed a significant increase in mouth opening but had no superior effect on subjective measures [20].

James et al. administered intralesional injection of dexamethasone 1.5 ml and hyaluronidase 1500 IU with 0.5 ml lignocaine biweekly for 4 weeks, to 27 OSF patients, with an average follow-up of 9 months. Improvement in mouth opening was observed with a net gain of 6 ± 2 mm (92%). There was a reduction in the burning sensation, pain, ulceration, and blanching of the oral mucosa. The authors concluded that submucosal injection of hyaluronidase with dexamethasone was an effective method of treating Grade III OSF [21].

16.4.2 Chymotrypsin

Chymotrypsin is a proteolytic enzyme (serine protease) found in the digestive systems of many organisms. It facilitates the cleavage of peptide bonds. Chymotrypsin is an end peptidase that hydrolyzes ester and peptide bonds. It has proteolytic and anti-inflammatory properties and has shown to provide some improvement in OSF symptoms [16, 22].

Ayub et al. compared the effectiveness of combined chymotrypsin and dexamethasone versus dexamethasone alone in patients with OSF. Their study included 146 OSF patients who were equally divided into two groups by a lottery method. Group A had 73 patients, treated with submucosal injection of a combination of chymotrypsin and dexamethasone, and group B, 73 patients treated with only dexamethasone, once a week for 1 month. Mouth opening was recorded on monthly follow-up without any other therapy for 3 months. Interincisal opening significantly increased by 3–5 mm in group A compared to group B suggesting that the combined regimen of chymotrypsin and dexamethasone was more effective than dexamethasone alone (74% vs. 57.5%) ($p = 0.036$) [23].

16.4.3 Collagenase

Collagenase is an enzyme capable of degrading various esters that are involved in the cross-linking of collagen. Clostridium histolyticum collagenase (Xiapex™) has been licensed for the treatment of fibrotic conditions, such as Dupuytren's contracture. It is highly potent in digesting collagen. Efficacy of collagenase in the treatment of Dupuytren's contracture was proven by Hurst et al. in their double-blind randomised control trial [24].

However, it is expensive, and the cost may preclude its availability in low-income countries.

Lin et al. studied the effect of collagenase treatment given as submucosal injections in 27 patients with well-developed OSF. They divided the patients into three groups (A, B, and C) with nine patients in each group: patients in group A, received phosphate-buffered saline (PBS) injection as a control; patients in group B were injected with 1 ml of triamcinolone diacetate (Ledercort) plus 1 ml of xylocaine and group C patients received 1 ml of collagenase (1% solution) mixed with 1 ml of xylocaine. All patients received their injections once a week for 6 weeks. The collagenase treatment not only resulted in a significant improvement of mouth opening, but also a striking reduction in hypersensitivity to spices, sour, cold and heat that helped restore normal eating in the study subjects. The mouth opening of patients who received PBS decreased approximately by 13–15% 6 weeks after the initial measurement. The OSF patients treated with triamcinolone diacetate or collagenase showed 9–13% and 64–82% increase in mouth opening, respectively. These results indicated that collagenase treatment was approximately fivefold more effective than triamcinolone diacetate alone [25].

16.5 Antioxidants in OSF

Constituents of betel quid generate substantial amounts of reactive oxygen species (ROS), which may create a biological imbalance between oxidants and antioxidants. OSF pathogenesis involves the accumulation of free radicals and production of lipid peroxides (LPO) [25]. On the basis of this hypothesis, several authors have used naturally occurring or synthetic antioxidants to treat OSF. Some of the agents that have been used include beta carotene, lycopene, tea pigments, aloe vera, curcumin, and spirulina.

16.5.1 Lycopene

Lycopene is a red carotenoid predominantly present in tomatoes and other pigment-containing vegetables and fruits [2–4]. It is a potent antioxidant and its antioxidant property is attributed to its high singlet oxygen quenching capacity with an increased propensity for quenching other free radicals *in vitro*. Experimental studies have established the role of lycopene in inhibiting cancer cell growth both *in vivo* and *in vitro* [27]. Lycopene has also been reported to be beneficial in the management of other potentially malignant oral disorders (e.g., oral leukoplakia and lichen planus) [16, 28, 29].

Kumar et al. recruited 83 participants who received either oral lycopene (n = 21; group A), oral lycopene with submucosal corticosteroids (n = 19; group B), or oral placebo tablets (n = 18; group C). The 2-month intervention period was completed by 58 people. Objective measurement of mouth opening improved with an average increase of 3.4 mm, 4.6 mm, and 0 mm for groups A, B, and C, respectively. The increases were maintained at 3- and 6-months follow-up. All patients who took lycopene reported relief of burning sensation within 2 weeks, whereas only one patient from the placebo group reported a similar improvement [30].

A randomized single-blind trial testing the effectiveness of lycopene was conducted in Maharashtra, India. Of the 92 participants enrolled, 46 were given 8 mg oral lycopene daily, and the rest were given a placebo tablet for 3 months and followed up for further 2 months. Significant improvement was reported with increase in mouth opening of 4.48 (±3.65) mm in the lycopene group compared with 1.13 (±1.6) mm in the control group, and 31% taking lycopene experienced a complete improvement in burning sensation compared with 7% in the control group [31].

A study by Beena et al. reported the effectiveness of dexamethasone and hyaluronidase to be superior to lycopene among 60 OSF patients [32]. However, as the lycopene group also showed improvement in mouth opening and reduction of burning sensation it may be used when dexamethasone is contraindicated due to medical comorbidities. Johny et al. evaluated the efficacy of lycopene and lycopene-hyaluronidase combination with placebo in the treatment of 45 OSF patients. There was a statistically significant improvement in mouth opening and burning sensation for lycopene and lycopene and hyaluronidase combination than in the placebo group in the treatment of OSF. The lycopene–hyaluronidase combination did not yield any statistically significant improvement when compared with lycopene alone [33]. Saran et al. compared the efficacy of oral lycopene with curcumin in 60 OSF patients. Lycopene showed better results than curcumin in improving mouth opening and both were equally effective in decreasing burning sensation in OSF patients [34]. Selvam et al. divided their cohort of 45 OSF patients into three groups: group A received oral lycopene with corticosteroid injections (dexamethasone + hyaluronidase), group B received oral antioxidant with corticosteroids, and group C received intralesional injections of dexamethasone and hyaluronidase. Lycopene used along with intralesional steroids was more effective in improving mouth opening compared to antioxidants

with steroids [35]. Similarly, Elizabeth et al., in their study comparing the efficacy of lycopene with intralesional corticosteroids, found that lycopene in combination with intralesional steroids was more effective in improving mouth opening compared to intralesional steroid and hyaluronidase injections alone [36]. In a RCT of 30 OSF patients, Subramaniyam et al. found that the mean improvement in tongue protrusion (3.53 mm) and burning sensation (2.73 using VAS) was significantly better in patients who received lycopene compared to those who underwent ultrasound therapy (tongue protrusion: 1.46 mm; burning sensation: 1.4 using VAS). The mouth opening was better in the ultrasound group (6.20 mm) compared to lycopene groups (5.10 mm), but the results were not statistically significant [37]. Singh et al. demonstrated that lycopene capsules were better than intralesional betamethasone injections in improving mouth opening and decreasing burning sensation in their cohort of 44 OSF patients [38]. Arshad et al. compared the efficacy of lycopene with methyl predinisolone as single drug regimen and in combination and found that combination of lycopene and methyl prednisolone yielded favorable results than corticosteroid or antioxidant alone [39]. Bhowmick et al. and Kumar et al. compared the clinical response in patients receiving lycopene and lycopene with intralesional corticosteroids. Combination therapy of lycopene with intralesional corticosteroids was more effective in relieving the clinical symptoms [30, 40].

16.5.2 Curcumin (Turmeric)

Curcumin (diferuloylmethane) is a component of turmeric, a rhizomatous plant—Curcuma longa, which is widely used in Asian cooking. It exhibits antioxidant, anti-inflammatory, proapoptotic, and anticancer properties [41, 42]. It suppresses the action of nicotinamide adenine dinucleotide phosphate oxidase, which is responsible for the generation of reactive oxygen species (ROS). Curcumin modulates inflammatory response by reduction of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) enzymes. It also inhibits the synthesis of the inflammatory cytokines, tumor necrosis factor-alpha (TNF-alpha), IL-1, 2, 6, 8, 12, monocyte chemoattractant protein (MCP), and migration inhibitory protein [43]. A comprehensive description of the properties of curcumin is given by Girisa and Kunnumakkara in Chap. 17.

Kopuri et al. compared submucosal layer thickness using ultrasonography in 30 OSF patients treated with oral lycopene and curcumin for 3 months. At the end of 3 months, all patients in both groups showed significant improvement in mouth opening, burning sensation and blanching. The submucosal fibrous bands were reduced in thickness on ultrasonographic examination in both groups. The authors proposed that Lycopene was better than curcumin in the treatment of OSF [44].

Lanjekar et al. compared the efficacy of topical curcumin mucoadhesive semisolid gel, triamcinolone acetonide/hyaluronidase mucoadhesive semisolid gel, and a combination of both in the treatment of 120 OSF patients. The use of three drug combinations showed better improvement in mouth opening (mean increase of 4.05 mm) and change in mucosal color as compared to the other two groups. The triamcinolone and hyaluronidase group reported a better reduction in burning sensation as compared to the other two groups. Curcumin had a synergistic effect when combined with triamcinolone and hyaluronidase [45].

The safety of the administration of turmeric oil was established using nine healthy volunteers [46]. The same group reported a pilot trial in patients with OSF [47]. Rai et al. also reported an increase in local and systemic antioxidative status in OSF by curcumin [48].

