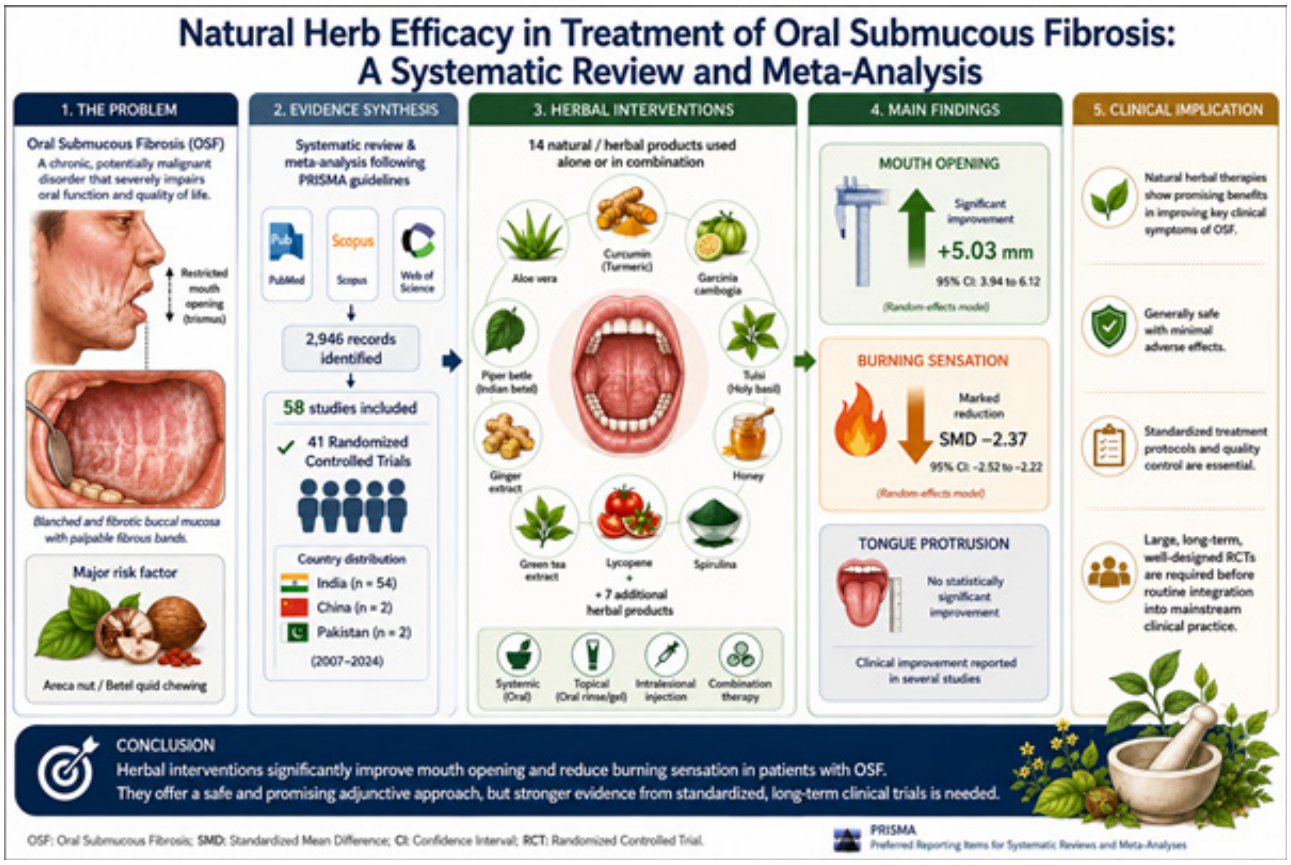
REVIEW ARTICLE

Natural Herb Efficacy in Treatment of Oral Submucous Fibrosis: A Systematic Review and Meta-Analysis

P. M. Peiris, Y. A. Jayasinghe, V. Dissanayake, A. Chandrasiri, D. Leuke Bandara, M. Yuwanati and R. D. Jayasinghe*

Graphical Abstract



Highlights

- Herbal therapies may improve mouth opening and burning symptoms in OSF
- Fifty-eight studies, including 41 RCTs, were reviewed using PRISMA
- Fourteen natural products were used alone or in combination
- Mouth opening improved significantly after herbal interventions
- Long-term trials with standardized protocols are still needed

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Natural Herb Efficacy in Treatment of Oral Submucous Fibrosis: A Systematic Review and Meta-Analysis

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Abstract

Oral Submucous Fibrosis (OSF) is a chronic, potentially malignant condition of the oral cavity that significantly affects patients' quality of life. Its clinical presentation varies with disease progression, and treatment remains a challenge due to inconsistent outcomes with conventional medical, surgical, and physical therapies. In recent years, natural and herbal remedies have attracted attention for their therapeutic potential in managing OSF. This systematic review assesses the effectiveness of such interventions. Following PRISMA guidelines, a systematic literature search was conducted across PubMed, Scopus, and Web of Science databases to identify studies evaluating natural/herbal therapies for OSF. Eligible peer-reviewed articles were selected based on predefined criteria. Data regarding mouth opening, burning sensation, and tongue protrusion were extracted. Meta-analysis was conducted using random-effects models to estimate pooled effect sizes with 95% confidence intervals. A total of 58 studies were included in this review, the majority of which were randomized controlled trials (n=41). Fourteen natural or herbal products were identified and used either alone or in combination. Meta-analysis showed that herbal interventions significantly improved mouth opening (MD: 5.03 mm; 95% CI: 3.94 to 6.12) and reduced oral burning sensation (random-effects SMD: -3.23; 95% CI: -4.03 to -2.42). Tongue protrusion improved significantly in pre-post analyses, but no significant difference was observed when natural herbs were compared with standard drugs. Herbal therapies exhibit encouraging potential in managing OSF symptoms. Standardized protocols and long-term clinical trials are essential for validating their effectiveness and integrating them into mainstream treatment strategies.

Keywords: Herbs; Natural products; Oral Potentially malignant disorder; Oral Submucous fibrosis

INTRODUCTION

Oral submucous fibrosis (OSF) is an oral potentially malignant disorder predominantly seen in South Asian populations (Rao et al., 2020). Its chronic, debilitating nature reduces the quality of life of patients who are suffering from OSF. It is characterized by the progressive fibrosis of the submucosal tissues in the mouth, leading to restricted mouth opening, difficulty in swallowing, and the formation of fibrous bands that can affect speech and eating (Anwar Sadat et al., 2022; Kundu et al., 2022). Depending on the stage of the disease, the clinical features may vary. OSF is primarily linked to the habit of areca nut chewing, along with other factors such as genetic predisposition (Prabhu et al., 2014; Rao et al., 2020). Early diagnosis and intervention are crucial in managing OSF to improve clinical symptoms, prevent progression of the disease, and, more importantly, prevent or minimize

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malignant transformation (Qin et al., 2023). Management of OSF is a challenging task for clinicians, and there are multiple methods reported in the literature. Main treatment methods of OSF can be categorized as medical, physical, and surgical therapies, together with preventive measures (Qin et al., 2023). Different medicinal preparations have been used in OSF with different levels of success. Various natural and herbal products have been explored for their potential benefits in managing OSF (Wang et al., 2023). Some commonly used natural remedies include Aloe vera, curcumin, and honey (Albahri et al., 2023). These natural remedies exhibit different properties, such as anti-inflammatory, antioxidant, and wound-healing properties, which can be beneficial for treating the clinical symptoms of OSF (Chen et al., 2023; Qin et al., 2023).

Several studies have shown that natural products can alleviate symptoms such as restricted mouth opening and pain, which are common in patients with OSF (Anwar et al., 2025). These remedies are often preferred because they are perceived as safer alternatives to conventional pharmacological treatments, which can sometimes have side effects or limited efficacy (Anwar et al., 2025). Additionally, natural remedies often offer a more holistic approach to treatment, addressing not only the clinical symptoms but also supporting the body's healing processes (Goyal & Chauhan, 2024). There is a significant number of research studies on the use of different natural products in the management of OSF. In particular, randomized controlled trials (RCTs) and case-control studies have been conducted to evaluate the effectiveness of herbal treatments. These studies generally report positive clinical outcomes with minimal or no side effects. However, the results are not always consistent, and the effectiveness of different natural products may vary depending on the formulation, dosage, and duration of use. In addition, heterogeneity in study design, methodology, populations studied and follow-up periods may have a significant impact on outcomes.

Despite the promising results from various studies, there is still a lack of standardized protocols for the use of natural products in OSF treatment. Many studies have focused on individual herbs or natural remedies, but there is limited evidence on the combined effects of multiple natural products used together. Furthermore, while many studies report positive outcomes, the methodological quality of some studies can be questioned, as factors like sample size, blinding, and control groups are not always adequately addressed. This highlights the need for more rigorous and large-scale clinical trials to confirm the efficacy of natural products for OSF treatment. In this review, we intend to gather evidence on the effectiveness of natural products reported in the literature and their role in the treatment of OSF. By analyzing available data, we hope to provide a clearer understanding of how these natural remedies can be integrated into the clinical management of OSF and whether they offer significant advantages over conventional treatments.

