

Spirulina: An Emerging Treatment Modality for the Management of Oral Submucous Fibrosis

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ABSTRACT

Spirulina is a nonconventional, palatable, and filamentous cyanobacterium. It is a microalgae that has emerged as an effective food supplement. *Spirulina* exhibits numerous biological functions that help control hypertension, protein energy malnutrition, etc. It is known for its high nutritional value. It is rich in proteins, beta-carotenes, vitamins, and other components with antioxidant action. Its role in the management of various oral mucosal lesions, especially leukoplakia, is recently established. With the advances and the exploration of the biochemical actions of *Spirulina*, its role regarding management in oral submucous fibrosis (OSMF) has also surfaced. The present review aims at elaborating the role of *Spirulina* in the management of OSMF.

Keywords: Food supplement, Iron, Microalgae, Oral submucous fibrosis, *Spirulina*.

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INTRODUCTION

The recent era has brought to light the use of traditional plants and other herbs for the treatment of various oral diseases.¹ These natural remedies are on a surge due to their low toxicity and high benefits.^{1,2} *Spirulina* (*Arthrospira platensis*) is one such emerging remedy.² It is also termed as being a "functional food."^{3,4} It is designated as being generally recognized as safe by the Food and Drug Association.⁵ It is an inhabitant of the sea and the fresh waters of African, American, Asian, and European countries.⁶ *Spirulina* has also been mentioned in the history where in Mexico, the Aztecs harvested *Spirulina* from the Texcoco Lake and Spanish soldiers used it as a regular component of their food and cakes.^{7,8} It grows

favorably in alkaline and warm media and occurs naturally in tropical-subtropical lakes with high pH values that are rich in salts.^{9,10} It is considered a well-balanced food supplement mainly due to its composition.⁹ This alga contains high amounts of proteins (60–70% dry weight), amino acids, essential oils (such as linoleum acid, alpha-linolenic acid, gamma-linolenic acid, stearidonic acid, docosahexaenoic acid, eicosapentaenoic acid, and arachidonic acid), minerals, vitamins predominantly the B complex, tocopherols, carotenoids, and other flavonoids and cyanins (C-phycoerythrin 20% dry weight).^{9,11,12} Essential oils are of importance mainly the gamma-linolenic acid, as it gets biotransformed to prostaglandins, leukotrienes, and thromboxanes, which play a huge role in arthritis, diabetes mellitus, cardiac disease, cellular aging, and other immune and inflammatory conditions.¹³ Gamma-linolenic acid is also well-known to have an anticancer effect.¹⁴⁻¹⁶

Spirulina contains 700 to 1700 mg/kg beta-carotene, which is a precursor of vitamin A. About 1 to 2 gm of *Spirulina* can meet the daily vitamin A requirement of the human body. Studies have verified that the use of this alga as a source of beta-carotene as compared to commercial products that contain retinol is favored due to its bioavailability and nontoxic nature.¹⁷⁻²² Carotenoids, the lipophilic antioxidants, are the second pigment key group present in *Spirulina*. It is believed that carotenoids and phycoerythrin are the two components of *Spirulina* with potential antioxidant activity.²³ It is available as powder or tablets formulated singly or even in combination with other algae.⁶ The antioxidant and anti-inflammatory activities have been largely recognized.² It has also been indicated for the removal of toxic elements like heavy metals.² *Spirulina*, the blue-green algae, was used as an anticancer agent and in treatment of radiation sickness in masses who suffered from the 1986 nuclear accident at Chernobyl.²⁴⁻²⁷ *Spirulina* due to its beta-carotene and micronutrient content is believed to have a chemopreventive effect.¹⁴

Clinical Studies on *Spirulina*

Numerous studies have enlisted the varied use of *Spirulina* in controlling malnutrition and vitamin A deficiency,²⁸⁻³⁰ inflammatory, neurodegenerative diseases, iron deficiencies, blood pressure, cholesterol, blood sugar, and even as