The effect of curcumin was compared with submucosal steroid injections in an RCT [49]. The experimental arm (n = 20) received curcumin orally: two tablets of a proprietary preparation film-coated tablet containing 300 mg Curcuma longa and 5 mg piperine) once daily for a period of 3 months. The control group received weekly submucosal injections of 4 mg dexamethasone and 1500 IU of hyaluronidase. Mouth opening improved by 3 mm in the curcumin group compared to control group (1.25 mm), and the burning sensation was significantly reduced in the curcumin group.

In another RCT, a combination of curcumin and turmeric oil was tested by Das et al. [50] Curcumin 1 g per day was given in two divided oral doses in one group, and a second group was given 12 drops of turmeric solution to hold in the mouth and then swallow twice daily. A control group received multivitamins 500 mg twice daily. Patients were followed up monthly for 6 months. Complete relief of pain was reported in both experimental groups after 1 month's treatment. A mean increase in mouth opening of 8.7 mm was noted in both test groups compared to a mean increase of 1.8 mm in the control group.

Pipaliya et al. compared the efficacy of turmeric and black pepper (Piper nigrum) together with black cumin (Nigella sativa) in 40 OSF patients. Turmeric with black pepper formulation showed better improvement than Nigella sativa. There was an improvement in the superoxide dismutase levels post-treatment in both groups [51].

Piyush et al. compared the efficacy of lycopene and curcumin with placebo in 90 OSF patients. Statistically

significant improvement in clinical symptoms was observed in both curcumin and lycopene treatment groups in comparison with placebo [51].

Hazarey et al. compared the efficacy of curcumin lozenges with topical clobetasol propionate in 30 OSF patients. The curcumin group showed better improvement in mouth opening and reduction in burning sensation on follow-up of the patients 6 months after treatment [53].

However, Rajbhoj et al. compared the clinical response of 60 OSF patients to aloe vera and curcumin (30 in each group) and found that reduction in burning sensation was statistically significant in the aloe vera group when compared to the curcumin group [54].

16.5.3 Tulsi/Holy Basil (Ocimum tenuiflorum/Ocimum sanctum Linn)

Synergistic effects of Tulsi and turmeric paste was reported by Srivastav et al. in 41 OSF patients [55]. Madhulatha et al. evaluated the efficacy of 500 mg of herbal Tulsi paste, twice daily for a duration of 1 month among a cohort of twenty OSF patients [56]. Promising results of tulsi were demonstrated in both studies.

16.5.4 Aloe Vera (AV)

Aloe vera is an adaptogen, that helps in enhancing the immune system and is a rich source of vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids, and amino acids. The vitamins A, C, and E in AV act as antioxidants and help to neutralize free radicals. AV also contains enzymes: alkaline phosphatase, amylase, bradykinase, carboxypeptidase, catalase, cellulase, lipase, and peroxidase [57, 58]. Bradykinase decreases inflammation on topical application. The gel of the leaves also has polysaccharides that promote wound healing and exhibit anti-inflammatory, anticancer, immunomodulatory, and gastroprotective properties. The anti-inflammatory action of aloe vera is due to the reduction of chemical mediators of inflammation like bradykinin, histamine, leukocyte adhesion, and TNF-α. It stimulates the production of hyaluronic acid and dermatan sulfate in the granulation tissue of a healing wound and imparts elasticity to the skin and mucosa [58].

Anuradha et al. evaluated the efficacy of systemic and topical AV to submucosal injection of hydrocortisone and hyaluronidase in 74 OSF patients for a duration of 6 weeks [59]. A statistically significant improvement in inter-incisal mouth opening was observed in both groups. The improvement in the VAS scale for burning sensation, tongue protrusion, and cheek flexibility were more significant in the AV group. Similar results were obtained by Sudarshan et al. and Singh et al. [60, 61].

Sudarshan et al. compared the effect of topical AV with an oral antioxidant capsule (beta-carotene, Vitamin E, C, zinc, copper, mixed carotenoids, chromium, manganese, selenium). Ten patients with OSF received topical application of aloe vera gel (5 mg applied three times daily to the buccal mucosa for 3 months) and 10 patients received antioxidant capsules twice daily. In the AV group, a 55–65% reduction in burning sensation and an improvement in mouth opening (4.3–7 mm) was observed [61].

Alam et al. studied the effectiveness of aloe vera gel as an adjunct to injection of a mixture of hyaluronidase and dexamethasone and surgical approaches in the treatment of OSF. Sixty patients were randomized to medicinal and surgical groups, and within each group ($n = 30$), half received the gel treatment. Improvements in both mouth opening and burning sensation were found in those treated with aloe vera [62]. However, when Patil et al., compared the efficacy of AV with lycopene in a cohort of 120 OSF patients, lycopene showed better improvement in mouth opening and reduction in burning sensation compared to AV [63].

16.5.5 Spirulina

Spirulina is a blue-green alga, with abundant vitamins (A and B12), minerals, carotenoids, and phycocyanin. Spirulina is known to reduce serum cholesterol levels. Spirulina increases IL-2 and decreases IL-6. It has chemopreventive properties due to the abundance of beta carotene and superoxide dismutase [58, 64–66]. Kanjani et al. in their study reported that the patients using a combination of physical exercise (mouth stretching) and spirulina 500 mg fared better than patients using spirulina alone in terms of burning sensation, mouth opening, tongue protrusion, and cheek flexibility [67]. Studies have shown that spirulina significantly improves the mouth opening, ulcers, erosions, and vesicles compared with those receiving topical aloe vera [64]; Spirulina also reduces the burning sensation compared with pentoxifylline [65]; and is more effective in improving both mouth opening and reducing burning sensation compared with a biweekly submucosal steroid injection of betamethasone (4 mg/ml for 3 months) [66].

Kulkarni et al. conducted a systematic review on the efficacy of spirulina in the management of OSF. Five studies were included in this systematic review. All five studies reported that spirulina is an effective herbal medicine in the improvement of mouth opening, reducing burning sensation, ulcers, erosions, or vesicles. In

three studies spirulina was compared with lycopene, aloe vera, and oxitard™ When compared with lycopene and oxitard, spirulina was found to be less effective in improving mouth opening; however, spirulina was more effective than AV. The spirulina group also demonstrated better results for reducing oral lesions when compared with these three interventions. All were equally effective, in reducing burning sensation [68].

16.5.6 Tea Pigments

Oxidation of Polyphenols in tea leaves produces tea pigments. The tea pigments contain aflavins, which possess antioxidant, antineoplastic, and anti-inflammatory properties. Both polyphenols and flavins reduce the activity of nuclear factor-kappa B (NF-kappa B) and thereby regulate the expression of proinflammatory cytokines. Tea pigments are beneficial in OSF treatment as they augment the actions of superoxide dismutase, reduce blood viscosity and improve microcirculation [4, 69, 70]. Li et al. found tea pigments to be beneficial in patients with early stages of OSF. The authors suggest that in addition to their antioxidant properties, the tea pigments are likely to act by improving microcirculation [71].

16.5.7 Salvianolic Acid (Sal-B)

Radix Salviae miltiorrhizae (Danshen), the dried root of Salvia miltiorrhiza Bge is a popular traditional Chinese medicine. Salvianolic acid B (Sal-B) is the most abundant and bioactive member of the hydrophilic components in Danshen. Sal-B contains seven phenolic hydroxyls, which are responsible for its antioxidant activities [72]. Jiang et al. studied the efficacy of salvianolic acid B (Sal-B) combined with triamcinolone acetonide in the treatment of OSF. A net gain of 5.5 mm of mouth opening was reported in the Sal-B group in 20 weeks. However, this relapsed to 3.5 mm in 44 weeks. The exact antifibrosis mechanism of Sal-B is not known [11].

16.5.8 Epigallocatechin Gallate (EGCG)

EGCG is a plant-based potent antioxidant that protects the cell against cellular damage caused by free radicals. Hsieh and colleagues noted that EGCG dose-dependently inhibited arecoline-induced transforming growth factor 1 (TGF-β1) activation in Buccal Mucosal Fibroblasts (BMFs). BMFs exposed to arecoline result in the generation of mitochondrial ROS, which activate latent TGF-β1, and, in turn, stimulated Cell Communication Network Factor (CCN2) and early growth response-1 (Egr-1) synthesis. TGF-β1 plays a pivotal role in the pathogenesis of OSF; thus, EGCG may be useful in the prevention and treatment of OSF. Hsieh et al. noted that arecoline induces overexpression of Egr-1, which enhances the profibrotic activity seen in OSF [73]. EGCG was shown to completely block arecoline-induced Egr-1 expression in human BMFs [26].

16.6 Vasodilators

The rationale for the use of a peripheral vasodilators is that they relax and dilate the blood vessels in the stromal tissues, ensuring blood supply to the ischemic tissues which help the nutritional and therapeutic agents to reach the affected tissues. The agents that have been used in OSF include pentoxifylline [74, 75]. nylidrin hydrochloride [76], buflomedil hydrochloride [77], Danxuan Koukang [78], Xantinol nicotinate [79] and isoxsuprine [3, 80].

16.6.1 Pentoxifylline (PTX)

Pentoxifylline (PTX) is a methylxanthine derivative and a nonspecific type IV phosphodiesterase inhibitor. It is prescribed for intermittent claudication and is known to have properties that alter the course of wound healing. PTX increases fibroblast collagenases and decreases collagen, fibronectin, and glycosaminoglycan production. Fibroblast responsiveness to tumor necrosis factor is also diminished by PTX [81]. PTX enhances red cell deformability, leukocyte chemotaxis, anti-thrombin, and anti-plasmin activities, and suppresses red cell and platelet accretion, granulocyte adhesion, fibrinogen levels, and whole blood viscosity [82]. It enhances the production of prostaglandins (E2 and I2) by vascular epithelium which is critical in preserving cellular integrity and homeostasis after acute phase injury. All these properties are potentially beneficial in the atrophic and ischemic condition of the oral mucosa in OSF.