MATERIALS AND METHODS

Protocol registration and reporting

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) registry (Ref. CRD42024547924). The reporting adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist (Page et al., 2021).

Research question

The following research question was addressed in this systematic review.

Are natural/herbal products (Intervention) effective in improving OSF (Population) in terms of mouth opening, burning sensation, and tongue protrusion (Outcome) compared to Standard medical treatment or placebo (Comparator)? (Steroid therapy, especially intralesional steroid injections, has been regarded as the conventional or "standard" nonsurgical treatment for comparison.)

Eligibility criteria

The eligibility of including retrieved literature was based on the inclusion and exclusion criteria set for this systematic review. The detailed criteria are as follows:

Inclusion

Studies conducted in OSF patients that have evaluated herbal/natural products/agents and compared with Standard medical treatment or placebo.

Studies that have evaluated the effect of herbal/natural products/agents on mouth opening and/or burning sensation and/or tongue protrusion.

Studies that have reported outcome values either pre-post or at the end of treatment as mean and standard deviation.

All types of primary studies (Observational, case-control, randomized controlled trials, and cross-sectional studies) were included.

Exclusion

Non-original research papers (e.g., commentaries, letters, reviews, case reports, etc.) in peer-reviewed journals

Publications not published in peer-reviewed journals (e.g., books, book chapters, etc.)

Databases and search strategy

The electronic search of all the relevant literature was carried out on three major databases (including PubMed, SCOPUS, Web of Science), which were searched from

inception till April 2024. The search strategy followed the PICO (P – Population, I – Intervention, C- Comparator, and O – Outcome) framework, where the population of interest was patients who were above 18 years of age who were clinically and histopathologically diagnosed with OSF, the intervention was natural/herbal products given to treat oral submucous fibrosis, the comparator was standard medical treatment or placebo products given to treat oral submucous fibrosis and the outcome of interest were improvement in mouth opening (mm) reduction in burning sensation (VAS) and improvement in tongue protrusion (mm). The different search terms on the use of natural products for the management of oral submucous fibrosis were searched with the aid of Boolean operators ("OR" and "AND") and truncation ("*"). The search terms used were as follows: Oral submucous fibrosis, OSF, OSMF, natural treatment, treatment, therapy, therapeutic, manag*, treat*, plant extract, leaf extract, root extract, latex extract, pulp extract, stem extract, ayurvedic, ayurved*, seed extract, plant antioxidants, antioxidant, plant enzyme, management, mouth opening, interincisal distance, burning sensation, tongue protrusion.

Literature selection

All the literature retrieved from the searched research databases were imported into the Rayyan web application to remove duplicate entries (Ouzzani et al., 2016). Subsequently, the literature was screened by at least two blinded independent reviewers (PMP, YAJ, AC, VD) in a two-stage process. In the first stage, titles and abstracts of the deduplicated literature were screened, and the irrelevant literature was excluded. Literature that was not excluded in the first stage proceeded to the second stage, where full-text screening was done. In case conflicts arose, additional senior reviewers (MY or RDJ) were consulted to resolve any conflicts during the screening process.

Data extraction

In this systematic review, a standardized data extraction sheet was utilized to extract relevant information from each included study (Afifi et al., 2023). The data extraction process comprised the author and year of publication, geographical location of the study, study design, sample size, sampling technique, case definition, characteristics of participants, interventions, and standard treatments. The interventions were documented, focusing on the type of natural products used, their dosage, administration, and the duration of treatment. Similarly, the dosage, administration, and the duration of the standard/ placebo medications were also extracted. Furthermore, the baseline and end-of-treatment means and standard deviations of mouth opening in mm, burning sensation via visual analogue scale, and tongue protrusion in mm of the outcomes assessed were meticulously recorded to facilitate comprehensive analysis.

Data synthesis

Data synthesis in this systematic review involved both qualitative and quantitative approaches to comprehensively evaluate the efficacy of natural products in managing oral submucous fibrosis. A narrative synthesis was initially conducted to summarize the findings across studies, highlighting common themes, effectiveness, and identified limitations. When sufficient homogeneity existed among the studies, a meta-analysis was performed to calculate pooled effect sizes, utilizing random-effects models to account for variability. Subgroup analyses were also undertaken to explore potential differences in treatment outcomes based on factors such as the type of natural product, severity of oral submucous fibrosis, and duration of treatment. This multifaceted synthesis strategy allowed for a nuanced understanding of the data, facilitating the identification of trends and variations that could inform clinical practice and future research directions.

Risk of bias assessment

The risk of bias assessment was conducted to evaluate the methodological quality of the included studies. Two independent reviewers assessed each study using standardized tools appropriate for the study design. For randomized controlled trials, the Cochrane Risk of Bias Tool was utilized, which encompassed various domains, including selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each domain was rated as low, unclear, or high risk of bias based on the information provided in the studies. Two reviewers independently assessed the risk of bias, resolving disagreements through consensus.

Data analysis

Data were analyzed using RStudio software (RStudio 2024.12.0+467 "Kousa Dogwood" Release for Windows) with the help of the meta package. Meta-analyses were performed where appropriate, and effect sizes were calculated as odds ratios (OR) or standardized mean differences (SMD) with 95% confidence intervals (CI). Heterogeneity was assessed using the I^2 statistic, and fixed- or random-effects models were chosen based on the level of heterogeneity. Sensitivity analyses were performed to assess the robustness of the findings by excluding studies with a high risk of bias or differing methodological quality. Funnel plots and Egger's regression test were conducted to evaluate potential publication bias.

RESULTS

Search results

The keyword search yielded a total of 2946 articles from various databases, including PubMed (n=1022), Scopus (n=978), and Web of Science (n=946). After removing 985 duplicates, 1961 articles were screened based on their titles and abstracts. A further exclusion of 1874 articles was performed due to irrelevance to the research question, leaving 87 articles for full-text evaluation. Full text could not be retrieved for three of the 84 remaining articles; 26

studies were excluded based on predetermined inclusion and exclusion criteria, such as study design, population characteristics, and outcome measures. Ultimately, 58 studies met all eligibility requirements and were included in the final analysis (Figure 1) (Haddaway et al., 2022). These studies comprised a diverse range of methodologies, including randomized controlled trials, cohort studies, and cross-sectional analyses, providing a robust foundation for understanding the research question. The results of this comprehensive search highlight the breadth of existing literature while ensuring that the studies included were directly relevant and methodologically sound.

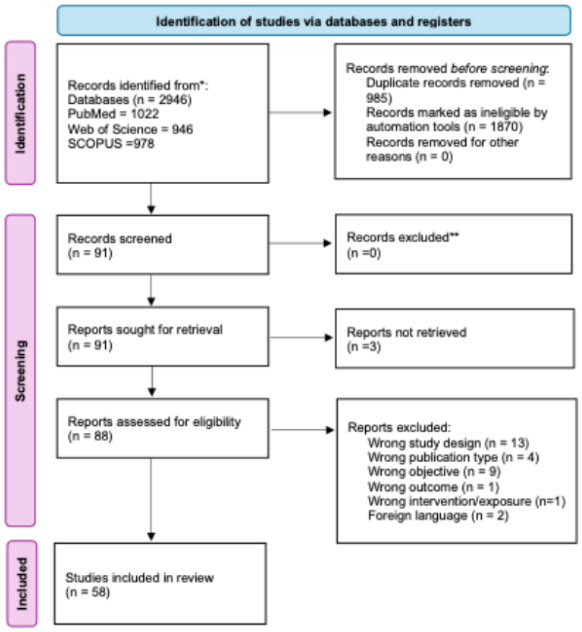


Figure 1: PRISMA flow diagram showing study identification, screening, eligibility assessment, and final inclusion

Study characteristics

A total of 58 studies were included in this systematic review, primarily conducted in India (n=54), China (n=2), and Pakistan (n=2), with publication years ranging from 2007 to 2024. 41 RCTs, 14 cohort studies, two cross-sectional studies, and one case-control study.