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an anticancer agent.^{9,23} Research has highlighted its role in the control of various diseases caused due to oxidative stress.²³ Additionally, *Spirulina* due to its high iron content (580–1800 mg/kg) and lack of oxalates or phytates in algal structure, does not interfere with iron absorption.^{31,32} This has led to its use in the treatment of anemia. Moreover, its calcium: Phosphorous ratio is comparable to that of milk and hence, helps in preservation and improvement of bone health.¹¹ Adjunctive role of *Spirulina* extract (*S. platensis*) in inhibiting the dysplastic changes was documented in a study by using mucosa of hamster cheek pouch.³³ An Indian study has also evaluated the role of *S. fusiformis* in the reversal of pan-tobacco-induced oral leukoplakia. They found a significant regression in 45% cases, with a marked response to therapy being observed in the patients with homogeneous leukoplakia. However, discontinuation of therapy led to recurrence in a few cases.¹⁴ It is probably the carotenoids and other antioxidants which are believed to contribute to the anticancer effect of *Spirulina*.⁹ Based on the antioxidant effects, numerous studies were done on precancerous lesions to evaluate the effect of *Spirulina*.^{14,34,35} *Spirulina* has been used for the treatment of several oral mucosal lesions with successful results.³⁶

Role in Periodontitis

Periodontitis is primarily an inflammatory condition caused by bacteria in plaque.^{23,37} Inflammatory responses set up against the gram negative bacterial organisms. Mahendra et al²³ were the first to use *Spirulina* in the treatment of periodontitis. They assessed the role of *Spirulina in situ* gel in periodontitis cases that were primarily treated by scaling and root planning (SRP). The group treated with both SRP and *Spirulina* gel after 120 days depicted a reduction in mean probing pocket depth and improvement in clinical attachment levels as compared to the group treated with SRP alone. They put forth that *Spirulina* by its anti-inflammatory activity greatly improved the gingival condition in patients with periodontitis and that it can serve as a promising treatment modality.²³

Role in Oral Submucous Fibrosis

Recently, light has been thrown to the use of *Spirulina* in the chronic and highly complex disease, oral submucous fibrosis (OSMF).^{36,38,39} The OSMF is a well-known condition documented as being similar to the condition mentioned in ancient medicine by Susrutha called as "Vidari."⁴⁰ It was 1952 when the first description of OSMF was given by Schwartz under the title of "atrophica idiopathica mucosae oris." The term OSMF was, however, coined by Dr Joshi, a year later in 1953.^{41,42} It is encountered frequently in the Southeast Asian countries.^{42,43} The prevalence of OSMF

is documented to be about 0.2 to 0.5%.⁴³ However, this fibrotic condition presents with a 7 to 30% malignant transformation rate, which is of great concern.⁴⁴ OSMF is hence, considered as a potentially malignant disorder.⁴⁵ It presents with various clinical signs and symptoms like restricted mouth opening, stiffness of mucosa, burning sensation, restricted movement of tongue, uvula, etc. depending on the stage of the disease.⁴⁶ The oral mucosa is blanched with the presence of fibrotic bands which can be palpated commonly in the buccal mucosa, palate, labial mucosa, tongue, and posterior pharynx.⁴⁶

The primary etiological agent is areca nut chewing, which by means of reactive oxygen species damages the cells. Further other conditions like vitamin deficiencies, anemia, etc. cause more damage to the inflamed oral mucosa and hinder the healing process, thereby further making the epithelium susceptible to effects of areca.⁴⁶ Patients with OSMF usually present in their late stages making the treatment of disease difficult.⁴⁶