Rajendran et al. studied 29 OSF patients who were prescribed either oral pentoxifylline or multivitamins. All those enrolled completed the study during a 7-month period [74]. The authors reported statistically significant improvements in the oral pentoxifylline group (n = 14) compared with controls with respect to mouth opening, tongue protrusion, and relief from circum-oral fibrotic bands and subjective criteria (intolerance to spices, burning sensations, tinnitus, difficulty in swallowing, and difficulty in speech).

Prabhu et al. assessed the use of PTX on the clinical and histopathologic changes of 30 OSF patients in comparison to conventional therapies [83]. They did not observe any significant clinical and histopathological improvement in the PTX group. Treatment with PTX was not superior to other drug regimens and concluded that their study did not recommend PTX.

Several studies have reported side effects caused by PTX including central nervous system (dizziness, headache, tremor, anxiety, and confusion) and gastrointestinal (dyspepsia, nausea and/or vomiting, bloating, flatus, and bleeding) symptoms [81, 83].

Zwiri et al. conducted a study comparing the efficacy of spirulina (control) and PTX in 112 OSF patients. The maximal mouth opening increased from 21.6 mm at baseline to 27.9 after 3 months in PTX group [84].

Patil et al. in a prospective study compared the efficacy of pentoxifylline with placebo (multivitamin) in 106 OSF subjects. The cohort was divided into two groups: Group A (n = 53) was administered 400 mg pentoxifylline twice daily and Group B (n = 53) was given multivitamins for 3 months. They reported a significant ($p < 0.05$) improvement in mouth opening, tongue protrusion, speech and swallowing, pain associated with the lesion, and burning sensation in OSF patients [85].

Sadaksharam et al. evaluated the therapeutic efficacy of oral PTX and dexamethasone in the treatment of 30 OSF patients [86]. The width of the submucosal layer and its echogenicity were assessed by ultrasonography, prior to and after treatment. Equivocal improvement was obtained in both groups. Nevertheless, the PTX group exhibited better results than the dexamethasone group. Therefore, the authors proposed, PTX as a safer substitute when intralesional steroids are intolerable or contraindicated.

Bhambhal et al. compared the efficacy of oral PTX 400 mg to placebo-multivitamin capsules, in 80 OSF patients [87]. Relief from pain, and burning sensation, was significant. No significant changes were observed with respect to mouth opening, tongue protrusion, cheek flexibility, or blanching of the mucosa in PTX group.

Mehrotra et al. report on 32 patients given pentoxifylline for a period of 7 months (initial 30 days dosage of 400 mg twice daily, increased to 400 mg three times daily for 6 months). The placebo group (n = 30) was given multivitamin therapy. They report improved mouth opening by 10 mm with pentoxifylline compared with 6 mm with multivitamins [75]. The improvement in total score (Subjective and Objective) was 25% in placebo and 49% in PTX group. This difference was found to be statistically significant. ($p < 0.05$). Central nervous system side effects such as dizziness, headache, tremor, anxiety, and confusion and gastrointestinal (dyspepsia, nausea and/or vomiting, bloating, flatus, and bleeding) were reported in a few patients [75, 86, 88].

Bishnoi et al. reported that patients on PTX showed a significant increase in mouth opening, decrease in burning sensation, and pain as compared with those on multivitamin capsules [89].

Leelakshi et al. in a cross-sectional study administered 400 mg PTX and two garlic pearls thrice daily for 2 months in 10 OSF patients. Patients exhibited a mean reduction of 95.68% in burning sensation and an increase of 5.37 mm in mouth opening. The cheek flexibility and tongue protrusion also showed significant improvements in the study groups [90].

16.6.2 Nylidrin Hydrochloride

Nylidrin hydrochloride marketed in India under the brand name "Arlidin" is available in tablet and injectable forms. "Arlidin" with its active component, nylidrin hydrochloride, is a peripheral vasodilator, that increases blood supply to ischaemic tissues with little or no change in blood pressure or heart rate of the individual. It has been used favorably in Meniere's disease, deafness, dementia, retinopathy, peripheral vascular disease, and premature labor. Sharma et al. in their study on Nylidrin hydrochloride (Arlidine™) in 58 cases of oral submucous fibrosis (6 mg orally), reported clinical improvement in 62% of patients. Side effects included flushing and warm skin in some patients [76].

16.6.3 Isoxsuprine

Isoxsuprine, a vasodilator was combined with physiotherapy, and compared with submucosal injections of dexamethasone with hyaluronidase and physiotherapy or physiotherapy alone in OSF patients [91]. Isoxsuprine was given for 6 weeks, with a 4-month follow-up period. Both isoxsuprine and dexamethasone with hyaluronidase treatments significantly alleviated the burning sensation and increased mouth opening by approximately 3 mm.

16.6.4 Xantinol Nicotinate

Xantinol nicotinate is a derivative of niacin. It is a vasodilator used to treat peripheral vascular disease. Singh et al. determined the efficacy and safety of intralesional Xantinol nicotinate with a placebo in the treatment of various stages of OSF. The patients had a significant respite from burning sensation and enhancement in the mouth opening, tongue protrusion, and cheek flexibility [79].

16.6.5 Buflomedial Hydrochloride

Buflomedial, a peripheral vasodilator, has been found to favourably affect tissues with diffuse fibrosis by improving local ischemia. Lai et al. observed positive treatment outcome for OSF using buflomedial (3 tablets of 450 mg each per day) and topical triamcinolone acetonide 0.1% on mucosal ulcers [77].

16.7 Biogenic Stimulation

16.7.1 Placental Extract

Intralesional placental extracts act by biogenic stimulation of the metabolic regenerative process of tissue. It was first used by Filatov in 1933. Aqueous extract of human placenta stimulates the pituitary and the adrenal cortex and regulates tissue metabolism [92, 93].

Placentrex™ is available as an injectable aqueous extract of human placenta that contains: (1) Enzymes: alkaline and acid phosphatase, glutamic oxaloacetic acid transaminase, glutamic acid, and pyruvic acid transaminase. (2) Nucleotides: RNA, DNA, and ATP. (3) Vitamins: Vit. E, B1, B2, pantothenic acid, biotin, PABA, folic acid, B12, choline and inositol. (4) Amino acids: Alanine, asparagine, asparagenic acid, cysteine, glyceine, histidine, leucine, lysine, phenylalanin, proline, serine, threonine, tryptophan, tryosine and valine. (5) Steroids: ketosteroids, cholestrin and cholesterol. (6) Fatty acids. (7) Trace elements, Sodium, K, Ca, Mg, Cu, Fe, P and Si [94].

Placental extract is anti-inflammatory and has significant analgesic action. It increases blood circulation and tissue vascularity. Placentrex contains Vitamin E, which has antioxidant properties. Vitamin A plays a major role in the induction and control of epithelial differentiation. Vitamin A slows, delays, arrests, reverses malignant potential and along with Vitamin E improves the mucosal color, mouth opening, and reduces fibrous bands [95].

Ramanjaneyalu and Rao used 2 cc placentrex injection at weekly intervals for 10 weeks in OSF patients. They found it to be superior to intralesional cortisone injections. They reported two cortisone-resistant cases that responded favorably to Placentrex [96].

Katharia et al. in an observational study, injected 2 ml of Placentrex locally in predetermined areas of oral mucosa, once a week for a total duration of 1 month in 22 OSF patients. A significant improvement in the mouth opening (28%) and the color of the oral mucosa (38 %) ($p < 0.01$) with a reduction in the fibrotic bands was observed [94].

Naik et al. reported a better improvement in mouth opening in OSF patients who were given intralesional 2 ml of placentrex at weekly intervals for 8 weeks when compared to OSF patients who received a combination of triamcinolone acetonide (10 mg/ml) + hyaluronidase (1500 IU) at weekly intervals for 8 weeks [97].

Raj et al. in a longitudinal study observed that treatment of OSF with placental extract injection was more effective in moderate fibrosis compared to moderately advanced fibrosis [98]. Significant improvement in mouth opening, color of the mucosa, tongue protrusion, and reduction in burning sensation was observed by Dinesh et al., in a prospective study where 30 OSF patients were administered 2 ml injection placental extract (Inj. Placentrex) submucosally [99]. Priyankar et al. in their cohort of 60 Stage II OSF patients reported maximum improvement in mouth opening with intralesional injection of hyaluronidase (MO = 9.20 mm) followed by placental extract (MO = 8.02 mm) and then dexamethasone (MO = 7.28 mm). They also reported that maximum improvement in burning sensation was observed with intralesional injection of dexamethasone followed by placental extract and the least improvement was seen with hyaluronidase [100].

Singh et al. used 2 ml submucosal injections of placental extract mixed with 2 ml of 2% lignocaine HCL weekly for an interval of 8 weeks and showed an average improvement in mouth opening by 8 mm (average pretreatment mouth opening of 8 mm and average posttreatment mouth opening of 26 mm) with a marked reduction in burning sensation [61].

Shah et al. divided their cohort of 25 patients into two study groups: Group A (placental extract + dexamethasone) and Group B (hyaluronidase + dexamethasone). In Groups A and Group B, the average increase in mouth opening from the baseline record to the eighth week of treatment was 3.53 ± 1.26 mm and 3.65 ± 1.42 mm respectively and the average decrease in burning sensation, as noted by VAS scale, was 5.13 ± 1.13 and 4.90 ± 1.29, respectively. The pre- and posttreatment differences were found to be statistically significant for both the groups ($p < 0.001$) and for both treatment outcomes [101].

Shinde et al. conducted a randomized, parallel-group, single-blinded outcome-based study, in a cohort of 40 cases of OSF. The patients were divided into two groups of 20 each: placental extract group and triamcinolone acetonide group, administered intralesionally for 10 weeks. There was a significant improvement in burning sensation, pain, mouth opening, tongue protrusion, and cheek flexibility in both groups. Better and earlier improvement in tongue protrusion and cheek flexibility was achieved in the triamcinolone group as against the placental extract group [102].