There are 14 different natural products that have been used to treat OSF. They are as follows, Astaxanthin (Perumal et al., 2024),Turmeric (Agarwal et al., 2014; Aich et al., 2019; Bohra et al., 2021; Ismail et al., 2020; Mobeen et al., 2023; Srivastava et al., 2015) Curcumin (Agarwal et al., 2014; Bhowate et al., 2020; Biswas et al., 2022; Chandrashekar et al., 2021; Kopuri et al., 2016; Dalai et al., 2023; Deepak et al., 2021; Hazarey et al., 2015; Ismail et al. 2020; Lanjekar et al. 2020; Mahato et al., 2019; Mobeen et al., 2023; Namratha et al., 2023; Piyush et al., 2019; Rai et al., 2019; Saran et al., 2018; Sharma et al., 2021; Srivastava et al., 2015; Srivastava et al., 2021; Tepan et al. 2023; Yadav et al., 2014), Tulsi (Agarwal et al., 2014; Bhowate et al., 2020; Chandrashekar et al., 2021; Kopuri et al., 2016; Deepak et al., 2021; Hazarey et al., 2015; Ismail et al., 2020; Mahato et al., 2019; Namratha et al., 2023; Piyush et al., 2019; Rai et al., 2019; Saran et al., 2018; Sharma et al., 2021; Srivastava et al., 2021; Yadav et al., 2014) Honey (Aich et al., 2019; Alam et al., 2013; Anuradha et al., 2017; Bohra et al., 2021; Dalai et al., 2023; Pazhanivel & Ganesan, 2022; Mobeen et al., 2023; Rajbhoj et al., 2021; Singh et al., 2016; Sudarshan et al., 2012) Aloe vera (Alam et al., 2013; Anuradha et al., 2017; Bohra et al., 2021; Dalai et al., 2023; Pazhanivel & Ganesan, 2022; Rajbhoj et al., 2021; Patil et al., 2015b; Patil et al., 2014a; Singh et al., 2016; Sudarshan et al., 2012), Lycopene (Arakeri et al., 2020; Biswas et al., 2015; Kopuri et al., 2016; Goel & Ahmed, 2015; Gowda et al., 2011; Hussain et al., 2023; Johny et al., 2019; Karemore & Motwani, 2012; Kumar et al., 2007; Mahato et al., 2019; Patil et al., 2014b; 2018; Piyush et al., 2019; Samuel & Renukananda, 2015; Saran et al., 2018; Selvam & Dayanand, 2013; Singh et al., 2014) , Colchicine (Mounika et al., 2021; Krishnamoorthy & Khan (2013), Triphala (Aich et al., 2019) Allicin (Jiang et al., 2015) Oxitard (Patil et al., 2014a; 2015a; 2018), Spirulina (Mulk et al., 2013; Patil et al., 2014b; 2015b; Shetty et al., 2013), natural beta-carotene (Thriveni et al., 2011) and Omega-3 (Raizada et al.,2017). They have been used alone or in combination with several natural products or with standard treatments. There are 32 studies where a combination of medications was used and 26 studies where only one natural product was used as the treatment. These natural herbs were administered to the patients with multiple ways both systemically, topically and as intra-lesional injections. In 14 studies only capsules of natural products were given to patients, but in most of the studies, a combination of capsules, mouthwash, intra-lesional injection, and systemic drugs was used. The majority of the studies (36 studies) had only clinical diagnosis of OSF, and in 22 studies both clinical and histopathological confirmation of disease were carried out. The main study characteristics are shown in Table 1 below.

Even though we intended to do a comparison of the effectiveness of natural products with standard treatments or placebo, we did not come across any study with reliable data on placebo for comparison.

Meta analysis

Mouth opening

Natural herb intervention

This meta-analysis of pre and post-treatment mouth opening in 1517 OSMF patients from 46 studies (Figure 2), showed a statistically significant mean difference of 5.03 mm (95% CI: 3.94 to 6.12, $p < 0.0001$) between pre and post-treatment mouth opening. While this indicates that the natural herb treatment has increased mouth opening by 5 mm, the meta-analysis also showed extremely high heterogeneity (I^2 = 99.9%, Tau^2 = 13.09), suggesting substantial variability between studies due to differences in populations.

Table 1: Study characteristics obtained through data extraction

Author & publication year	Journal	Country	Type of study	Composition	Form	Intervention used	Ethnicity/ Population	Case definition	Total OSMF patients investigated
Perumal et al. (2024)	Cureus Journal of Medical Sciences	India	Randomized Clinical Trial	Combination	Capsule	5 mg astaxanthin capsules twice daily	Indian	Clinically diagnosed with OSMF	68
Mobeen et al. (2023)	Cureus Journal of Medical Sciences	India	Randomized Clinical Trial	Combination	Paste	Combination (10 mg of turmeric powder (Curcuma longa), 10 mg of tulsi powder, and 10 ml of honey)	Indian	Clinically and histopathologically proven OSMF	80
Dalai et al. (2023)	Journal of Pharmacy and Bioallied Sciences	India	Cross-sectional	Alone	Paste	Group A- 1 gm of aloe vera with glycerin, Group B- 1 gm of Tulsi with glycerin	Indian	Not specified	30
Namratha et al. (2023)	Journal of Indian Academy of Oral Medicine	India	Case-Control	Combination	Capsule	Capsule of curcumin 400 mg	Indian	Clinically and histopathologically confirmed OSMF	42
Tepan et al. (2023)	Journal of Indian Academy of Oral Medicine & Radiology	India	Randomized Clinical Trial	Combination	Tablet	Experimental group: Curcumin-Piperine (1054.6 mg curcumin + 2.5 mg piperine per tablet), 2 tablets 3x/day for 2 months with antioxidants. Control: Antioxidants only	Indian	Based on Khanna and Andrade (1995) for the clinical diagnosis of OSMF	40
Hussain et al. (2023)	Medical Forum	Pakistan	Cross-sectional	Combination	Capsule (Lycopene)	Experimental group: Lycopene (16 mg daily), Hyaluronidase (1500 IU mixed with lignocaine, twice daily), Dexamethasone (1.5 mg intralesional injection, twice weekly); Control group; Group B; Hyaluronidase (1500 IU mixed with lignocaine, twice daily), Dexamethasone (1.5 mg intralesional injection, twice weekly), Multivitamins (daily); Control group; Dexamethasone (1.5 mg intralesional injection, twice weekly), Hyaluronidase (1500 IU mixed with lignocaine, twice daily)	Pakistan	Patients with addiction to areca nut chewing and its relevant products, limited mouth opening, burning sensation on ingestion.	399
Dhole et al. (2023)	Journal of Indian Academy of Oral Medicine & Radiology	India	Randomized Clinical Trial	Alone	Capsule	Group A: Bee pollen capsules, 500 mg, taken orally twice daily, for 90 days.	India	Based on Khanna and Andrade classification (1995), Grade I, II, III	96

Biswas et al. (2022)	Indian Journal of Dental Research	India	Cohort	Alone	Paste	Tulsi paste, 250 mg extract per application, applied topically twice daily, for 90 days.	India	Based on Lai DR classification (Grades I, II, III)	60
Pazhanivel & Ganesan (2022)	International Journal of Chemical and Biochemical Sciences	India	Randomized Clinical Trial	Alone	Gel	Aloe vera gel, 5 mg, applied topically three times daily, for 90 days.	India	Based on Khanna and Andrade classification	11
Bohra et al. (2021)	Asian Pacific Journal of Cancer Prevention	India	Cohort	Combination	Gel	Group A: Kali Haldi 2 mg and Aloe Vera gel 2 mg, applied topically thrice daily for 90 days.	India	Based on Pindborg et al. classification for OSMF (Stages 2 and above).	42
Srivastava et al. (2021)	Journal of Contemporary Dental Practice	India	Cohort	Alone	Lozenges	Group A: Curcumin lozenges (100 mg turmeric extract + 10 mg clove oil), taken orally three times daily for 90 days.	India	Based on Khanna and Andrade classification (Group III OSMF: moderately advanced cases)	80
Deepak et al. (2021)	Journal of Pharmacy and Bioallied Sciences	India	Cohort	Alone	Tablets	Curcubest tablet, 500 mg, taken orally twice daily for 90 days.	India	Clinically diagnosed OSMF based on inability to open mouth, blanching, burning sensation, and palpable fibrous bands.	30
Chandrashekar et al. (2021)	Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology	India	Cohort	Alone	Gel and as an adhesive patch	Group A: Curcumin gel (5 mg per application), applied topically twice daily for 8 weeks. Group B: Curcumin buccal patches (2 cm x 3 cm), applied twice daily for 56 days.	India	Clinical diagnosis	40
Rajbhoj et al. (2021)	Asian Pacific Journal of Cancer Prevention	India	Randomized Clinical Trial	Combination	Gel	Group A: Curcumin gel (5 mg/ application), applied topically 3–4 times daily for 6 weeks. Group B: Aloe Vera gel (100%), applied topically 3–4 times daily for 42 days.	India	Based on inter-incisal distance, as classified by Lai DR 2	60
Tahir et al. (2021)	Pakistan Armed Forces Medical Journal	Pakistan	Cohort	Combination	Gel	Group I: Alpha Lipoic Acid (300 mg BID or 600 mg OD) + Aloe Vera Gel, applied topically thrice daily for 3 months. Group II: Intralesional hydrocortisone (100 mg mixed with lignocaine) injected biweekly for 3 months.	Pakistan	Based on trismus, burning sensation, blanching, stiffness and palpable fibrotic bands	28

