

## Systematic Review

# Efficacy of spirulina in management of oral submucous fibrosis — a systematic review

Rashmi Kulkarni<sup>1,\*</sup> , Ashita Kalaskar<sup>1</sup>, Ritesh Kalaskar<sup>2</sup>, Neha Gupta<sup>1</sup>

<sup>1</sup> Department of Oral Medicine and Radiology, Government Dental College and Hospital, Nagpur 440003, India

<sup>2</sup> Department of Pedodontics and Preventive Dentistry, Government Dental College and Hospital, Nagpur 440003, India

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**Abstract – Objective:** The aim of this systematic review was to evaluate the efficacy of spirulina in the management of oral submucous fibrosis. **Methodology:** Databases (MEDLINE via PubMed, Cochrane, EBSCO-host, Scopus, Science Direct, Clinical Trial Registry- India (CTRI) and Google scholar), review articles, bibliographies and related journal were searched from 1st January 2010 to 30th May 2020, using various combinations of MeSH terms and keywords. **Results:** A total of 5 clinical trials were analysed for the review, of which 4 were randomized controlled trials and 1 was non-randomized controlled trial. Mouth opening and burning sensation were analysed as primary outcome in all 5 studies. For both outcomes some studies reported statistically significant difference whereas others showed non-significant results on comparing with different interventions. Also, high risk of bias was observed among studies after performing quality analysis. **Conclusion:** Although the studies suggest efficacy of spirulina in management of OSF, but due to the high risk of bias there is a weak evidence regarding the effectiveness of spirulina in treating OSF. So, more uniform and standard trials on larger population should be carried out.

## Introduction

Oral submucous fibrosis (OSF) is a chronic, progressive, potentially malignant condition of the oral cavity that predominantly affects people of South-East Asian origin [1] and is characterized by a juxta-epithelial inflammatory reaction followed by fibroelastic change in the lamina propria and epithelial atrophy which leads to stiffness of the oral mucosa, trismus and inability to eat [2]. This entity has a long history of nomenclature starting from “atrophica idiopathica (tropica) mucosae oris” as given by Schwartz (1952) to the recent categorization as “Oral Potentially Malignant Disorder (OPMD) by Warnakulasuriya *et al.* [3,4]. But it is most commonly recognised by the term “Oral Submucous Fibrosis(OSF) coined by Joshi.

The pathogenesis of the disease is considered to be multifactorial. Various studies have confirmed areca nut as the major (and the only) risk factor of oral submucous fibrosis, among people who probably have a genetic predisposition to the disease. Areca nut is composed of alkaloids, flavonoids and trace elements which directly affect collagen metabolism. Other risk factors include chewing of smokeless tobacco, high

intake of chilies, toxic levels of copper in food, vitamin deficiencies, malnutrition resulting in low levels of serum proteins and anaemia [5].

Data elucidate that, cases have increased dramatically from an estimated 2.5 million in 1980 to 14 million cases in 2010. [1] The prevalence rate of OSF range from 0.1 to 30%, varying by geographical location [6]. The prevalence of OSMF in India has been estimated to range from 0.2 to 2.3% in males and 1.2–4.6% in females, with a broad age range from 11 to 60 years [7].

Ever since its recognition as a possible precancerous lesion by Paymaster, its prevalence is increasing steadily with malignant transformation rate ranging from 7% to 13% [8]. A recent study from India has reported that 25.77% OSF cases converted to oral squamous cell carcinoma (OSCC) which is an alarming condition [9]. Teh *et al.* [10] gave a first and foremost evidence that genomic instability present in OSF patients correlate with OSF grade and plays a crucial role in OSF progression and conversion to malignancy. Mechanical trauma, excessive alcohol intake, smoking, presence of immune disorders, aging and association with other OPMDs (leukoplakia, oral lichen planus) are other risk factors for malignant transformation.