Kisave et al. evaluated the efficacy of Placentrex and hydrocortisone injection in two groups: Group A had 30 patients injected with 2 ml of placentrex in the areas where fibrous bands were present, twice a week for 3 months. Group B comprised of 30 patients injected with 2 ml of hydrocortisone twice a week for 3 months. A statistically significant difference in the mean mouth opening (5.19 ± 1.33 in Group A and 11.69 ± 1.26 mm in Group B; $p = 0.0001$) was observed. The authors concluded that hydrocortisone was better in increasing the mouth opening compared to placentrex. However, placentrex reduced the burning sensation more effectively than hydrocortisone [95]. They concluded that local injection of placentrex was safe, cheap, and effective without any significant side effects or contraindications. It has a long-lasting effect and can be administered in the early stages of OSF [95].

Similarly, Kale et al., observed that improvement in mouth opening was better with corticosteroids compared to placental extract; however, in their study, the difference between the study groups were not statistically significant [103].

16.8 Micronutrients (Vitamins and minerals)

Vitamins and minerals treat the deficiency states and promote normal cellular processes present in health that help to protect against adverse events, including carcinogenesis. Vitamins (A, B complex, C, D, E) are known to accelerate ulcer healing and relieve symptoms in OSF.

Minerals including zinc and magnesium are essential components for many enzymes and play a crucial role in DNA synthesis and cell division. Zinc controls the complex effects of copper-associated lysyl oxidase upregulation, while magnesium stabilizes excitable membranes. Multivitamins, micronutrients, and antioxidants are effective in controlling the signs and symptoms of OSF [16]. Antioxidants, nutrients, and micronutrients therapy (AONMT) is based on the rationale that reactive oxygen species (ROS) found in areca nut may damage the cellular structure, including lipids and cell membranes, proteins, and nucleic acids resulting in pathological processes. Micronutrient deficiencies impede the healing of inflamed oral mucosa leading to mucosal atrophy which becomes more susceptible to the effects of areca nut.

16.8.1 Vitamins

Vitamin A, C, and E are antioxidants that aid in scavenging free radicals. Beta-carotene, an important precursor of vitamin A, when combined with vitamin E has been shown to be effective in increasing mouth opening and tongue protrusion. In one study, treatment with topical vitamin A 50,000 IU in the form of chewable tablets once daily and oral ferrous fumarate tablets in a dose of 200 mg once daily were found to be safe and effective [104]. Vitamin E given concomitantly with submucosal hyaluronidase and betamethasone was better than hyaluronidase and betamethasone alone [105]. The efficacy of vitamin E is attributed to its antioxidant property. Nallapu et al. showed that the addition of vitamin E (400 IU once daily, for a period of 8 weeks) had a significant synergistic effect with the submucosal injections of dexamethasone 2 ml (2 mg/ml) and hyaluronidase (1500 IU) in 0.2 cc lignocaine (2%) [106]. Singh reported that vitamin C given in combination with placentrex and liver extract gave better results than vitamin C alone. It has been suggested that Vitamin C reduces the edema between the collagen bundles and helps in the regeneration of new normal collagen bundles [107]. Nayak et al. conducted a prospective study in 72 OSF patients to compare the clinical outcome of lycopene and lycopene with vitamin E. Lycopene when combined with vitamin E was better in reducing the burning sensation and improving mouth opening [108]. Thakur et al. in a clinical prospective study of 64 OSF patients reported that micronutrients (vitamins, minerals, and omega-three fatty acid) along with physiotherapy substantially improved the mouth opening compared to the use of micronutrients or physiotherapy as sole treatment modality [109].

Raizada et al. conducted an open labeled randomized controlled trial in 48 OSF patients divided into two groups (24 in each group) to study the effectiveness of omega 3 in the treatment of OSF. Group A received a placebo (lactose capsule) for 3 months while group B received 1gm of omega 3 (flaxseed oil) three times daily continuously for 3 months. Patients of both groups were given biweekly intralesional injections of dexamethasone 1.5 ml and hyaluronidase 1500 IU mixed with lignocaine for 6 weeks. After 3 months, statistically significant ($p < 0.05$) improvement among all three clinical parameters, i.e., inter-incisal distance (mean improvement in group $A = 3.79 \pm 1.07$ mm and group $B = 6.58 \pm 1.24$ mm, $p = 0.019$), tongue protrusion (mean improvement in group $A = 1.87 \pm 1.54$ mm and group $B = 4.62 \pm 1.78$ mm, $p = 0.044$), and cheek flexibility (mean improvement in group $A = 2.08 \pm 1.38$ mm and group $B = 3.50 \pm 1.84$ mm, $p = 0.035$) was observed. A significant improvement in burning sensation was observed after 1 month itself in group B when compared to group A (mean drop in group $A = 2.5 \pm 0.78$ points and group $B = 6.0 \pm 1.144$ points, $p < 0.05$). The authors concluded that Omega 3 in conjunction with intrale-

sional injections can be an effective therapy when compared to intralesional injections alone in treating patients with OSF (grade II and III) [110].

16.8.2 Minerals

Many studies have shown decreased levels of hemoglobin and serum ferritin in OSF [111]. Iron supplements in patients with anemia can improve the nutritional status of OSF patients and alleviate the burning sensation by correcting epithelial atrophy [4]. Maher et al. reported that micronutrient supplements: vitamins A, B complex, C, D, E; and minerals iron, calcium, copper, zinc, and magnesium were effective ($p < 0.05$) in reduction of signs and symptoms of OSF over a period of 3 years [112].

Dhariwal et al. reported that diet supplementation with zinc acetate along with vitamin A, in a 24-year-old OSF patient, increased mouth opening and reduced burning sensation in the 4 months follow-up period. Histopathologically re-epithelialization was evident along with the appearance of normal rete pegs. The data for mouth opening, collagen content, and epithelial thickness of six other cases similarly treated also showed a significant increase in mouth opening and epithelial thickness and a decrease in collagen content. The authors proposed the use of zinc acetate and vitamin A for the management of OSF [113]. Anil et al. administered Zinc (220 mg) in combination with vitamin A and observed good results in OSF. Zinc plays an essential role in DNA synthesis and cell division [114].

16.8.3 Oxitard ™

This is an ayurvedic antioxidant, which contains extracts of "Mangifera indica, Withania somnifera, Daucus carota, Glycyrrhiza glabra, Vitis vinifera, Emblica officinalis and Yashada bhasma, and Triticum sativum." "Mangifera indica" has antibiotic and antiviral action. "Withania somnifera" supresses anxiety, stress, and inflammation. "Daucus carota" is a potent source of vitamin A. "Glycyrrhiza glabra" suppresses the inflammation and is an immunostimulant. "Vitis vinifera" decreases inflammation and burning sensation. "Emblica officinalis" contains vitamin C and "Yashada bhasma" contains zinc which enhances wound healing and cell renewal. "Triticum sativum" contains potent minerals which suppresses oxidative stress [115]. Patil et al. compared the effectiveness of Oxitard capsules with a placebo in the treatment of OSF [116]. The authors concluded that the Oxitard group displayed a significant improvement in the subjective signs and symptoms. Additionally, they also reported improvement in dysphagia and speech articulation.

Oxitard was shown to be the most effective in improving mouth opening [MD, 10.29 (95% CI 6.34–14.25)] followed by a combination therapy of lycopene, hyaluronidase and corticosteroids [MD, 7.07 (95% CI 1.82–12.31)]. Two studies reported abdominal discomfort in eight patients due to Oxitard [75]. Patil et al. in a prospective, randomized single-blinded study observed a significant improvement in mouth opening, tongue protrusion, reduction in burning sensation, difficulty in swallowing and speech, and pain associated with the lesion in oxitard group compared to the aloe vera group [117].

16.8.4 Garlic

Garlic (*Allium sativa* L.) is a bulbous flowering plant that belongs to the family of Amaryllidaceae and is a horticultural crop originating from central Asia. Garlic and its products are used for culinary and therapeutic purposes in many countries. Bulbs of raw garlic have been investigated for their role in oral health, which are ascribed to a myriad of biologically active compounds it has such as alliin, allicin, methiin, S-allylcysteine (SAC), diallyl sulfide (DAS), S-ally-mercapto cysteine (SAMC), diallyl disulfide (DADS), diallyl trisulfide (DATS), and methyl allyl disulfide. Garlic has anti-inflammatory, antioxidant, antibacterial, antiviral, antifungal, and antimutagenic properties [118].

Jiang et al., gave submucosal injection of thio-2-propene-1-sulphinic acid S-allyl ester for 16 weeks to their cohort of 26 patients in stage II oral submucous fibrosis. The net gain in mouth opening was 5.16 ± 1.04 mm, burning sensation and the oral health impact profile score improved [119]. In another clinical trial, 15 patients with oral submucosal fibrosis were given pentoxifylline (400 mg) for 3 months with garlic pearls thrice daily. Patients had a 95% reduction in burning sensation and a 5 mm increase in the mouth opening [120].

Jain et al. systemically administered oral Pentoxifylline (400 mg) thrice daily along with garlic pearls, (2 pearls; thrice daily) after food for 3 months, in 15 OSF patients and observed a mean reduction of 95% in the burning sensation and increase of 5 mm in mouth opening. The cheek flexibility and tongue protrusion also showed significant improvements in the study groups [121].

16.9 Novel Therapies

16.9.1 Colchicine

Colchicine is a natural alkaloid derived from two plants of the lily family: Colchicum autumnale and Gloriosa superba, respectively known as meadow saffron and glory lily. Colchicine is an alternative therapeutic option for idiopathic recurrent aphthous stomatitis (RAS), especially when unresponsive to first-line treatments, such as topical or systemic corticosteroids. Additionally, colchicine might play a role in preventing oral aphthous-like ulcers associated with Bechet disease (BD) or immune-mediated disorders, such as periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome and mouth and genitals ulcers with inflamed cartilage (MAGIC) syndrome [122].