Sharma et al. (2021)	Journal of Orofacial Sciences	India	Randomized Clinical Trial	Combination	Tablets	Curcumin 300 mg + Piperine 5 mg (TurmixR), taken orally thrice daily for 90 days, with dexamethasone injection biweekly for 12 weeks.	Indian	Based on Haider et al. classification for OSMF	50
Mounika et al. (2021)	Journal of Indian Academy of Oral Medicine & Radiology	India	Randomized Clinical Trial	Alone	Tablets	Group A: Colchicine (0.5 mg) tablets, taken orally twice daily, for 90 days. Group B: Intralesional injection of dexamethasone (2 mL) + hyaluronidase (1500 IU), administered biweekly for 42 days.	Indian	Clinical diagnosis based on the criteria given by Babu S et al. (1996). Staging done according to the criteria given by More CB et al. (2011).	30
Arakeri et al. (2020)	Journal of Oral Pathology and Medicine	India	Cohort	Alone	Capsule	Group A: Lycopene, 8 mg/day in two divided doses, for 90 days. Group B: Placebo capsules, for 90 days.	Indian	Based on Khanna and Andrade classification	400
Ismail et al. (2020)	International Journal of Dentistry and Oral Sciences	India	Cohort	Alone	Tablets	Turmeric tablets (Turmix), 300 mg curcumin and 5 mg piperine, taken orally thrice daily for 30 days.	Indian	Based on inter-incisal distance: Lai's classification	60
Lanjekar et al. (2020)	Journal of Contemporary Dental Practice	India	Cohort	Combination	Gel	Group I: Mucoadhesive semisolid gel of curcumin, applied topically thrice daily, for 42 days. Group II: Mucoadhesive semisolid gel of triamcinolone acetonide and hyaluronidase, applied topically thrice daily, for 42 days. Group III: Mucoadhesive semisolid gel of curcumin in addition to triamcinolone acetonide and hyaluronidase, applied topically thrice daily, for 42 days.	Indian	Based on Haider et al. classification (Stages A, B only; Stage C excluded)	120

Rai et al. (2019)	Journal of investigative and Clinical Dentistry	India	Randomized Clinical Trial	Combination	Capsule, tablet, mouthwash	Group I - antioxidant capsule Group II - Turmix tablet (curcumin 300mg, piperine 5mg) Group III - Turmix tablet and Turmix mouthwash (Curcuma longa dry extract 0.10% w/v)	Indian	Current or previous use of any form of areca nut with/ without smokeless tobacco (any duration and frequency); complaints of burning sensation of the mouth when eating hot and spicy food and/ or difficulty in swallowing and chewing; and presenting with clinical features like restricted MO and/or changes in the oral mucous membrane including presence of vertical fibrous bands, stiffness, blanching and circumoral bands.	119
Mahato et al. (2019)	The Journal of Contemporary Clinical Dentistry	India	Cohort	Combination	Tablet	BIOCUMIN tablet [curcumin (500 mg), piperine (5 mg), and lycopene (25 mg)]	Indian	Clinically and histopathologically diagnosed with OSMF	40
Johny et al. (2019)	The Journal of Pharmacy and Bioallied Sciences	India	Randomized Clinical Trial	Combination	Systemic and intralesional injections	Group I - LycoRed (lycopene, with zinc, selenium, and phytonutrients) Group II - LycoRed with hyaluronidase (Hynidase) intralesional injection	Indian	Clinically and histopathologically diagnosed with OSMF	39
Beenakumary et al. (2019)	The journal of contemporary dental practice	India	Randomized Clinical Trial	Combination	Systemic and intralesional injections	Group 1: capsule lycopene group 2: capsule lycopene and injection dexamethasone group 3: injection dexamethasone and hyaluronidase	Indian	Stage II OSMF based on habitual history and clinical findings	60
Piyush et al. (2019)	Oral Diseases	India	Randomized Clinical Trial	Combination	Tablets, capsules	Group A - tablet with a combination of curcumin and piperine 300 mg Group B - lycopene capsules 8 mg Group C - placebo capsules constituting starch IP and lactose monohydrate IP	Indian	Patients with clinical characteristic of OSMF (areca nut habit with blanching and palpable fibrous bands) whose diagnosis was confirmed histopathologically	90
Kapoor & Arora (2019)	Oncology and Radiotherapy	India	Cohort	Alone	Capsule	400 mg of curcumin	Indian	Clinical-histopathologically diagnosed with leukoplakia, lichen planus, and OSMF	20

Saran et al. (2018)	Indian Journal of Dental Research	India	Randomized Clinical Trial	Combination	Capsule, tablet	Group A – lycopene capsules (lycopene: 4 mg, zinc: 7.5mg, selenium: 35mg), Group B – curcumin tablets (curcuma longa extract: 300 mg and piper nigrum: 5 mg).	Indian	Characteristic signs and symptoms of OSMF such as restricted mouth opening, presence of blanching with palpable vertical fibrous bands, burning sensation on eating spicy food	60
Aich et al. (2019)	Journal of Indian Academy of Oral Medicine & Radiology	India	Cohort	Combination	Mouthwash	Mouth rinse containing turmeric (curcuma longa- 10.5 mm), triphala (400 mg), and honey (10 gm)	Indian	Chronic OSMF characterized by difficulty in opening mouth, blanched mucosa, and pain at rest in the oral cavity	40
Patil et al. (2018)	Pesquisa Brasileira em Odontopediatria e Clinica Integrada	India	Randomized Clinical Trial	Alone	Capsule	Group A - 2 oxitard capsules twice daily Group B - 8 mg lycopene in 2 divided doses of 4 mg	Indian	Clinico-pathologically diagnosed OSMF	120
Raizada et al. (2017)	Journal of Oral Pathology and Medicine	India	Randomized Clinical Trial	Combination	Capsule, intralesional injections	Group A - intralesional injections of dexamethasone and hyaluronidase mixed with lignocaine and a placebo Group B - intralesional injections of dexamethasone hyaluronidase mixed with lignocaine with omega-3	Indian	Clinically confirmed adult patients with OSF	10
Anuradha et al. (2017)	Journal of Oral Pathology and Medicine	India	Randomized Clinical Trial	Combination	Systemic, topical	Group A - systemic (juice) and topical aloe vera (gel) Group B - intralesional injection of hydrocortisone and hyaluronidase with antioxidant supplements	Indian	Patients with OSMF (stage 2 according to Pindborg)	74
Singh et al. (2016)	The Journal of Contemporary Dental Practice	India	Randomized Clinical Trial	Alone	Gel, capsule	Group A - Aloe vera gel (forever living gel) with physiotherapy Group B - antioxidant capsules with physiotherapy	Indian	Clinically proven individuals with OSMF (presenting with clinical signs and symptoms of OSMF)	40
Kopuri et al. (2016)	Journal of International Oral Health	India	Randomized Clinical Trial	Alone	Capsule	Group A - Lycored 8 mg/day in 2 divided doses Group B - curcumin 800 mg/day in 2 divided doses	Indian	Clinically diagnosed and ultrasonographically confirmed OSMF cases	30
Jiang et al. (2015)	International Journal of Oral and Maxillofacial Surgery	China	Randomized Clinical Trial	Alone	Intralesional injections	Group A - intralesional injection of triamcinolone acetonide (2 mg) Group B - intralesional injection of allicin (1 mg)	Chinese	Clinical stage II OSMF (Pindborg)	48

Hazarey et al. (2015)	Journal of Oral and Maxillofacial Pathology	India	Randomized Clinical Trial	Alone	Lozenge, topical application	Test - Longvida lozenges (400 mg lozenges) 2 g daily Control - topical clobetasol propionate	Indian	Clinically diagnosed patients with OSF (diagnosed on the basis of reduction in interincisal distance on maximum mouth opening and palpable fibrous bands involving oral mucosa)	30
Patil et al. (2015a)	Journal of Cancer Research and Therapeutics	India	Randomized Clinical Trial	Alone	Capsule	Group A - oxitard capsules Group B - placebo tablets	Indian	Clinico-pathologically diagnosed OSMF	120
Samuel & Renukananda (2015)	International Journal of Scientific Study	India	Randomized Clinical Trial	Combination	Tablet, intralesional injection	Group A - intra-lesional triamcinolone injections (40 mg/ml) Group B - 6 mg oral lycopene Group C - weekly steroid injections with oral lycopene tablets	Indian	Patients of clinical OSMF	75
Goel & Ahmed (2015)	Journal of Cancer Research and Therapeutics	India	Randomized Clinical Trial	Combination	Capsule	Lycopene group -2 mg capsule lycopene Betamethasone group - intralesional injection of betamethasone (4 mg/ml) Placebo - no treatment	Indian	Clinicopathologically diagnosed OSMF	270
Srivastava et al. (2015)	Journal of Ayurveda & Integrative Medicine	India	Cohort	Combination	Paste	1 gm of turmeric powder and 1 gm of tulsi powder in glycerine	Indian	Clinico-pathologically diagnosed OSMF	41
Patel et al. (2015)	Journal of Research in Ayurveda	India	Randomized Clinical Trial	Combination	Paste and mouthwash	Madhupippalyadi Pratisarana (external application): 3–6 g of paste applied twice daily Ksheerabala Taila (gargling): 10–15 ml, twice daily Rasayana Yoga (internal therapy): 6 g orally with honey and ghee, twice daily	Indian	Clinically diagnosed OSMF	22
Patil et al. (2015b)	Journal of Oral Biology and Craniofacial Research	India	Randomized Clinical Trial	Combination	Oral for spirulina, Topical for aloe vera	500 mg of spirulina administered in two doses daily for three months, and 5 mg of aloe vera gel applied topically three times daily for the same duration	Indian	Clinically diagnosed OSMF	42
Biswas et al. (2015)	Indian Journal of Public Health Research & Development	India	Randomized Clinical Trial	Combination	Oral Capsule	Lycopene capsule (16 mg/day) with intralesional Dexamethasone and Hyaluronidase	Indian	Clinically and histopathologically diagnosed with OSMF	45