For such a chronic potentially malignant disorder various treatment protocols have been aimed with symptomatic approach to prevent further progression. Thus, treatment

\* Correspondence: [rashmivcoolkarni@gmail.com](mailto:rashmivcoolkarni@gmail.com)

**Table I.** Eligibility criteria of included studies according to Participants, Intervention, Comparator and Outcomes (PICO).

INCLUSION	EXCLUSION
<ul style="list-style-type: none"> <li>● Participants (P):</li> <li>○ Patients clinically and/ Or histopathologically diagnosed with Oral Submucous Fibrosis.</li> <li>○ No history of prior treatment for the same or have discontinued treatment since one to two weeks.</li> <li>● Intervention (I): Spirulina used in any form (topical / intralesional / systemic).</li> <li>● Comparator(C): Placebo or Any other medicinal treatment or any other treatment modality.</li> <li>● Outcomes (O):</li> <li>Main outcomes-</li> <li>○ Maximum mouth opening measured from the incisal edges of maxillary central incisor to mandibular central incisor using the Vernier caliper or any other method of measurement.</li> <li>○ Reduction in burning sensation and pain measured using Visual analogue Scale (VAS) or any other appropriate standard method.</li> <li>Additional outcomes-</li> <li>○ Cheek flexibility.</li> <li>○ Uvula and tongue movements.</li> <li>○ Reduction in ulcers/ erosions/ vesicles.</li> <li>● Study design (S): Clinical trials (Randomized and non- Randomized).</li> </ul>	<ul style="list-style-type: none"> <li>● Patients with systemic disease.</li> <li>● Patients with restricted mouth opening due to other reason (pericoronitis, space infection, abscess, fractures).</li> <li>● Pregnant and lactating mother.</li> <li>● Presence of other potentially malignant lesions like leukoplakia, oral lichen planus <i>etc.</i></li> <li>● History of hypersensitivity reaction to spirulina.</li> <li>● Study design(S): Case reports, case series, clinical trials without comparator/control group, Review studies, review paper, editorials letters to the editor &amp; monographs</li> </ul>

starts with educating patient regarding the ill-effects of areca nut chewing, followed by complete cessation of the habit of betel nut or tobacco chewing or intake of chillies. A wide range of treatment modalities are available, ranging from Medicinal, nutritional supplements, physiotherapy, LASERs, ultrasound, herbal medicines to surgical managements.

In spite of so many years of research, the pathogenesis of the disease is still not fully understood. Recent systematic reviews explicate that no single regime has proved to be entirely satisfactory [11,12]. So newer treatment options are continued to be tried. Spirulina is a filamentous, blue-green microalga used in daily diet of African and American natives. It contains high amounts of proteins, amino acids, essential oils, minerals, vitamins predominantly the B complex, tocopherols, carotenoids, and other flavonoids and cyanins. Its therapeutic role in health and disease have been evaluated in many conditions (diabetes, hypertension, arthritis *etc.*) with beneficial results [13–15]. With its well-established antioxidant and anti-inflammatory potentials [16–18], its use in OSF has also been evaluated by various studies. But due to inadequate comprehensive analysis of its effect in OSF, this systematic review was planned to analyse the efficacy of Spirulina in management of Oral Submucous Fibrosis.

## Methods

### Protocol and registration

The present systematic review was registered at the National Institute for Health Research PROSPERO International Prospective Register of Systematic Reviews (registration

number: CRD42020189399). This research protocol was designed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines 2009 [19]. SWiM (Synthesis Without Meta-analysis) guidelines were intended to be followed in the absence of meta-analysis [20].

### Eligibility criteria

Eligibility criteria for inclusion and exclusion of the studies in regards to Participants, Intervention, Comparator and Outcomes (PICO) was as shown in Table I.