Ever since the condition has been recognized, the treatment of OSMF has remained a huge enigma. A wide range of treatment modalities have been used, however, none have evolved as a promising treatment option.³⁶ Mainline of treatment used are quitting of betel nut and/or tobacco chewing habit, counseling for diet, especially regarding spicy foods and chillies, and medicinal therapy. Commonly employed treatment includes medical therapy by use of corticosteroids, placental extracts, hyaluronidase, interferon gamma, and physiotherapy.^{44,46} However, considering the adverse effects caused by steroids, interferons, etc., the focus has shifted onto the development of safer modalities of treatment.^{42,46,47} The role of minerals and micronutrients in treatment of OSMF has received impetus as they have been observed to bring about significant improvement in mouth opening (41%).³⁶ Similarly, vitamin A and oxtard capsules are also used for the treatment of OSMF.^{36,47}

Recently, Shetty et al³⁸ have delineated the role of *Spirulina* as an adjuvant therapy in the management of OSMF. They conducted an interventional study on 40 cases of OSMF. The treatment groups were divided into two of twenty each, with the first group receiving *Spirulina* 500 mg BID (Twice a day) and biweekly intralesional injections of steroid Betamethasone 4 mg/mL for a period of 3 months and the second group receiving placebo capsules BID and biweekly intralesional steroid injection of Betamethasone 4 mg/mL for 3 months. They found that *Spirulina* was effective in alleviating the burning sensation in patients probably due to its beta-carotene, phenolic acid, tocopherol, and micronutrient content. Additionally, they stated that use of beta-carotene systemically and topically helps in improving the epithelial integrity and brings about redifferentiation of dysplastic epithelium.

They suggested that *Spirulina* can be advocated as an adjuvant therapy in the early treatment of OSMF.³⁸

Similarly, Mulk et al³⁹ studied the effect of *Spirulina* (500 mg) and Pentoxifylline (400 mg). Each group (20 cases of OSMF per group) used the individual formulations twice daily for a period of 4 months. They obtained significant results in relation to burning sensation, mouth opening, and tongue protrusion. Efficacy wise, however, they were similar in respect to mouth opening and protrusion of the tongue. Although even with this study, the reduction in burning sensation was more in the *Spirulina* group. Further, they highlighted that no adverse effects were noted in the patients using *Spirulina*.³⁹

Another study, using two natural antioxidants was performed by Patil et al.³⁶ They studied 42 cases of OSMF by dividing them equally in two groups, first the *Spirulina* group (500 mg *Spirulina* in two divided doses for 3 months) and second the aloe vera group (5 mg gel for topical application thrice daily for 3 months) with an additional follow-up period of 2 months. In concordance with the Mulk study, they found no side effects in both the study groups. Both the study drugs brought about a similar reduction in burning sensation. *Spirulina* brought about significant clinical improvements in mouth opening and ulcers/erosion/vesicles. They put forth that *Spirulina* brings about better treatment outcomes as compared with aloe gel.³⁶

Similarly, Patil et al⁴⁸ also evaluated the efficacy of *Spirulina* and lycopene in 68 OSMF patients. They administered two divided doses of 500 mg of *Spirulina* in group I for a period of 3 months and two divided doses of lycopene 4 mg for the same time period. They observed that lycopene brought about improvements in the clinical symptoms, such as mouth opening, whereas *Spirulina* improved ulcers/erosion/vesicles in the OSMF patients. They also observed similar effects in terms of alleviation of pain and burning sensation and thus put forth that both the drugs can act as useful modality of treatment in cases of OSMF.⁴⁸

Future Applications

Most studies indicated a significant result demonstrating the effectiveness of *Spirulina* in the treatment of OSMF. However, further clinical trials with large sample size and detailed molecular experiments in relation to OSMF and *Spirulina* are needed. Development of various local and nanoparticle-based delivery systems will further aid to potentiate the action of *Spirulina* in the treatment of OSMF.

CONCLUSION

Spirulina holds a strong position in terms of being an unconventional source to combat the various oral and

systemic diseases. Its high nutritional value, safety, antioxidant, anti-inflammatory, and other actions make the future use of this food supplement as an adjuvant therapy quite promising.

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