Yadav et al. (2014)	Journal of Oral Biology and Craniofacial Research	India	Randomized Clinical Trial	Combination	Tablets (Curcumin), Injections (Steroid + Hyaluronidase)	Weekly intralesional steroid injections + hyaluronidase vs. daily oral curcumin (300 mg) tablets	-	Clinically and histopathologically diagnosed with OSMF	40
Patil et al. (2014a)	Journal of Clinical and Experimental Dentistry	India	Randomized Clinical Trial	Alone	Capsules (oxitard) and topical gel (aloe vera)	Oxitard (Group A) - 2 capsules twice daily; Aloe Vera (Group B) - 5 mg applied topically thrice daily	Indian	Clinically and histopathologically diagnosed with OSMF	120
Singh et al. (2014)	Journal of Indian Academy of Oral Medicine & Radiology	India	Randomized Clinical Trial	Combination	Soft gel (Lyconex)	Lycopene (10,000 mcg daily, split dose) vs. intralesional betamethasone injections (4 mg)	Indian	Clinically diagnosed	44
Patil et al. (2014b)	Clinical Cancer Investigation Journal	India	Randomized Clinical Trial	Combination	Oral tablets (500 mg Spirulina, 8 mg Lycopene)	Spirulina (500 mg, 2 divided doses), Lycopene (8 mg, 2 divided doses of 4 mg).	Predominantly Indian	Clinico-pathologically diagnosed OSMF	68
Agarwal et al. (2014)	Journal of Indian Academy of Oral Medicine & Radiology	India	Cohort	Alone	Tablet	Commercially available turmeric tablet administered orally	Indian	Clinically diagnosed with OSMF	30
Alam et al. (2013)	Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology	India	Randomized Clinical Trial	Alone	Local application	Aloe vera gel applied to the buccal mucosa, palate, and other areas	Indian	Diagnosis confirmed by clinical and histopathologic findings	60
Mulk et al. (2013)	Journal of Clinical and Diagnostic Research.	India	Randomized Clinical Trial	Alone	Oral tablet	Spirulina and Pentoxyfilline administered orally.	Indian	Clinically and histopathologically diagnosed cases of OSMF	40
Krishnamoorthy & Khan (2013)	Dental Research Journal	India	Randomized Clinical Trial	Alone	Tablet	Colchicine tablets and intralesional hyaluronidase/hydrocortisone acetate injections.	Indian	Based on WHO criteria and confirmed histopathologically	50
Shetty et al. (2013)	Indian Journal of Dental Research	India	Randomized Clinical Trial	Alone	Oral capsule	Spirulina (500 mg) orally twice daily for Group A, and placebo for Group B	South Karnataka and North Kerala patients	Clinically and histopathologically confirmed OSMF (Stages 1 and 2)	40
Jiang et al. (2013)	Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology.	China	Randomized Clinical Trial	Alone	Intralesional injection.	Triamcinolone acetonide (TA) and salvianolic acid B (SA-B).	Not specified in the provided contexts.	Clinically suspected cases confirmed by biopsy and histologic examination.	44
Selvam & Dayanand (2013)	Asian J Pharm Clin Res	India	Randomized Clinical Trial	Combination	Oral lycopene and intralesional steroids	Lycopene therapy combined with intralesional steroid therapy	Indian	Patients with signs and symptoms of OSMF	45

Sudarshan et al. (2012)	Journal of oral medicine and pathology	India	Randomized Clinical Trial	Combination	Aloe vera gel and antioxidant capsules	Aloe vera gel (5 mg) applied topically	Not specified	OSMF diagnosed based on clinical and histopathological criteria	20
Karemore & Motwani (2012)	Indian Journal of Dental Research.	India	Randomized Clinical Trial	Alone	Lycored softgel tablets.	8 mg of lycopene per day, divided into two doses of 4 mg each.	Indian population	Diagnosis based on clinical and histopathological criteria	92
Thriveni et al. (2011)	Journal of Indian Academy of Oral Medicine and Radiology.	India	Randomized Clinical Trial	Combination	Injections and capsules	Group A received intralesional injections of hyaluronidase and hydrocortisone and beta-carotene capsules; Group B received similar injections and Revox capsule	Indian	Based on WHO criteria for oral submucous fibrosis (OSMF).	50
Gowda et al. (2011)	Journal of Clinical and Diagnostic Research.	India	Randomized Clinical Trial	Combination	Capsule	Oral Lycopene (LycoRed capsules)	Indian	OSMF diagnosed through clinical symptoms (pallor, fibrous bands, reduced pliability)	12
Kumar et al. (2007)	Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology	India	Randomized Clinical Trial	Alone	Capsules	Lycopene (16 mg daily) and intralesional betamethasone injections for one group	Indian	Based on clinical and histopathological findings, history of areca nut chewing, restricted mouth opening, and oral mucosa changes.	58

A 95% prediction interval for mouth opening is given by -2.34 to 12.40. According to Cook's distances, several studies (Arakeri et al., 2020; Kapoor & Arora, 2019; Patil et al., 2015b; Patil et al., 2018; Tahir et al., 2021) could be considered to be overly influential. Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (p = 0.07 and p = 0.55, respectively).

Considering the high heterogeneity, a sensitivity analysis was performed according to sample size. Studies were subgrouped as sample size <30 versus ≥30 (Figure 3). No significant subgroup difference was observed (p = 0.7965), indicating that sample size did not significantly modify the estimated effect of natural-herb treatment on mouth opening.

Natural herb versus standard drug treatment

The meta-analysis included 27 studies carried out in 1,893 OSMF patients (961 in "Natural Herb" and 932 in "Standard Drugs") analyzes the effect of natural herb and standard drug treatment on mouth opening (Figure 4). The meta-analysis indicated a moderate benefit of natural herbs. Compared to standard drugs, the common-effect model revealed a significant standardized mean difference (SMD) of 0.47 (95% CI: [0.36, 0.57; p = 0.0001]). However, there was high heterogeneity (I^2 = 96.7%, p = 0.0001), indicating variation across studies. The random-effects model indicated a non-significant SMD of -0.49 (95% CI: [-1.5707, 0.59; p = 0.3560]) in mouth opening between the two treatment groups, with a wide prediction interval of -5.90 to 4.92.

This meta-analysis analyzed the effects of natural herb alone compared to natural herb in combination with other treatments on mouth opening in OSMF patients from four studies, with 322 patients (Figure 5). 168 patients were in the "Natural Herb + Other (Post)" group and 154 were in the "Natural Herb (Post)" group. The common-effect model showed a statistically significant SMD of 0.28 (95% CI: [0.05, 0.50], p = 0.0156) in mouth opening. This suggests the combination treatment had some benefit ("Natural Herb + Other") over the single treatment ("Natural Herb"). In contrast, the random-effects model observed an SMD of 0.5182 (95 % CI: [-0.54, 1.57]) which was not statistically significant (p = 0.2163). The prediction interval ranged between -1.62 and 2.66, indicating high variability in treatment effect between Natural Herb + Other and Natural Herb. There was considerable heterogeneity among the studies, resulting in an I^2 value of 82.6% (95% CI: [55.4%, 93.2%]), meaning that most variability in effect sizes is due to differences between studies. The test for heterogeneity revealed marked differences among the included studies (Q = 17.26, p=0.0006), confirming these variations were not random.