### Search

Databases (MEDLINE via PubMed, Cochrane, Scopus, Science Direct, EBSCO-host, Clinical Trial Registry- India (CTRI) and Google scholar), review articles, bibliographies and related journal were searched from 1st January 2010 to 30th May 2020 by using various combinations MeSH terms and keywords describes below. This 10 years time span was selected after performing a pilot search which revealed lack of studies in literature before 10 years.

Disease – Oral submucous fibrosis, OSMF, Juxta epithelial fibrosis, Asian sideropenic dysphagia, OSF Intervention – Spirulina, *Arthrospira maxima*, *spirulina maxima*, seaweed algae, All – trans spirulina, All – cis spirulina.

All the articles available in the English language were included.

## Study selection

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources were screened independently by two review authors (A and C). The full text of these potentially eligible studies was retrieved and independently assessed for eligibility by two review team members (A and C). Any disagreement between them over the eligibility of particular studies was resolved through discussion with a third reviewer (B). Authors and editors were communicated for retrieving full-text of the eligible articles.

## Data collection process

Data collection was performed using a customized data extraction form that used following prefixes:

- Title of the study.
- Author's name.
- Duration of study.
- Year of publication.
- Study setting.
- Study design.
- Study population details.
- Method of randomization used (if any).
- Details of intervention.
- Details of comparator.
- Indicators of acceptability of users.
- Outcomes (primary & secondary).
- Adverse effect and side effects.
- Conclusion.

## Risk of bias in individual studies

To evaluate the risk of bias in individual studies, different tools were used for randomized controlled trials (RCTs) and non-randomized controlled trials (NRCT). Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) was used for RCTs [21] and Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) was used for non-randomized controlled trials [22].

## Synthesis of results

The result was provided for the findings from the included studies, focusing on intervention details (dose, type), characteristics of participants (age, gender, type of outcome (primary, secondary, side effects *etc.*) and summaries of intervention effects for studies were provided by calculating risk ratio (for dichotomous outcomes) or standardized mean difference (for continuous outcomes). Heterogeneity of previously mentioned characteristics was assessed using chi square test (significance 0.1) and  $I^2$  statistics. Meta-analysis, if possible, would be formulated.

## Results

### Literature search and study selection

Figure 1 shows the study search process conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Database and hand searches of the reference list yielded 226 articles. After duplicate removal 162 articles were obtained. After screening title and abstract of articles, 155 studies were excluded. The full-text of remaining 7 articles were screened which excluded 2 studies, as these two studies did not include the comparator groups. Finally, five studies were included for systematic review.

### General characteristics of the included studies

The general characteristics of included studies are presented in Table II for four randomized controlled trials [23–26] and one non-randomized controlled trial [27]. A total of 240 subjects participated in the studies. All the studies were conducted in India except one which was conducted in Saudi Arabia [25]. All of the reported investigations were hospital/institution based and none were conducted in community settings. The average age of participants ranged from 18 to 56 years. Most studies showed male dominance except one study in which no information about gender was provided. Table II highlights the details of population, intervention and control or comparator of the included studies. In all five studies [23–27], diagnosis of Oral Submucous Fibrosis was based on clinical findings which was confirmed by histopathological investigation. Only one study mentioned about the clinical staging of OSF that used classification system by Ranganathan *et al.* [23] Enrolled population had a wide spectrum of OSF (i.e., from early to advanced), except one study [27] which included only Stage 1 and stage 2 of OSF.

### Formulation

Two studies [23,27] used a dosage of 500 mg twice daily whereas three studies [24–26] used a dosage 500 mg in two divided doses (250 mg BD). In three studies [24–26]. Spirulina was given alone, whereas in other two studies [23,27] it was given as an adjuvant therapy. In one study it was combined with mouth opening exercises [23] and in another study with intralesional steroid injection (Betamethasone 4 mg/ml). [27] Comparator groups showed variability amongst studies [23–27] (Tab. II). All studies were conducted for a period of 3 months with intermediate visits. During each visit all parameters were checked and recorded. The post-treatment follow-ups were carried out in three studies for a period of 2 months in two studies [24,25] and for 3 months in one study [26].