Colchicine reduces collagen synthesis by disrupting microtubule formation and preventing extrusion of collagen from fibroblasts and increasing the activity of collagenase in the underlying submucosa. It neutralizes cytokines that synthesize collagen-like TGF-β, IL-6, and IL-4 [123, 124]. Krishnamoorthy et al. studied the effects of colchicine in two groups of 25 patients each. One group was given 0.5 mg colchicine orally twice daily with 0.5 ml submucosal injection Hyaluronidase 1500 IU into each buccal mucosa once a week. The second group was given 0.5 ml submucosal injection Hyaluronidase 1500 IU and 0.5 ml submucosal injection Hydrocortisone acetate 25 mg/ml in each buccal mucosa once a week alternately [19]. The group that had colchicine had better mouth opening and relief from burning sensation. However, the study by Daga et al. could not find any beneficial effect for systemic colchicine [125] except for improvement in the blanching of the mucosa. The side effects with Colchicine include diarrhea and gastrointestinal adverse events [126]. Colchicine should be used with caution in patients with medical comorbidities. Severe side effects are observed at higher doses and are not advised in subjects with liver disorders. Continuous monitoring of blood count, renal and liver function are required during the entire course of treatment.

16.9.2 Interferon Gamma (IFN-γ)

Interferon gamma has immuno-regulatory and anti-fibrotic effects and plays an important role in collagen metabolism. *In vitro* Increase in collagen synthesis in response to arecoline is inhibited by IFN-γ (0.01–10.0 U/ml) in a dose-dependent manner [127]. Studies of submucosal injection of 0.01–10.0 U/ml IFN-γ three times a day for 6 months have shown improvement of OSF symptoms. In an open uncontrolled study, submucosal IFN-γ treatment resulted in improvement in the patients' mouth opening: from a pretreatment inter-incisal distance of 21 ± 7 mm, to 30 ± 7 mm immediately after treatment and 30 ± 8 mm 6 months later, giving a net gain of 8 ± 4 mm (42%) (range 4–15 mm). There was also a decrease in burning and dysaesthesia, and increase in suppleness of the buccal mucosa. Post-treatment immunohistochemistry showed a decreased amount of inflammatory cell infiltrate and altered levels of inflammatory cytokines compared with the pre-treatment lesional tissue. However, prohibitive costs of IFN gamma precludes its use in low- and middle-income countries [15, 127].

16.9.3 Anti-TGF-β Drugs

Upregulation of TGF-β1, downregulation of bone morphogenic protein (BMP) and remodeling of ECM are characteristic features of the fibrotic process in OSF. The alkaloid and polyphenol components of areca nut induce and activate TGF-β1 in epithelial cells. Exposure to areca nut and stimulation of the TGF-β1 pathway are responsible for overproduction of collagen and decrease in degradation of collagen in OSF. TGF-β1 induces transcription of COL1A1 procollagen gene, increases activity of procollagen proteinases, and promotes the expression of lysyl oxidase (LOX), an enzyme essential for cross-linking collagen fibers. Furthermore, activated TGF-β1 induces myofibroblast transdifferentiation in OSF [128].

Upregulation of TGF-β1 has been described as a key mediator in the pathogenesis of OSF. Activated TGF-β1 induces myofibroblast transdifferentiation in OSF. Several key trials are underway using anti-TGF-β in other fibrotic disorders, e.g., idiopathic lung fibrosis. Drugs that are being developed include Imatinib, Pirfenidone (PFD), and Nintedanib. There have been no trials reported for OSF.

Few agents are discussed below:

- Imatinib

  Imatinib exerts its anti-fibrotic activity by interfering with TGF-β signaling pathways. It has been used successfully as an anti-fibrotic drug in preclinical models for the treatment of scleroderma [129, 130]. Therefore, it has been suggested that it can also be effective in OSF treatment [4].

- Pirfenidone (PFD)

  Pirfenidone (5(1H)-pyridone) is a novel anti-fibrotic agent with anti-inflammatory properties presently used in treating idiopathic lung fibrosis (ILF) which is an inflammatory condition mediated through transforming growth factor beta (TGF-β), like in OSF. PFD is hypothesized to be a novel anti-fibrotic agent beneficial in treating the early stages of OSF as

both conditions are mediated through TGF-β. PFD acts by inhibiting tissue inhibitors of metalloproteinases-1 (TIMP1), proinflammatory cytokines TNF-α and fibroblast growth factor (b-FGF), which are upregulated in OSF [4, 128].

It has been hypothesized that PFD could reduce fibrosis in OSF by the following mechanisms:

1. Decreasing the levels of mRNA encoding type I and III collagen and also inhibiting TGF-β1-induced collagen production from fibroblasts [131].
2. Inhibiting tissue inhibitor of metalloproteinases-1 (TIMP1), which is upregulated in OSF [132, 133].
3. Suppressing proinflammatory cytokines TNF-α, which is upregulated in OSF [134, 135].
4. Downregulating fibroblast growth factor (b-FGF), which interacts synergistically with other growth factors enhancing the extracellular matrix deposition in OSF [136, 137].
5. Reducing the level of plasminogen activator inhibitor-1 (PAI-1), which is upregulated by TGF-β1 in OSF [138].

Nintedanib may be beneficial in OSF through the following mechanisms [4, 128]:

1. Directly preventing phosphorylation of TGF-β1 receptor and reducing excessive ECM production, which is a hallmark of OSF [139].
2. Targeting PDGF receptor-α and -β and thus reducing the level of PDGF, which is upregulated in OSF [140].
3. Targeting fibroblast growth factor receptor-1, −2, and − 3 and thereby reducing the level of fibroblast growth factor [141].

16.9.4 Valdecoxib

Valdecoxib is a novel selective cyclooxygenase-2 inhibitor used in the management of osteoarthritis, pain, and dysmenorrhea [142, 143]. Averineni et al. developed a mucoadhesive buccal film of valdecoxib for the treatment of OSF. This was a sustained release polymeric film of valdecoxib impregnated in Hydroxypropyl Methylcellulose (HPMC K4M) and chitosan polymers along with sodium taurocholate as a permeation enhancer for local action. Prepared films were thin, flexible, smooth, and transparent. Bioadhesive force and tensile strength of the optimized formulation were found to be 75 ± 4 kg m^{-1} S^{-2} and more than 2.5 kg/3 cm^2, respectively. The percent drug content was 98.5 ± 1.3%. The *in vitro* drug release from the selected formulation showed that about 69.34% of the drug payload was released for up to 6 hours. Pharmacokinetic studies of the buccal mucoadhesive film showed that the drug was released locally at the target site of action, and very small amount is absorbed systemically.

16.9.5 Meta analysis of intervention in OSF

Gopinath et al. conducted a systematic review of randomized controlled trials (RCTs) that compared the efficacy of interventions for OSF [144]. A network meta-analysis was performed, and the interventions were ranked according to their efficacy based on the surface under the cumulative ranking. This systematic review included 32 RCTs comprising 2063 patients. Oxitard, a herbal formulation was ranked as the most efficacious agent in improving mouth opening, [MD, 10.29 (95%CI 6.34–14.25)] followed by combination therapy of Lycopene with corticosteroids and hyaluronidase [MD, 7.07 (95%CI 1.82–12.31)]. Aloe vera ranked first in reducing burning sensation [MD, 6.14 (95%CI 4.58–7.70)] followed by corticosteroids with antioxidants [MD, 6.13 (95%CI 4.12–8.14)] and corticosteroids in combination with hyaluronidase and antioxidants [MD, 5.95 (95%CI 3.79–8.11)].

Summary and Conclusion

A wide range of drugs have been used in the medical management of OSF—anti-inflammatory agents, immunomodulatory agents, corticosteroids, antioxidants, vasodilators, biogenic stimulators, fibrinolytic enzymes, vitamins, minerals, micronutrients, and herbal remedies. Many randomized controlled trials have been conducted to study the efficacy of these therapeutic agents as single or combined drug regimens. Most of the studies have short follow-up periods. There is minimal information on cessation of habits. No evidence on reduction in malignant transformation is provided by long-term follow-up studies. Combination of therapeutic agents used makes it difficult to assess the role of individual agents. None of the medical agents studied have yielded a consistent relief of signs and symptoms in OSF. However, the results reported from lycopene and curcumin trials are promising. The medical management of OSF for each patient varies, based on disease stage and individual response to treatment.

References

1. Tilakaratne WM, Ekanayaka RP, Warnakulasuriya S. Oral submucous fibrosis: a historical perspective and a review on etiology and pathogenesis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(2):178–91.
2. Kerr AR, Warnakulasuriya S, Mighell AJ, Dietrich T, Nasser M, Rimal J, Jalil A, Bornstein MM, Nagao T, Fortune F, Hazarey VH, Reichart PA, Silverman S, Johnson NW. A systematic review of medical interventions for oral submucous fibrosis and future research opportunities. Oral Dis. 2011;17(Suppl. 1):42–57.