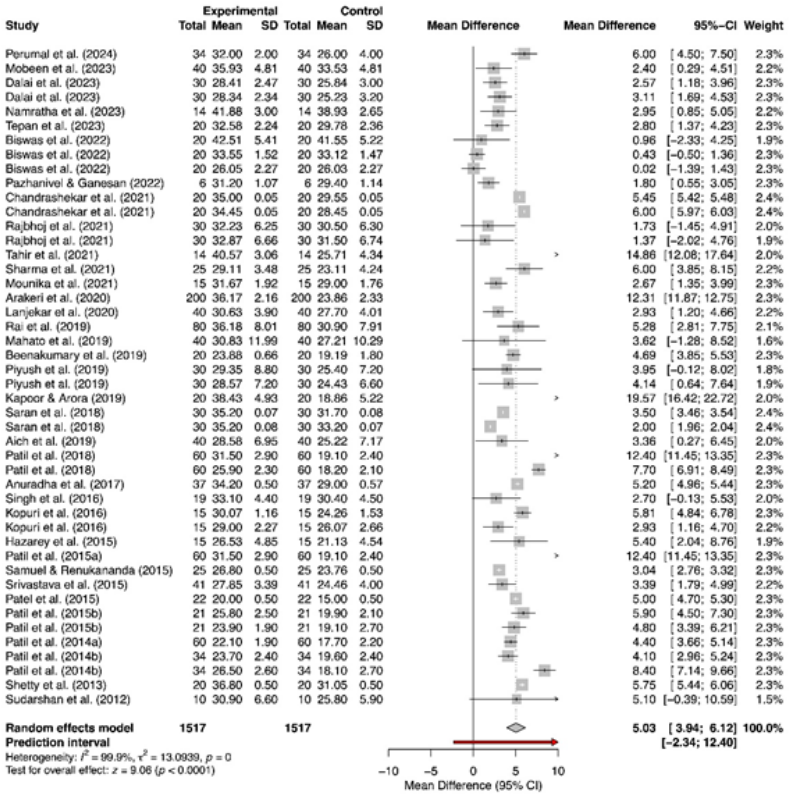


Figure 2: Meta-analysis of pre-post change in mouth opening after natural herbal interventions in OSF

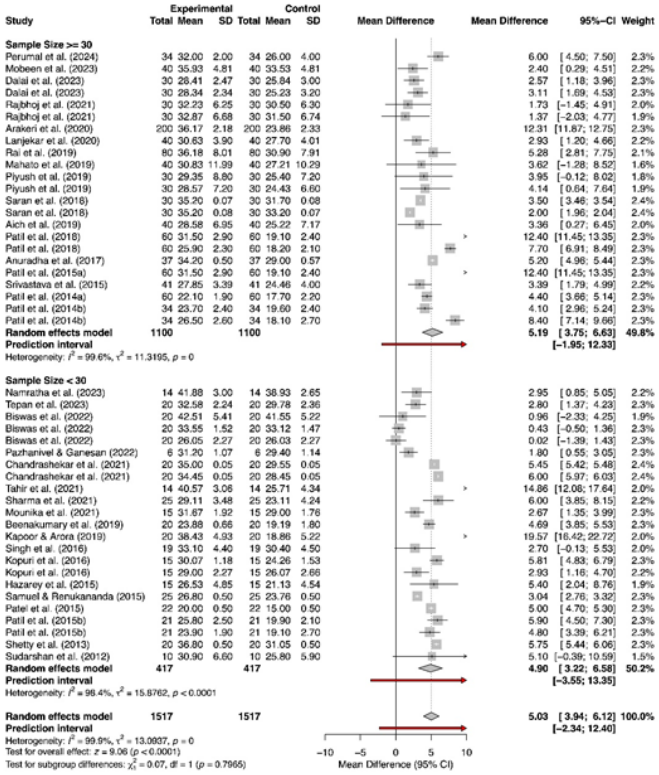


Figure 3: Subgroup analysis of pre and post-natural herb treatment for sample sizes below 30 vs above 30

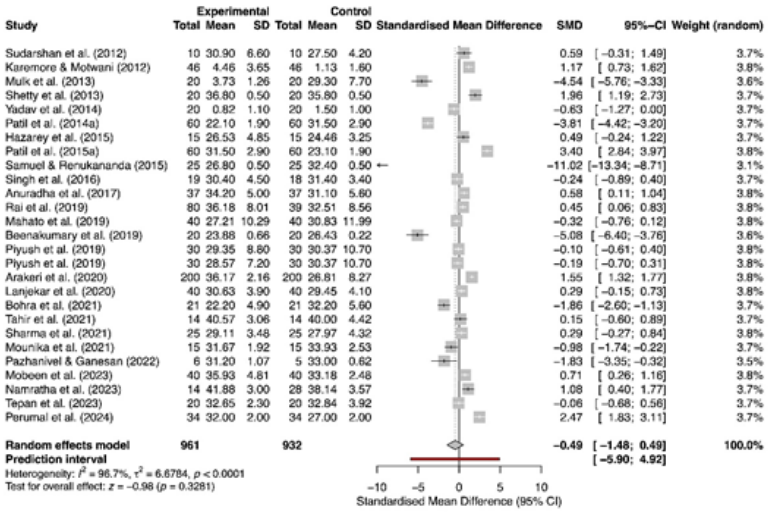


Figure 4: Meta-analysis of mouth opening in OSMF patient treated with natural herb versus standard drugs

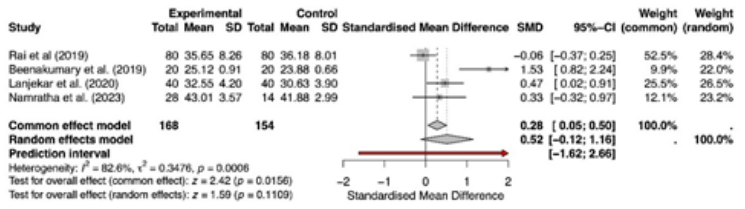


Figure 5: Meta-analysis of mouth opening; Natural herb alone vs Combination

Risk of bias (Mouth opening)

The Risk of Bias (ROB) was assessed in included studies across five key domains (Figure 6). 25 studies were high risk, 6 had some concerns, whereas 6 studies were low risk. Most of the high-risk studies did not mention or provide information about the randomization process or blinding of the outcome assessor. Similarly, studies with some concerns also did not clearly mention randomization or outcome assessor blinding.

Burning sensation

Natural herb intervention alone

This meta-analysis evaluated the efficacy of natural herbs on burning sensation by analyzing the difference between pre-treatment and post treatment outcomes for 25 studies that involved a total of 684 OSMF patients (Figure 7). Most of the participants, after treatment, experienced a significant reduction in burning sensation with a strong treatment effect (SMD: -2.37, 95% CI; -2.52 to -2.22, $p < 0.0001$). However, the prediction interval (-7.40 to 0.95) indicates impact of certain factors. High degree of heterogeneity ($I^2 = 92.0\%$) suggests that there is considerable variability within the studies. Even though these results provide evidence toward the efficacy of natural herbs, further studies are warranted to substantiate these findings.

Natural herb versus standard drug treatment

This meta-analysis analyzed 17 studies with 1,231 OSMF patients (630 in the "Natural Herb" group and 601 in the "Standard Drugs" group). The common-effect model found a moderate benefit for natural herbs, with an SMD of -0.3156 ($p < 0.0001$). However, the random-effects model showed no significant effect, and the wide prediction interval (-12.7680 to 9.6289) showed considerable variability. High heterogeneity ($I^2 = 98.4\%$, $p < 0.0001$) suggests differences across studies. While natural herbs show potential, more consistent research is needed.

Natural herb alone versus combination with other herbs

The meta-analysis for burning sensation included two studies which compared "Natural Herb Alone" to "Natural Herb in Combination" involving 202 OSMF patients (108 in Natural Herb in Combination group and 94 in the Natural Herb Alone group) (Figure 9). The common effect model indicated a better effect with combination treatment, with a standard mean difference (SMD) of -0.7802 ($p = 0.0001$) compared to natural herb alone in reducing the burning sensation. However, the random-effects model was not significant; the prediction interval (-10.6844 to 9.6103) revealed rather great variance. High heterogeneity ($I^2 = 85.7\%$ $p = 0.0083$) shows variations in the results of the studies.

Risk of bias of burning sensation

Fourteen studies out of 23 studies who have assessed the burning sensation in OSMF were of high risk, three had some concerns, whereas only five studies were of low risk. High risk was mostly attributed to lack of randomization or outcome measurement (Figure 10).