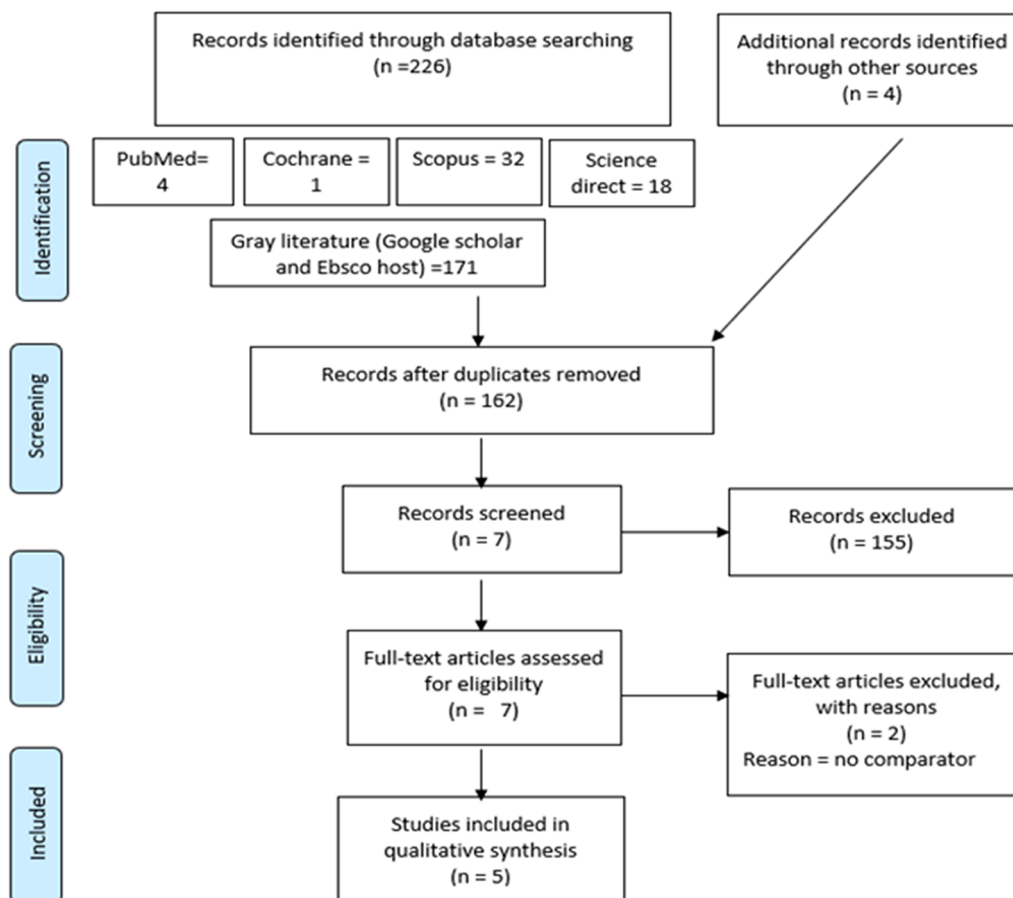


Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

## Clinical parameters

Mouth opening and burning sensation were analysed as primary outcome in all five studies [23–27]. Other outcomes which were analysed are—tongue protrusion, reduction in ulcers/erosions/vesicles, reduction in pain associated with lesion. Three studies [23,24,27] used vernier caliper for measuring mouth opening whereas, two studies [25,26] did not mention about measurement tool. For burning sensation and pain associated with lesion Visual Analogue Scale (VAS) were used as a measurement tool. Table II shows the details of outcomes for included studies.