3. Warnakulasuriya S, Kerr AR. Oral submucous fibrosis: a review of the current management and possible directions for novel therapies. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(2):232–41.
4. More CB, Jatti Patil D, Rao NR. Medicinal management of oral submucous fibrosis in the past decade: a systematic review. J Oral Biol Craniofac Res. 2020;10(4):552–68.
5. Awan KH, Patil S, Habib SR, Pejcic A, Zain RB. Evaluation of medicinal interventions for the management of oral submucous fibrosis: a systematic review of the literature. J Contemp Dent Pract. 2014;15(6):812–7.
6. Aishwarya V, Amudhan A, Amudhan A. Management of oral submucous fibrosis – An update. Eur J Mol Clin Med. 2020;7(5):1380–92.
7. Tsai CC, Ma RH, Shieh TY. Deficiency in collagen and fibronectin phagocytosis by human buccal mucosa fibroblasts in vitro as a possible mechanism for oral submucous fibrosis. J Oral Pathol Med. 1999;28(2):59–63.
8. Alora Veedu R, Balan A, Sankar SP. A randomized double-blind, multiple-arm trial comparing the efficacy of submucosal injections of hyaluronidase, dexamethasone, and combination of dexamethasone and hyaluronidase in the management of oral submucous fibrosis. Oral Surg Oral Med Oral Pathol. Oral Radiol. 2015;120(5):588–593 e1.
9. Panigrahi R, Maheshwari A. A prospective, randomized double-blind study comparing intralesional triamcinolone acetonide and hyaluronidase combination versus triamcinolone acetonide alone in the treatment of oral submucosal fibrosis. J Pharm Biomed Sci. 2014;4(4):365–70.
10. Goel S, Ahmed J. A comparative study on efficacy of different treatment modalities of oral submucous fibrosis evaluated by clinical staging in population of Southern Rajasthan. J Canc Res Therapeut. 2015;11(1):113–8.
11. Jiang XW, Zhang Y, Yang SK, Zhang H, Lu K, Sun GL. Efficacy of salvianolic acid B combined with triamcinolone acetonide in the treatment of oral submucous fibrosis. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 2013;115:339–44.
12. Jirge V, Ali SM, Anshumalee N. Levamisole and antioxidants in management of oral submucous fibrosis: a comparative study. J Ind Acad Oral Med Radiol. 2009;20:135–9.
13. Shinge AA, Talreja PK, Das D, Navalkar A, Talreja PS, Kakade A. Comparative evaluation of the efficacy of systemic levamisole and antioxidant in the management of oral submucous fibrosis – A randomized control trial. J Adv Clin Res Insights. 2019;6(2):33–8.
14. Tai YS, Liu BY, Wang JT, Sun A, Kwan HW, Chiang CP. Oral administration of milk from cows immunized with human intestinal bacteria leads to significant improvements of symptoms and signs in patients with oral submucous fibrosis. J Oral Pathol Med. 2001;30:618–25.
15. Seema B. Etiopathogenesis and management of oral submucous fibrosis. Qual Primary Care. 2015;23(6):327–32.
16. Arakeri G, Rai KK, Boraks G, Patil SG, Aljabab AS, Merkx MAW, Carrozzo M, Brennan PA. Current protocols in the management of oral submucous fibrosis: an update. J Oral Pathol Med. 2017;46(6):418–23.
17. Chole RH, Gondivkar SM, Gadbail AR, et al. Review of drug treatment of oral submucous fibrosis. Oral Oncol. 2012;48:393–8.
18. Angadi PV, Rao S. Management of oral submucous fibrosis: an overview. Oral Maxillofac Surg. 2010;14:133–42.
19. Krishnamoorthy B, Khan M. Management of oral submucous fibrosis by two different drug regimens: a comparative study. Dent Res J. 2013;10:527–32.
20. Cox S, Zoellner H. Physiotherapeutic treatment improves oral opening in oral submucous fibrosis. J Oral Pathol Med. 2009;38:220–6.
21. James L, Shetty A, Rishi D, Abraham M. Management of oral submucous fibrosis with injection of hyaluronidase and dexamethasone in Grade III oral submucous fibrosis: a retrospective study. J Int Oral Health. 2015;7(8):82–5.
22. Gupta D, Sharma SC. Oral submucous fibrosis--a new treatment regimen. J Oral Maxillofac Surg 1988;46(10):830–833.
23. Ayub S, Siddiqui S, Abrar SK, Atif M, Raheel Allana R, Ahmad M. Effectiveness the combination therapy of chymotrypsin and dexamethasone vs dexamethasone alone in patients with oral sub mucous fibrosis. Rawal Med J. 2021;46(4):932–5.
24. Hurst LC, Badalamente MA, Hentz VR, et al. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. N Engl J Med. 2009;361(10):968–77.
25. Lin HJ, Lin JC. Treatment of oral submucous fibrosis by collagenase: effects on oral opening and eating function. Oral Dis. 2007;13:407–13.
26. Saso L, Reza A, Ng E, Nguyen K, Lin S, Zhang P, Fantozzi PJ, Armagan G, Romeo U, Cirillo N. A comprehensive analysis of the role of oxidative stress in the pathogenesis and chemoprevention of oral submucous fibrosis. Antioxidants (Basel). 2022;11(5):868.
27. Heber D, Lu QY. Overview of mechanisms of action of lycopene. Exp Biol Med (Maywood). 2002;227(10):920–3.
28. Singh M, Krishanappa R, Bagewadi A, Keluskar V. Efficacy of oral lycopene in the treatment of oral leukoplakia. Oral Oncol. 2004;40:591–6.
29. Saawarn N, Shashikanth MC, Saawarn S, Jirge V, Chaitanya NC, Pinakapani R. Lycopene in the management of oral lichen planus: a placebo-controlled study. Indian J Dent Res. 2011;22:639–43.
30. Kumar A, Bagewadi A, Keluskar V, Singh M. Efficacy of lycopene in the management of oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103:207–13.
31. Karemore TV, Motwani M. Evaluation of the effect of newer antioxidant lycopene in the treatment of oral submucous fibrosis. Indian J Dent Res. 2012;23:524–8.
32. Beenakumary TP, AG T, Varghese M, Raghavan R, Vm MN, Pius A. Evaluation of therapeutic efficacy of different treatment modalities in oral submucous fibrosis: a comparative study. J Contemp Dent Pract. 2019;20(3):390–4.
33. Johny J, Bhagvandas SC, Mohan SP, Punathil S, Moyin S, Bhaskaran MK. Comparison of efficacy of lycopene and lycopene-hyaluronidase combination in the treatment of oral submucous fibrosis. J Pharm Bioallied Sci. 2019;11(2):S260–4.
34. Saran G, Umapathy D, Misra N, et al. A comparative study to evaluate the efficacy of lycopene and curcumin in oral submucous fibrosis patients: a randomized clinical trial. Indian J Dent Res. 2018;29(3):303–12.
35. Selvam NP, Dyanand AA. Lycopene in the management of oral submucous fibrosis. Asian J Pharmaceut Clin Res. 2013;6(3):58–61.
36. Elizabeth N, Gurumani S, Bala AG, Tukalan G. A comparative study between management of oral submucous fibrosis. J Evol Med Dent Sci. 2014;3(47):11344–8.
37. Subramaniam AV, Subramaniam T, Agrawal N. Assessment of the effectiveness of antioxidant therapy(lycopene) and therapeutic ultrasound in the treatment of oral submucous fibrosis. Int J Pharm Therapeut. 2014;5(5):344–50.
38. Singh D, Shashikanth MC, Misra N, Agrawal S. Lycopene and intralesional betamethasone injections in the manage-