Figure 6: Risk-of-bias assessment using the RoB 2 tool for mouth opening

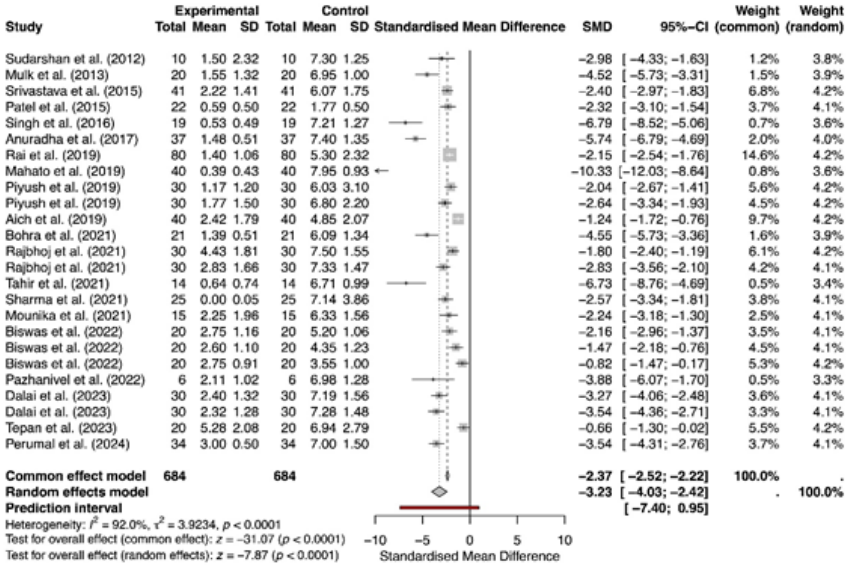


Figure 7: Meta-analysis of pre-post natural herb treatment of burning sensation

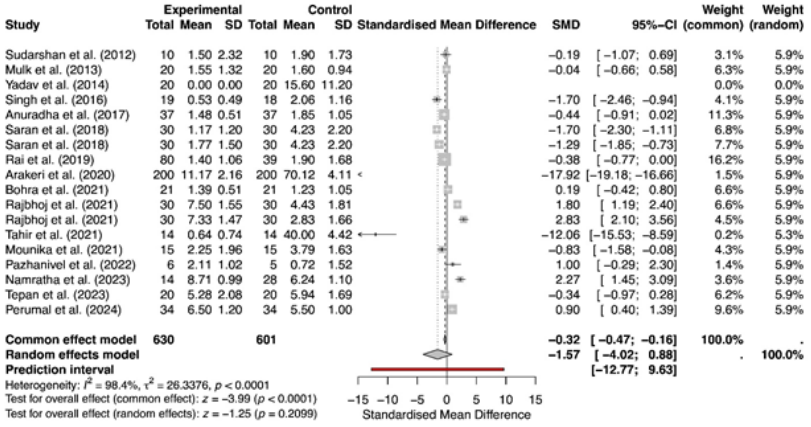


Figure 8: Meta-analysis of burning sensation in OSMF patients treated with natural herbs versus standard drugs

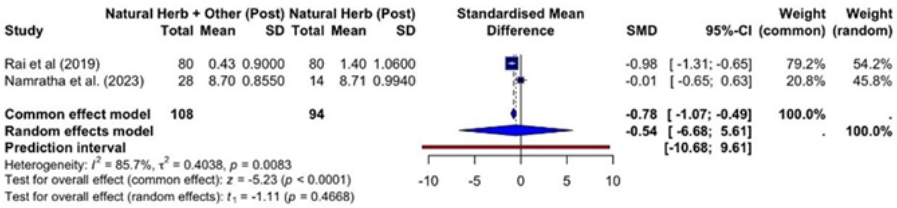


Figure 9: Meta-analysis of burning sensation; natural herb alone versus combination therapy

Tongue protrusion

Natural herb intervention alone

The meta-analysis of tongue protrusion in OSMF patients reveals that the natural herb significantly improves tongue protrusion after treatment when compared to pre-treatment levels (Figure 11). The common effect model indicates a strong and statistically significant improvement with an SMD of 1.42 mm (95% CI: 1.26–1.57, p < 0.0001). The random-effects model showed a significant effect having higher SMD of 2.88 mm (95% CI: 1.19–4.58, p = 0.0025). However, the variability between studies is high, with an I^2 value of 97.4%, pointing to considerable differences in how each study was conducted or in the populations studied. The range of the prediction interval (-3.91 to 9.68) reflects variability, indicating that while the overall outcome is positive, individual study results may vary widely, even including negative outcomes.



Figure 10: Risk-of-bias assessment using the RoB 2 tool for burning sensation

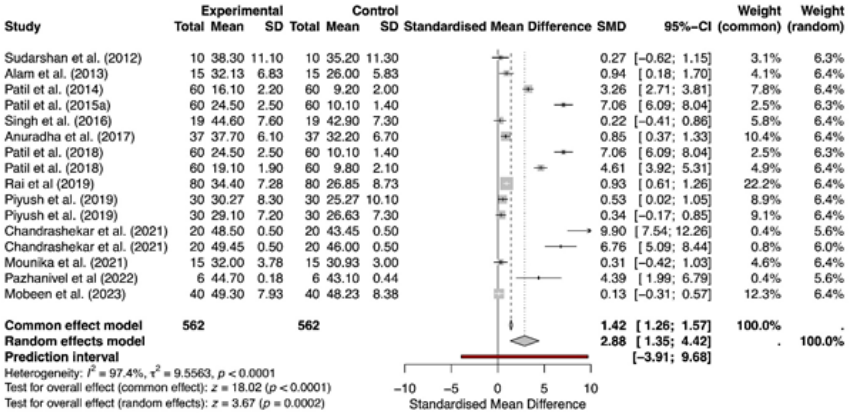


Figure 11: Meta-analysis of pre-post natural herb treatment of tongue protrusion

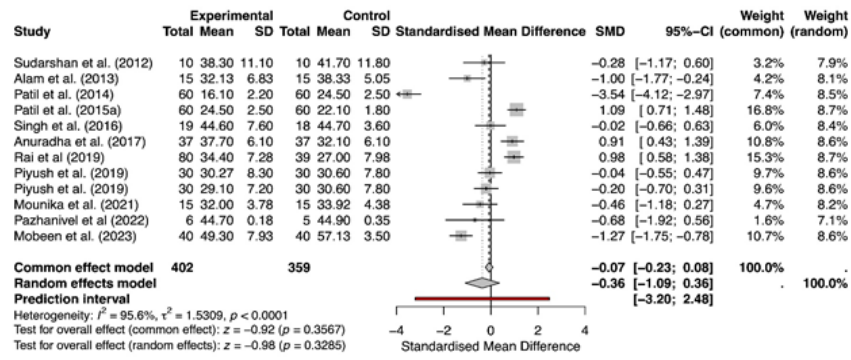


Figure 12: Meta-analysis of tongue protrusion in OSMF patients treated with natural herbs versus standard drugs

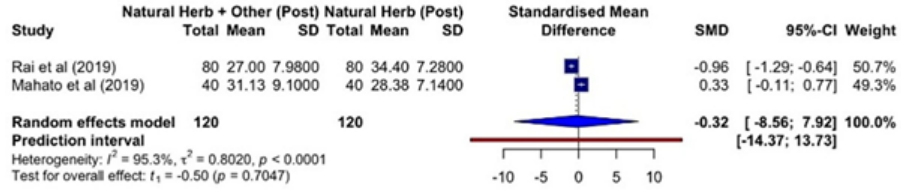


Figure 13: Meta-analysis of tongue protrusion; natural herb alone versus combination therapy

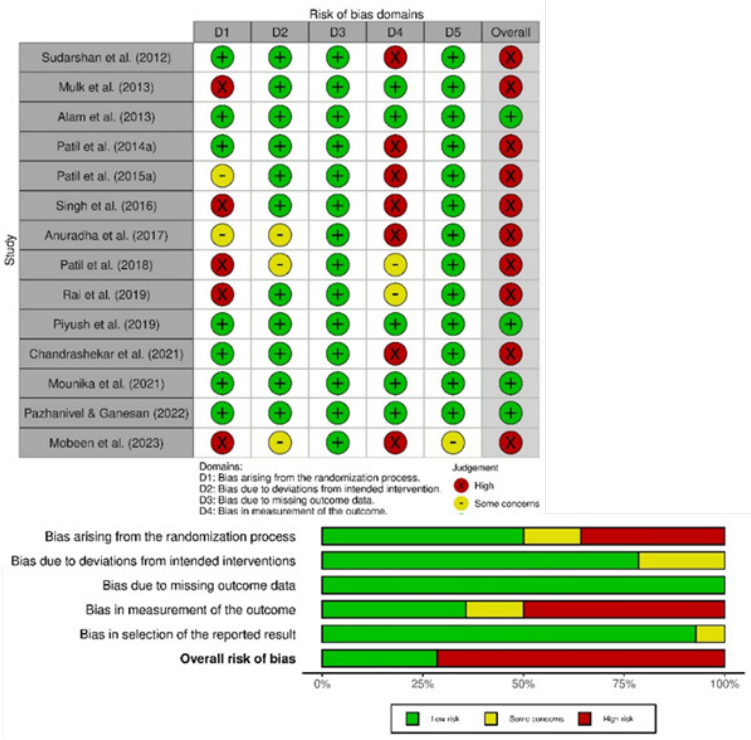


Figure 14: Risk of bias assessment using the RoB 2 tool for tongue protrusion

Natural herb versus standard drug treatment

The meta-analysis compared "Natural Herb" and "Standard Drug" in terms of improving tongue protrusion in OSMF patients by analyzing data from 12 studies with 761 subjects altogether (402 in the "Natural Herb" group and 359 in the "Standard Drug" group) (Figure 12). The common-effect model showed an insignificant difference in treatment effect, with the standardized Mean difference (SMD) of -0.0741 (p = 0.3567). Similarly, the random-effects model showed no difference, with an SMD at -0.3617 (p = 0.3440). Outcomes under the prediction interval (-3.2042 to 2.4808) reflect inconsistently favorable results. The heterogeneity was considerably high (I^2 = 95.6%, p < 0.0001), indicating differences between the studies.