## Main outcomes

### Mouth opening

Three studies by Patil *et al.* [24–26] used spirulina as a substitute therapy. Out of which one study showed statistically significant difference in mouth opening with better results in spirulina group as compared to Aloe vera group [25]. Whereas, other two studies showed statistically significant results in lycopene and oxtard group compared to spirulina group [24,26].

In the remaining two studies spirulina was used as an adjuvant therapy along with isometric exercises and intralesional steroid injections [23,27]. Study conducted by Shetty

*et al.*, which combined spirulina with intralesional steroid injection, showed highly significant improvement in mouth opening in spirulina group as compared to placebo [27]. Another combination study by Mulk *et al.*, which combined spirulina with isometric exercises, showed statistically non-significant difference between spirulina group and pentoxifylline.

### Burning sensation

Two studies by Mulk *et al.* [23] and Shetty *et al.* [27] showed statistically significant results in reducing burning sensation in spirulina group as compared to pentoxifylline and placebo respectively. Whereas studies by Patil *et al.* [24–26], showed statistically non-significant difference in spirulina group as compared to lycopene, aloe vera and oxtard [24–26].

## Other outcomes

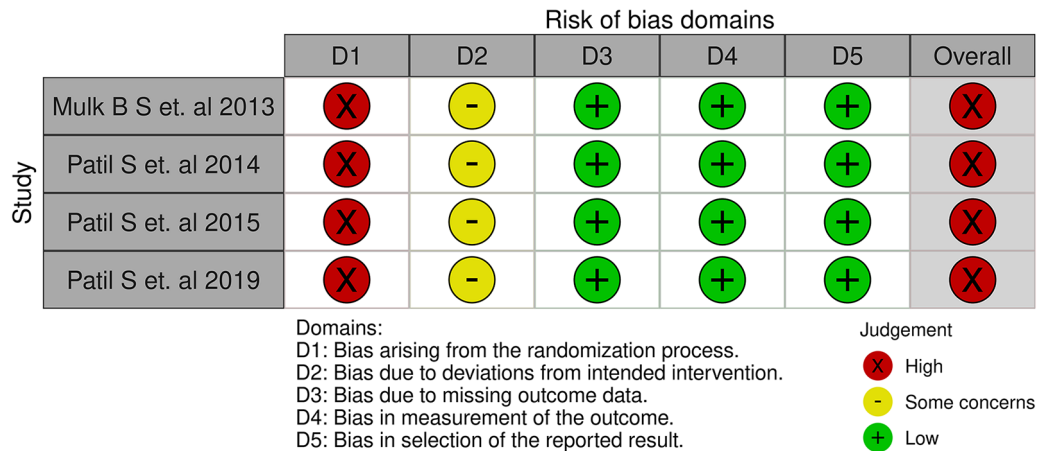
### Tongue protrusion

This outcome was evaluated in two studies by Mulk *et al.* [23] and Patil *et al.* [26]. Former study showed statistically significant results in spirulina group as compared to pentoxifylline. Whereas, later one showed statistically significant results in oxtard group as compared to spirulina.

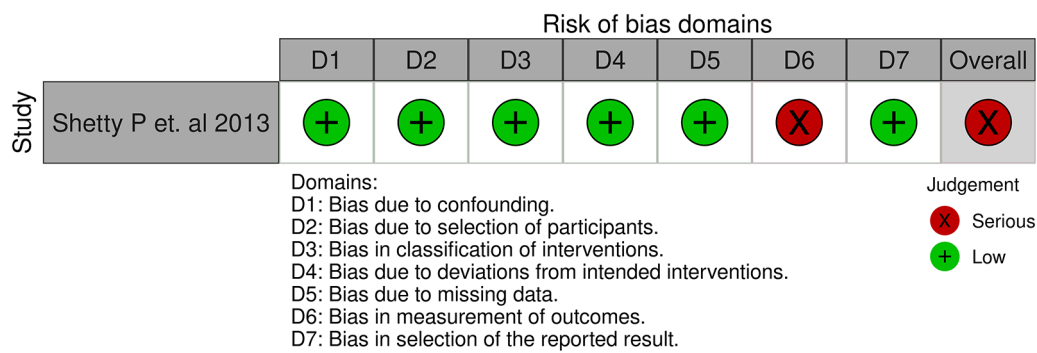
**Table II.** Details of population, study groups and outcome (PICO) of included studies.