ment of oral submucous fibrosis. J Indian Acad Oral Med Radiol. 2014;26:264–8.
39. Arshad O, Siddiqi KM, Rana ZA. Oral submucous fibrosis: comparison of different treatment modalities. Pak Oral Dental J. 2015;35:3.
40. Bhowmick D, Kumar S, Nasreen S, Saba R, Iqbal H, Bhatia LK. Comparative evaluation of Lycopene-Hyaluronidase combination and Lycopene alone in the treatment of OSMF. Int J Health Clin Res. 2021;4(5):102–5.
41. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: a component of turmeric (Curcuma longa). J Alternat Complement Med. 2003;9:161–8.
42. Epstein J, Sanderson IR, Macdonald TT. Curcumin as a therapeutic agent: the evidence from in vitro, animal and human studies. Br J Nutr. 2010;103:1545–57.
43. Al-Maweri SA. Efficacy of curcumin for management of oral submucous fibrosis: a systematic review of randomized clinical trials. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019;127(4):300–8.
44. Kopuri RKC, Chakravarthy C, Sunder S, et al. A comparative study of the clinical efficacy of lycopene and curcumin in the treatment of oral submucous fibrosis using ultrasonography. J Int Oral Health. 2016;8:687.
45. Lanjekar AB, Bhowate RR, Bakhle S, Narayane A, Pawar V, Gandagule R. Comparison of efficacy of topical curcumin gel with triamcinolone-hyaluronidase gel individually and in combination in the treatment of oral submucous fibrosis. J Contemp Dent Pract. 2020;21(1):83–90.
46. Joshi J, Ghaisas SD, Vaidya A, et al. Early human safety of tumeric oil (Curcuma longa oil) administered orally in healthy volunteers. JAPI. 2003;51:1055–60.
47. Hastak K, Lubri N, Jakhi SD, et al. Therapeutic responses to turmeric oil and turmeric oleoresin in oral submucos fibrosis. Amala Res Bullet. 1998;18:23–8.
48. Rai B, Kaur J, Jacobs R, Singh J. Possible action mechanism for curcumin in pre-cancerous lesions based on serum and salivary markers of oxidative stress. J Oral Sci. 2010;52:251–6.
49. Yadav M, Aravinda K, Saxena VS, et al. Comparison of curcumin with intralesional steroid injections in oral submucous fibrosis—a randomized, open-label interventional study. J Oral Biol Craniofac Res. 2014;4:169–73.
50. Das DA, Balan A, Sreelatha KT. Comparative study of the efficacy of curcumin and turmeric oil as chemopreventive agents in oral submucous fibrosis: a clinical and histopathological evaluation. J Indian Acad Oral Med Radiol. 2010;22:88–92.
51. Pipalia PR, Annigeri RG, Mehta R. Clinicobiochemical evaluation of turmeric with black pepper and nigella sativa in management of oral submucous fibrosis-a double-blind, randomized preliminary study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(6):705–12.
52. Piyush P, Mahajan A, Singh K, Ghosh S, Gupta S. Comparison of therapeutic response of lycopene and curcumin in oral submucous fibrosis: a randomized controlled trial. Oral Dis. 2019;25(1):73–9.
53. Hazarey VK, Sakrikar AR, Ganvir SM. Efficacy of curcumin in the treatment for oral submucous fibrosis—a randomized clinical trial. J Oral Maxillofac Pathol. 2015;19(2):145–52.
54. Nerkar Rajbhoj A, Kulkarni TM, Shete A, Shete M, Gore R, Sapkal R. A comparative study to evaluate efficacy of curcumin and aloe vera gel along with oral physiotherapy in the management of oral submucous fibrosis: a randomized clinical trial. Asian Pac J Cancer Prev. 2021;22(S1):107–12. https://doi.org/10.31557/APJCP.2021.22.S1.107.
55. Srivastava A, Agarwal R, Chaturvedi TP, Chandra A, Singh OP. Clinical evaluation of the role of tulsi and turmeric in the management of oral submucous fibrosis: a pilot, prospective observational study. J Ayurveda Integr Med. 2015;6(1):45–9.
56. Madhulatha G, Vijayalaxmi N, Harshavardhan T. Tulasi a magical herb and a boon for management of oral submucous fibrosis: a clinical study. Int J Res Med Sci. 2017;5(11):4719–23.
57. Dwivedi N, Agarwal A. Aloe vera: magic or myth. SRM J Res Dent Sci. 2013;4:119.
58. Miranda MS, Cintra RG, Barros SB, Mancini FJ. Antioxidant activity of the microalga Spirulina maxima. Braz J Med Biol Res. 1998;31:1075–9.
59. Anuradha A, Patil B, Asha VR. Evaluation of efficacy of aloe vera in the treatment of oral submucous fibrosis—a clinical study. J Oral Pathol Med. 2017;46(1):50–5.
60. Singh N, Hebbale M, Mhapuskar A, Ul Nisa S, Thopte S, Singh S. Effectiveness of aloe vera and antioxidant along with physiotherapy in the management of oral submucous fibrosis. J Contemp Dent Pract. 2016;17(1):78–84.
61. Sudarshan R, Annigeri RG, Sree VG. Aloe vera in the treatment for oral submucous fibrosis - a preliminary study. J Oral Pathol Med. 2012;41(10):755–61.
62. Alam S, Ali I, Giri KY, et al. Efficacy of aloe vera gel as an adjuvant treatment of oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;116:717–24.
63. Patil S, Sghaireen MG, Maheshwari S, Kunsi SR, Sahu R. Comparative study of the efficacy of lycopene and aloe vera in the treatment of oral submucous fibrosis. Int J Health Allied Sci. 2015;4:13–7.
64. Patil S, Al-Zarea BK, Maheshwari S, Sahu R. Comparative evaluation of natural antioxidants spirulina and aloe vera for the treatment of oral submucous fibrosis. J Oral Biol Craniofac Res. 2015;5(1):11–5.
65. Mulk BS, Deshpande P, Velpula N, Chappidi V, Chintamaneni RL, Goyal S. Spirulina and pentoxyfilline: a novel approach for treatment of oral submucous fibrosis. J Clin Diagn Res. 2013;7:3048–50.
66. Shetty P, Shenai P, Chatra L, Rao PK. Efficacy of spirulina as an antioxidant adjuvant to corticosteroid injection in management of oral submucous fibrosis. Indian J Dent Res. 2013;24:347–50.
67. Kanjani V, Annigeri RG, Revanappa MM, Rani A. Efficacy of spirulina along with different physiotherapeutic modalities in the management of oral submucous fibrosis. Ann Maxillofac Surg. 2019;9(1):23–7.
68. Kulkarni R, Kalaskar A, Kalaskar R, Gupta N. Efficacy of spirulina in management of oral submucous fibrosis—a systematic review. J Oral Med Oral Surg. 2022;28:8.
69. More CB, Gavli N, Chen Y, Rao NR. A novel clinical protocol for therapeutic intervention in oral submucous fibrosis: an evidence-based approach. J Oral Maxillofac Pathol. 2018;22(3):382–91.
70. Fedorowicz Z, Chan Shih-Yen E, Dorri M, Nasser M, Newton T, Shi L. Interventions for the management of oral submucous fibrosis. Cochrane Database Syst Rev 2008;8(4):CD007156.
71. Li X, Tang J. Hua Xi, Kou Qiang, Xue Yi, Zhi Za. Clinical treatment observation of tea pigment for oral submucous fibrosis. West China J Stomatol. 1998;16(1):50–2.
72. Zhao Y, Guo Y, Gu X. Salvianolic acid B, a potential chemopreventive agent, for head and neck squamous cell cancer. J Oncol. 2011;2011:534548.
73. Hsieh YP, Wu KJ, Chen HM, Deng YT. Arecoline activates latent transforming growth factor β1 via mitochondrial reactive oxygen species in buccal fibroblasts: suppression by epigallocatechin-3-gallate. J Formos Med. 2018;117:527–34.
74. Rajendran R, Rani V, Shaikh S. Pentoxifylline therapy: a new adjunct in the treatment of oral submucous fibrosis. Indian J Dent Res. 2006;17:190–8.

75. Mehrotra R, Singh HP, Gupta SC, Singh M, Jain S. Pentoxifylline therapy in the management of oral submucous fibrosis. Asian Pac J Cancer Prev. 2011;12:971–4.
76. Sharma JK, Gupta AK, Mukhija RD, Nigam P. Clinical experience with the use of peripheral vasodilator in oral disorders. Int J Oral Maxillofac Surg. 1987;16:695–9.
77. Lai DR, Chen HR, Lin LM, Huang YL, Tsai CC. Clinical evaluation of different treatment methods for oral submucous fibrosis. A 10-year experience with 150 cases. J Oral Pathol Med. 1995;24:402–6.
78. Tan J, Li YC, Chen A, et al. Clinical research of Danxuan Koukang on treatment of oral submucous fibrosis. J Tradit Chin Med. 2006;26:41–3.
79. Singh U. Efficacy and safety of intralesional Xantinol nicotinate in the treatment of various stages of oral submucous fibrosis. J Clin Diagn Res. 2016;10(10):ZC34–ZC37.
80. Liu SF, Shen TH, Tang ZG, Su HP, Luo CF. On treatment of oral submucous fibrosis with glucosidorum tripterygii totorum. Beijing J Stomatol. 1999;7:167–9.
81. Samlaska CP, Winfield EA. Pentoxifylline. J Am Acad Dermatol. 1994;30(4):603–21.
82. Zhou Q, Zheng F, Hou F. Inhibition of tubulointerstitial fibrosis by PTX is associated with improvement of vascular endothelial growth factor expression. Acta Pharmacol Sin. 2009;30(1):98–106.
83. Prabhu N, Rao SS, Kotrashetti SM, et al. PTX in patients with oral submucous fibrosis a randomized clinical trial. J Maxillofac Oral Surg. 2015;14(1):81–9.
84. Zwiri AMA, Patil S, Yadav N. Comparative evaluation of newer drugs pentoxifylline and spirulina in the management of OSMF. Int J Pharmacol Toxicol. 2015;5:141–5.
85. Patil S, Maheshwari S. Efficacy of pentoxifylline in the management of oral submucous fibrosis. J Orofac Sci. 2014;6:94–8.
86. Sadaksharam J, Mahalingam S. Evaluation of oral PTX in the management of oral submucous fibrosis - an ultrasonographic study. Contemp Clin Dent. 2017;8(2):200–4.
87. Bhambal AM, Bhambal A, Shukla US, et al. Effectiveness of Pentoxifylline in the treatment of oral submucous fibrosis patients: a case-control study. Appl Cancer Res. 2019;39:15.
88. Gopinath D, Hui LM, Veettil SK, Nair AB, Maharajan MK. Comparative efficacy of interventions for the management of oral submucous fibrosis: a systematic review and network meta-analysis. J Pers Med. 2022;12:1272.
89. Bishnoi S, Sharma M, Bishnoid S, Sharma Y. Drug pentoxifylline in management of oral submucous fibrosis. Int J Res Rev. 2020;7(4):311–4.
90. Leelakshi NB, Gaurav. Efficacy of garlic in conjunction with pentoxifylline in the management of oral submucous fibrosis—a cross-sectional pilot study. Acta Scientific Dental Sci. 2020;7(4):154–60.
91. Bhadage CJ, Umarji HR, Shah K, Valimaa H. Vasodilator isoxsuprine alleviates symptoms of oral submucous fibrosis. Clin Oral Investig. 2013;17:1375–82.
92. Koneru A, Hunasgi S, Hallikeri K, Surekha R, Nellithady G, Vanishree M, et al. A systematic review of various treatment modalities for oral submucous fibrosis. J Adv Clin Res Insights. 2014;1:64–72.
93. Johar N, Chaurasia S, Phulambrikar T. Management of oral submucous fibrosis: A Review. Int J Oral Health Dent. 2017;3(3):154–7.
94. Katharia SK, Singh SP, Kulshreshtha VK. The effects of placenta extract in management of oral submucous fibrosis. Indian J Pharmacol. 1992;24:181–3.
95. Kisave P, Shekhar V, Babu PS, Hussaini SW, Bhanot R, Kumar A, et al. The study of placentrex and hydrocortisone as an adjunct treatment in oral submucous fibrosis. J Family Med Prim Care. 2020;9:2469–74.
96. Rananjaneyulu P, Rao P. Submucous fibrosis new treatment. J Indian Dent Assoc. 1980;52:379–80.
97. Naik SM, Appaji MK, Ravishankara S, Goutham MK, Devi NP, Mushannavar AS, Naik SS. Comparative Study of intralesional triamcinolone acetonide and hyaluronidase vs placental extract in 60 cases of oral submucous fibrosis. Int J Head Neck Surg. 2012;3(2):59–65.
98. Raj AG, Jayaprasad A, Manasa AM, Darshan DD, Ambili A. A longitudinal study of the effect of placental extract in the treatment of moderate and moderately advanced oral submucous fibrosis. RGUHS J Dent Sci. 2013;5(1):13–6.
99. Dinesh S, Sudhir P, Sara S, Nazima B, Sandeep KV, Aleem AK. Injection placentrex in the management of oral submucous fibrosis. Int J Modern Sci Eng Technol. 2015;2(1):23–30.
100. Priyankar S, Anil P, Ashish S, Tarun A, Sunil S, Sanjay RB, Mridula T. Efficacy of intralesional placental extract, dexamethasone, and hyaluronidase in treatment of oral submucous fibrosis: a comparative study. JK Pract. 2016;21(1–2):29–34.
101. Shah PH, Venkatesh R, More CB, Vassandacoumara V. Comparison of therapeutic efficacy of placental extract with dexamethasone and hyaluronic acid with dexamethasone for oral submucous fibrosis—a retrospective analysis. J Clin Diagn Res 2016;10(10):ZC63–ZC66.
102. Shinde CV, Saawarn N, Kohli S, Khare P, Singh A, Sagar KM. Comparative efficacy of intralesional placental extract and intralesional triamcinolone acetonide in the management of OSMF. J Indian Acad Oral Med Radiol. 2019;31:328–32.
103. Kale MV, Gaikwad NS. Oral submucous fibrosis: a study of qualitative and analytical treatment using intralesional injections: placental extract versus combination of steroid with hyaluronidase. Int J Otorhinolaryngol Head Neck Surg. 2020;6(7):1321–5.
104. Borle RM, Borle SR. Management of oral submucous fibrosis: a conservative approach. J Oral Maxillofac Surg. 1991;49:788–91.
105. Reddi R. Oral Submucous Fibrosis - A recent trend in its treatment. JIAOMR. 1993;4:7–8.
106. Nallapu V, Balasankulu B, Vuppalapati HB, Sambhana S, Mala D, Koppula SK. Efficacy of vitamin E in oral submucous fibrosis: a clinical and histopathologic study. J Indian Acad Oral Med Radiol. 2015;27:387–92.
107. Singh N, Singh J, Singh U. Oral sub mucous fibrosis. A new approach to treatment with combined therapy. J Indian Dent Assoc. 1996;67:168–70.
108. Nayak A, Anitha B, Bhattacharya A, Podder S. Efficacy of lycopene in combination with vitamin E in management of oral submucous fibrosis—a clinical prospective study. J Adv Med Dent Sci Res. 2015;3(3):21–5.
109. Thakur N, Keluskar V, Bagewadi A, Shetti A. Effectiveness of micronutrients and physiotherapy in the management of oral submucous fibrosis. Int Nat Contemp Dentist. 2011;2(1):101–5.
110. Raizada MK, Sable DM. Clinical assessment of efficacy of Omega 3 in oral submucous fibrosis patients—a randomized controlled trial. Asian Pac J Cancer Prev. 2022;23(4):1185–92.
111. Nagaraj T, Santosh HN. Estimation of serum hepcidin in oral submucous fibrosis before and after supplementation with oral iron: a randomized control clinical trial. J Oral Maxillofac Pathol. 2018;22(3):303–6.
112. Maher R, Aga P, Johnson NW, Sankaranarayanan R, Warnakulasuriya S. Evaluation of multiple micronutrient supplementation in the management of oral submucous fibrosis in Karachi. Pakistan Nutr Cancer. 1997;27(1):41–7.