Natural herbs alone versus combination with other herbs

The meta-analysis evaluated the effect of "Natural Herb Alone" and "Natural Herb in Combination" on tongue protrusion within two studies of 240 OSMF patients (with 120 in each group). For the combination therapy, it appeared to have a slight impact with an SMD of 0.2419, though not statistically significant (p=0.0620). The studies were homogeneous (I^2 = 0%), but the interval prediction (-1.4051 and 1.8889) suggests that the effectiveness is inconsistent (Figure 13). Although the results indicate that combination therapy could be better than single therapy, the weak evidence does not permit any definite conclusion.

Fourteen studies evaluated the treatment effect on tongue protrusion (Figure 14). Out of these, only four were low risk whereas ten were of high risk. Most of high risk was attributed to concerns regarding randomization and outcome assessment in the studies.

DISCUSSION

This systematic review and meta-analysis utilized evidence from 58 studies assessing the use of natural herbs in OSMF management, focusing on clinical outcomes: mouth opening, burning sensation, and tongue protrusion. The findings suggest that natural herbs can be considered as an effective treatment modality; However, the extent of the substantial heterogeneity in the studies reviewed warrants the need for further high-quality trials.

One of the primary clinical concerns in OSMF patients is restricted mouth opening, which significantly affects

mastication, speech, articulation, and quality of life. Restricted mouth opening is secondary to fibrosis in the oral mucosa and deeper muscle tissue in cheeks. Fibrosis involves excessive collagen deposition in connective tissue. This is mediated by several mechanisms, including TGF-beta-mediated collagen synthesis, fibroblast stimulation by arecoline, and ROS production by areca nut. Natural herbs have properties to mitigate these effects, which is evident from the present meta-analysis findings. We notice use of several natural herbs for the treatment of OSF. These natural herbs have different properties. For example, astaxanthin can reduce inflammation and oxidative stress through its potent antioxidant action. Turmeric powder and its active component curcumin are well-known for their anti-inflammatory and healing properties. Further, turmeric can reduce ROS and prevent oxidative damage. Tulsi powder may also aid in soothing inflammation and strengthening oral tissues. Similarly, honey has been reported to have antioxidant and healing effect can promote wound healing, whereas aloe vera is recognized for its soothing effects on oral discomfort. Piperine may enhance the bioavailability of other compounds, making treatments more effective, and lycopene, with its antioxidant properties, can protect tissues from damage. Glycerin has hydrating properties and keeps oral tissues moist, while clove oil may provide analgesic relief from pain associated with OSMF. Furthermore, alpha-lipoic acid may enhance healing and decrease inflammation, and bee pollen has anti-inflammatory benefits. Spirulina, a nutrient-dense algae, has additional anti-inflammatory properties that support tissue repair. The improvement in mouth opening can enhance the ability to eat, speak, and maintain oral hygiene as well as allow visibility and exploration of developing OPMD/ Oral cancer lesions.

Burning sensation is another common complaint among OSF patients, especially in early stages, and often precedes clinical fibrosis (Sarode & Sarode, 2013). It often impacts food intake due to discomfort in the oral mucosa while eating. Further, reduced food intake results in nutritional deficiency, further aggravating the OSF condition. Burning sensation is sometimes due to mucosal irritation by areca nut or other food items. Areca nuts are known to cause mouth dryness. In addition, fibrosis of minor salivary glands leads to decreased saliva, causing dryness of mucosa. Dry mucosa is prone to minor ulceration, abrasion, and mucosal inflammation. To avoid the dryness and burning sensation, topical medication such as steroids, Hyaluronidase, and benzocaine are prescribed (Chen et al., 2023). However, these have side effects as well as are not practically feasible for long-term use considering the chronic nature of OSF. In these situations, natural herbal therapies may be more suitable for long-term use. Curcumin, which is a common household herb have shown promising effects in reducing these symptoms. Another herb, Aloe Vera, possesses a healing and soothing effect on mucosa. Aloe vera contains several compounds such as vitamins A, C, and E, which act as antioxidants. Further, it keeps mucosa moisten compensating for reduced saliva. Rajbhoj et al. (2021) found aloe vera effective in reducing the burning sensation compared to steroids (Rajbhoj et al., 2021). If the burning sensation is reduce overtime, OSF patient can improve their diet rich in antioxidants as well as overall health. Further, decreased mucosal irritation can reduce the chance of developing dysplasia or malignancy (Piemonte & Lazos, 2018).

Tongue protrusion is an indirect indicator of the extent of fibrosis and its impact on oral mobility. The tongue is involved in many oral functions and parafunctions, making it a crucial structure. Reduced tongue movement due to fibrosis affects its mobility and leads to depapillation. The tongue surface, especially the lateral border, becomes prone to frictional trauma from adjacent teeth and results in ulceration. In addition, the tongue helps move food from tooth surfaces. Restricted tongue movement impairs this function, causing an increased risk of dental caries and gingival inflammation. Therefore, it is important to improve tongue mobility as early as possible.

Natural herbs have been found to improve tongue mobility. Our meta-analysis indicated the benefits of natural herbs in enhancing tongue protrusion. When pre- and post-treatment comparisons were made within herbal treatment groups, a significant improvement was noted. In contrast, when natural herbs were compared with standard drugs, no substantial improvement in tongue protrusion was observed. Natural herbs, such as curcumin, can reduce inflammation and indirectly decrease fibrosis. Unfortunately, there is limited information on how natural herbs are beneficial in improving tongue protrusion. The majority of clinical studies investigate the reduction of symptoms like burning sensation, mouth opening, and the flexibility of the oral mucosa rather than investigating the underlying mechanism involved in tongue protrusion. One of the mechanisms that plays a role in the movement of the tongue through functional rehabilitation, particularly when combined with physiotherapy. Although our meta-analysis showed promising evidence of the role of natural herbs in improving tongue protrusion in OSF, there is a lack of studies investigating the underlying mechanism of natural herbs in improving tongue protrusion or flexibility. Detailed investigations might help uncover this mechanism.

Clinical evidence supports the integration of natural herbs into standard OSMF management, particularly in resource-limited settings where conventional pharmacotherapies may not be readily accessible. Herbal treatments not only offer symptom relief but also demonstrate better patient compliance due to their minimal side effects compared to corticosteroids and immunosuppressive agents (Warnakulasuriya & Kerr, 2016). However, the inconsistency in treatment protocols, lack of standardized dosages, and variations in study methodologies limit the generalizability of these findings.

Despite good results, several limitations must be acknowledged in this study. High heterogeneity across studies, stemming from differences in study design, sample sizes, duration of follow-up, and variations in herbal

formulations, remains a significant concern. The absence of standardized clinical outcome assessments further complicates data interpretation. Additionally, while most studies report short-term symptomatic relief, long-term data on malignant transformation prevention are lacking (Arakeri et al., 2017).

Future research should prioritize well-designed, large-scale randomized controlled trials (RCTs) with standardized herbal formulations, consistent dosing strategies, and well-structured outcome assessment. Longitudinal studies evaluating the impact of herbal therapies on preventing malignant transformation and improving survival outcomes are also warranted. Moreover, trials exploring comparative effectiveness and synergistic combinations of herbal therapies with conventional treatments could provide valuable insights into optimizing current consensus on OSF management.

CONCLUSION

The natural herbs hold significant potential in alleviating OSF symptoms, particularly in improving mouth opening, reducing burning sensation, and limited success in increasing tongue protrusion. While herbs appear to be a promising adjunct or alternative therapy to conventional treatments, high-quality evidence from rigorously conducted RCTs is necessary to establish definitive clinical guidelines. Standardizing treatment protocols and conducting long-term outcome studies will be pivotal in integrating herbal medicine into mainstream OSF management.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: **M.Y., R.D.J., Y.A.J., P.M.P., V.D., A.C., D.L.;** Search strategy: **Y.A.J., M.Y.;** Screening**: Y.A.J., P.M.P., A.C., V.D.;** Data collection: **V.D., A.C., D.L.;** analysis and interpretation of results: **M.Y., Y.A.J.;** Risk of bias assessment: **Y.A.J., P.M.P.;** Draft manuscript preparation: **M.Y., Y.A.J., P.M.P., D.L., V.D., R.D.J.** All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

The quantitative and descriptive data supporting this Systematic Review or Meta-Analysis are from previously reported studies and datasets, which have been cited.

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