S. No	Study (Adjuvant/Substitute therapy)	Population	Intervention	Control/Comparator group	Primary Outcome	Secondary Outcome
<b>Randomized controlled trial</b>						
1.	Mulk BS <i>et al.</i> 2013 India [23] (Adjuvant)	Total = 40 Group I (Pentoxifylline) – 20 Group II (Spirulina) – 20	Spirulina – 0.5gm capsules orally twice daily + mouth opening exercises for 20 min daily. Duration – 3 months	Pentoxifylline – 400 mg orally twice daily + mouth opening exercises for 20 min daily Duration – 3 months	Mouth opening – SNSD Burning sensation – Spirulina group showed SSD	Tongue protrusion – SNSD
2	Patil S <i>et al.</i> 2014 India [24] (Substitute)	Total = 68 Group I (Spirulina) – 34 Group II (Lycopene) – 34	Spirulina – 500 mg capsules orally in two divided dosage Duration – 3 months	Lycopene – 8 mg lycopene (Lycored™, Jagsonpal Pharmaceuticals, New Delhi) in 2 divided doses of 4 mg Duration – 3 months	Mouth opening – Lycopene group showed SSD Burning sensation – SNSD	Pain associated with lesion – SNSD Reduction of ulcers/ vesicles/ erosion – Spirulina group showed SSD
3.	Patil S <i>et al.</i> 2015 Saudi Arabia [25] (Substitute)	Total = 48 Group I (Spirulina) – 24 Group II (Aloe vera) – 24	Spirulina – 500 mg capsules orally in two divided dosages Duration – 3 months	Aloe vera – 5 mg aloe vera gel (Sheetal Lab, Surat) to be applied topically thrice daily Duration – 3 months	Mouth opening – Spirulina group showed SSD Burning sensation – SNSD	pain associated with lesion – SNSD Reduction of ulcers/ vesicles/erosion – Spirulina group showed SSD.
4.	Patil S <i>et al.</i> 2019 India [26] (Substitute)	Total = 50 Group I (Spirulina) – 25 Group II (Oxitar) – 25	Spirulina – 500 mg in 2 divided doses 250 mg in morning and 250 mg at night Duration- 3 months	Oxitar – 2 capsules twice daily Duration- 3 months	Mouth opening – Oxitar group showed SSD. Burning sensation – SNSD	Tongue Protrusion – Oxitar group showed SSD Reduction of ulcers/ vesicles/erosion – Spirulina group showed SSD.
<b>Non-Randomized controlled trial</b>						
5.	Shetty P <i>et al.</i> 2013 India [27] (Adjuvant)	Total = 40 Group I (Spirulina) – 20 Group II (Placebo) – 20	Spirulina – 500 mg capsules orally twice daily + biweekly steroid injection (Betamethasone 4 mg/ml, by the multiple puncture method Duration – 3 months	Placebo – Capsules twice daily + biweekly steroid injection (Betamethasone 4 mg/ml, by the multiple puncture method Duration – 3 months	Mouth opening – Spirulina group showed SSD Burning sensation – Spirulina group showed SSD	Tongue Protrusion – Oxitar group showed SSD

Abbreviations: SSD – Statistically significant difference; SNSD – Statistically non-significant difference.



**Fig. 2.** Risk of bias assessment for randomized controlled trial done by Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) tool.



**Fig. 3.** Risk of bias assessment for non-randomized control trial done by ROBINS-I tool.

**Ulcers, erosions and vesicles**

Three studies by Patil *et al.* [18–20] evaluated this parameter which showed statistically significant results for reduction in ulcers, erosions and vesicles in spirulina group as compared to lycopene, aloe vera and oxtard groups respectively.