113. Dhariwal R, Mukherjee S, Mohanty S, Chakraborty A, Ray J, Chaudhuri K. Zinc and vitamin A can minimise the severity of oral submucous fibrosis. BMJ Case Rep. 2010:bcr1020092348.
114. Anil K, Sharma SC, Sharma P, Chandra O, Singhal KC, Nagar A. Beneficial role of zinc in the treatement of oral submucous fibrosis. Indian J Pharmac. 1991;23:236–41.
115. Singh BP, Mittal N, Sharma V, Palani. Evaluation of role of Oxitard capsules in the treatment of oral submucous fibrosis. Antiseptic. 2009;106:103–7.
116. Patil S, Santosh BS, Maheshwari S, Deoghare A, Chhugani S, Rajesh PR. Efficacy of oxitard capsules in the treatment of oral submucous fibrosis. J Canc Res Therapeut. 2015;11(2):291–4.
117. Patil S, Halgatti V, Maheshwari S, Santosh BS. Comparative study of the efficacy of herbal antioxdants oxitard and aloe vera in the treatment of oral submucous fibrosis. J Clin Exp Dent. 2014;6(3):e265–70.
118. Sasi M, Kumar S, Kumar M, Thapa S, Prajapati U, Tak Y, et al. Garlic (*Allium sativum* L.) Bioactives and its role in alleviating oral pathologies. Antioxidants (Basel). 2021;10(11):1847.
119. Jiang X, Zhang Y, Li F, Zhu Y, Chen Y, Yang S, Sun G. Allicin as a possible adjunctive therapeutic drug for stage II oral submucous fibrosis: a preliminary clinical trial in a Chinese cohort. Int J Oral Maxillofac Surg. 2015;44:1540–6.
120. Jiang XW, Zhang Y, Song GD, Li FF, Peng HY, Yang SK, Sun GL. Clinical evaluation of allicin oral adhesive tablets in the treatment of recurrent aphthous ulceration. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113:500–4.
121. Jain N, Annigeri RG, Pipalia PR. Efficacy of garlic in conjunction with pentoxifylline in the management of oral submucous fibrosis—a preliminary study. Int J Pharm Sci Res. 2016;7:5017.
122. Cabras M, Carrozzo M, Gambino A, Broccoletti R, Sciascia S, Baldovino S, Arduino PG. Value of colchicine as treatment for recurrent oral ulcers: a systematic review. J Oral Pathol Med. 2020;49(8):731–40.
123. Segovia A, Niembro RF, Ibanez KG, Alcocer G, Tamayo P. Long term evaluation of colchicine in the treatment of scleroderma. J Rheumatol. 1979;6:705–12.
124. Diegelmann RF, Peterkofsky B. Inhibition of collagen secretion from bone and cultured fibroblasts by microtubular descriptive drugs. Proc Natl Acad Sci U S A. 1972;69:892–6.
125. Daga D, Singh RK, Pal US, Gurung T, Gangwar S. Efficacy of oral colchicine with intralesional hyaluronidase or triamcinolone acetonide in the Grade II oral submucous fibrosis. Natl J Maxillofac Surg. 2017;8(1):50–4.
126. Stewart S, Yang KCK, Atkins K, et al. Adverse events during oral colchicine use: a systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther. 2020;22:28.
127. Haque MF, Meghji S, Nazir R, Harris M. Interferon-gamma (IFN-gamma) may reverse oral submucous fibrosis. J Oral Pathol Med. 2001;30:12–21.
128. Sheshaprasad R, Pai A. Oral sub mucous fibrosis: exploring therapeutic strategies using -anti TGF β drugs. Asian Pac J Cancer Care. 2018;3(2):21–7.
129. Moinzadeh P, Hunzelmann N, Krieg T. Pharmacology and rationale for imatinib in the treatment of scleroderma. J Exp Pharmacol. 2013;5:15–22.
130. Akhmetshina A, Venalis P, Dees C, et al. Treatment with imatinib prevents fibrosis in different preclinical models of systemic sclerosis and induces regression of established fibrosis. Arthritis Rheum. 2009;60(1):219–24.
131. Gan Y, Herzog EL, Gomer RH. Pirfenidone treatment of idiopathic pulmonary fibrosis. Therap Clin Risk Manage. 2011;7:39–47.
132. Garcia L, Hernandez I, Sandoval A, Salazar A, Garcia J, Vera J, et al. Pirfenidone effectively reverses experimental liver fibrosis. J Hepatol. 2002;37(6):797–805.
133. Yu CC, Tsai CH, Hsu HI, Chang YC. Elevation of S100A4 expression in buccal mucosal fibroblasts by arecoline: involvement in the pathogenesis of oral sub mucous fibrosis. PLoS One. 2013;8(1):e55122.
134. Nakazato H, Oku H, Yamane S, Tsuruta Y, Suzuki R. A novel anti-fibrotic agent pirfenidone suppresses tumor necrosis factor-alpha at the translational level. Eur J Pharmacol. 2002;446(1–3):177–85.
135. Kaur J, Jacobs R. Proinflammatory cytokine levels in oral lichen planus, oral leukoplakia, and oral sub mucous fibrosis. J Korean Assoc Oral Maxillofac Surg. 2015;41(4):171–5.
136. Bishen KA, Radhakrishnan R, Satyamoorthy K. The role of basic fibroblast growth factor in oral submucous fibrosis pathogenesis. J Oral Pathol Med. 2008;37(7):402–11.
137. Tsai CH, Lee SS, Chang YC. Hypoxic regulation of plasminogen activator inhibitor-1 expression in human buccal mucosa fibroblasts stimulated with arecoline. J Oral Pathol Med. 2015;44(9):669–73.
138. Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res. 2008;68(12):4774–82.
139. Seema Nayak MMG, Makker A, Bhatia V, Chandra S, Sandeep Kumar SP, Agarwal. Fibroblast Growth Factor (FGF-2) and its receptors FGFR-2 and FGFR-3 may be putative biomarkers of malignant transformation of potentially malignant oral lesions into oral squamous cell carcinoma. PLoS One. 2015;
140. Haque MF, Meghji S, Khitab U, Harris M. Oral submucous fibrosis patients have altered levels of cytokine production. J Oral Pathol Med. 2000;29(3):123–8.
141. Hajari Case A, Johnson P. Clinical use of nintedanib in patients with idiopathic pulmonary fibrosis. BMJ Open. Respir Res. 2017;4(1)
142. Joshi M, Patravale V. Formulation and evaluation of nanostructured lipid carrier (NLC)-based gel of valdecoxib. Drug Dev Ind Pharmacy. 2006;32:911–8.
143. Averineni RK, Sunderajan SG, Mutalik S, et al. Development of mucoadhesive buccal films for the treatment of oral submucous fibrosis: a preliminary study. Pharm Dev Technol. 2009;14:199–207.
144. Gopinath D, Hui LM, Veettil SK, Balakrishnan Nair A, Maharajan MK. Comparative efficacy of interventions for the management of oral submucous fibrosis: a systematic review and network meta-analysis. J Pers Med. 2022;12(8):1272.