**Pain associated with lesion**

This parameter was evaluated in two studies by Patil *et al.* which showed statistically non-significant difference in both the studies [24,25].

**Adverse effects**

Four studies [23–26] reported no adverse effects in spirulina group whereas one study [21] did not mention about side effects.

**Quality of included studies**

In this review, quality assessment was done for each study (Figs. 2 and 3). For Randomized controlled trials, Cochrane Tool of Risk of Bias (RoB2) was used (Fig. 2). The four RCT studies

showed high risk of bias. This high risk of bias was due to inadequate information about randomization process, lack of allocation concealment and blinding. Similarly risk of bias assessment for non-randomized studies was done with ROBINS-I tool (Fig. 3) and the study was found to have serious risk of bias because of inadequate measurement of outcomes.

**Meta-analysis**

There was limited scope for meta-analysis because of the range of different comparators measured across the small number of existing trials as seen by grouping studies into categorical model.

**Discussion**

Oral Submucous Fibrosis (OSF) is a potentially malignant disease and it shows increased prevalence in India [6,7]. This high prevalence is attributed to widespread marketing of commercial tobacco and areca nut products. It is estimated that areca nut is consumed by 10–20% of the World’s population [6]. Although the disease is observed in 11–60 year old individuals, occurrence in children is not rare with cases of 2.5–10 year old children being reported [28–30].

Patients with OSF mainly complains of two problems – an inability to open mouth which impedes function and burning sensation which restricts the intake of spicy food. Management is usually based on severity of disease and focuses on alleviating the signs and symptoms. Two recent systematic reviews failed to show evidence for effectiveness of any specific treatment for treating OSF [11,12]. This may be due to lack of standardisation in the study designs and paucity of data available. So, no single regime has proved to be entirely satisfactory.

A chronic disease like OSF might require treatment for longer time depending on the severity of symptoms. Therefore, considering natural therapies which are mostly safe could probably benefit such patients. Spirulina, a blue green alga have been studied in OSF (and many other conditions) due to its various beneficial effects. It contains  $\beta$ -carotene, carotenoids and phycocyanin which are believed to have antioxidant and anti-inflammatory activity. Phycocyanin in spirulina inhibits proinflammatory cytokine formation, suppresses cyclooxygenase-2 (COX-2) expression and decreases prostaglandin E2 production [18]. It also scavenges free radicals, including alkoxyl, hydroxyl and peroxy radicals thus exhibiting its antioxidant activity. Another component of spirulina,  $\beta$ -carotene inhibits the production of nitric oxide and prostaglandin E2. Thus, producing an anti-inflammatory activity. This could be beneficial in OSF, in which there is upregulation of various cytokines. Additionally, increased oxidative stress in these patients due to generation of reactive oxygen species (ROS) that causes activation of NF- $\kappa$ B, JNK and p38 stimulated by Arecoline, could be benefited by the potential antioxidant activity of carotenoids and phycocyanin components of spirulina [18].

Spirulina is useful in various diseases like nutritional deficiencies (Vit A, iron), cardiac diseases, diabetes mellitus, dyslipidaemia, inflammatory and degenerative diseases, hepatocellular carcinoma and breast cancer [31,32]. Some recent systematic reviews reported the beneficial effects of spirulina supplementations on plasma lipid concentration [33], obesity [34], human health [13], glycaemic control and serum lipoproteins [14,15]. In dentistry, apart from its use in OSF, it has been tried in treatment of periodontitis (topically in gel form) [35], reducing dental plaque and gingivitis (topical as 0.5% mouthwash) [36] and in oral mucosal lesions like leukoplakia [37,38]. Spirulina extracts have also been shown to inhibit DMBA (7,12 dimethylbenz(a)-anthracene) induced epidermoid carcinoma of buccal pouch in animal studies by stimulating TNF- $\alpha$  positive cells and subsequently causing tumour regression [39–41].

With regard to dosage, a systematic review reported that spirulina consumption for a period varying from 1 to 12 months, with doses ranging from 0.5 to 20 g day<sup>-1</sup> showed significant benefits in various conditions [13]. These studies used spirulina systemically, but topically in the form of gel [35] and mouthwash [36] had also been tried. In the present review,

two studies [23,27] used a dosage of 500 mg twice daily whereas three studies [24–26] used a dosage 500 mg in two divided doses (250 mg BD).

All five included studies reported that spirulina is an effective herbal medicine in improvement of mouth opening, reducing burning sensation and lesions like ulcers, erosions or vesicles. In three studies spirulina was compared with single intervention like lycopene [24], aloe vera [25] and oxitard [26]. When compared with lycopene and oxitard, spirulina was found to be less effective in improving mouth opening, in contrast to aloe vera in which spirulina was more effective [24–26]. Spirulina group also demonstrated better results for reducing lesions when compared with these three interventions [24–26]. Whereas, for burning sensation, all were equally effective [24–26].

Other two studies used combination therapy. In one study spirulina along with isometric exercises was compared with pentoxifylline combined with isometric exercises [23] while in another study spirulina along with intralesional steroids was compared with placebo combined with intralesional steroid (betamethasone) injection [27]. When compared with pentoxifylline spirulina proved to be equally effective in improving mouth opening [23]. However, spirulina showed better results on combining it with intralesional steroids [27]. For alleviating burning sensation spirulina group showed significant outcomes as stated by these two studies [23,27].

In this review, all enrolled studies showed that spirulina is a safe, well-tolerated and without any adverse effects. Lycopene, aloe vera and pentoxifylline have well established antioxidant and anti-inflammatory potential [42–44]. Spirulina showed efficacy somewhat similar to them. Thus, it could be inferred that although spirulina has been evaluated as an effective herbal medicine in improvement of mouth opening and reducing burning sensation, the high risk of bias associated with all the studies warrant cautious interpretation of its precise effect as a substitute or adjuvant therapy compared to other interventions or along with other interventions respectively, mainly due to the heterogenous data available.

In all included studies spirulina was used as a supplementary treatment modality for OSF. Dietary Supplements Information Expert Committee (DSI-EC) of the United States Pharmacopeial Convention (USP) assigned it, a class A safety rating [45]. Considering its safety and beneficial effects in health and diseases, spirulina could probably be considered as a dietary biomass in the management of OSF.

## Limitations and future scope

The main limitations of the present review are limited number of studies with considerable heterogeneity and high risk of bias. This high risk of bias is because of inadequate information about randomization process, lack of allocation concealment and lack of blinding. Therefore, to exactly define

the efficacy of spirulina, more number of studies with more standard and uniform trials on larger population with different regimens of spirulina should be carried.

## Conclusion

Management of OSF has been a challenge always. Newer drugs have been emerging continuously for the treatment of this disease. When considering natural therapies mainly due to their safety concerns, spirulina needs to be evaluated further in OSF due to the weak evidence obtained in the present systematic review, regarding the effectiveness of spirulina in treating OSF. Thus, well-designed and standard clinical trials are still required to accurately provide the evidence of effectiveness of spirulina as compared to other interventions in the management of OSMF.

## Authors contribution

Dr. Rashmi Kulkarni: Conceptualization, Methodology, Writing- Original draft. Dr. Ashita Kalaskar: Supervision, Validation, review editing. Dr. Neha Gupta: Writing - Review & Editing. Dr. Ritesh Kalaskar: Validation & editing.

## Conflicts of interest

The authors declare that there is no conflict of interest.

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## Ethical approval

Ethical approval was not required.

## Informed consent

This article does not contain any studies involving human subjects.

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