Review Article

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Aloe vera in the management of oral submucous fibrosis

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Abstract:

Oral submucous fibrosis is a pre-malignant condition commonly prevalent in India, Pakistan, Taiwan and Sri Lanka. Patients characteristically exhibit progressive reduction in mouth opening. The disease has a high malignant potential and thus should be diagnosed and treated at the earliest. However, none of the currently used medical therapies show promising results. The current article briefly reviews the role of *Aloe vera* in the management of oral submucous fibrosis.

Key words:

Oral submucous fibrosis, *Aloe vera*, pre-malignant condition, medical management, treatment

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Introduction

Oral submucous fibrosis (OSMF) is a pre-malignant chronic inflammatory condition with an insidious course.[1] Oral submucous fibrosis is defined as "an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx, although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxtaepithelial inflammatory reaction followed by fibroelastic changes in the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and difficulty in eating".[2] It commonly occurs in South East Asian population.[3] Oral submucous fibrosis has the tendency to transform into oral squamous cell carcinoma.[3] The malignant transformation rate is estimated to be approximately 7-13%.[1] Chewing areca nut in the form of betel quid and commercially available products, such as gutka, is chiefly implicated as the aetiology for the development of OSMF.[4] Gutka is a mixture of tobacco, areca nut and molasses.[5] Some common brand names of gutka are Manikchand, Moolchand, Tulsi, Shimla, Sikandar, Parag, Sir, Shikhar, Goa and Sikandar.[6] The constituents of betel quid are betel quid leaf (*Piper betel*), areca nut (*Areca catechu*), slaked lime [$Ca(OH)_2$] and catechu (*Acacia catechu*).[6] Clinical presentation of the lesion include hypersalivation or dryness of mouth (25% of patients), burning sensation, vesiculation, ulceration, blanching and stiffening of oral mucosa, presence of fibrous bands in the lips, buccal mucosa and soft palate, progressive decrease in mouth opening, restriction in tongue movement and difficulty in swallowing.[3,4,7] Patients with OSMF exhibit decreased antioxidant and increased free radicals in their blood.[8] Apart from habit and diet counselling, some of the medical interventions used in the management of OSMF include nutritional supplements such as vitamin B complex, antioxidants like lycopene and curcumin, placental extract, spirulina, hyaluronidase, collagenase, dexamethasone, levamisole and pentoxifylline.[9] However, OSMF has remained resistant to most of the currently used medical and chemopreventive therapies.[9]

Literature review reveals that there is scarcity of articles that reviewed the exact role of *Aloe vera* in the management of OSMF. Hence, this review was undertaken to fill this research gap. The present article attempts to briefly review and assess the role of *A. vera* in the management of OSMF. A search for English-language articles in PubMed without any restriction on dates was made using the keywords 'oral submucous fibrosis', 'aloe vera', 'pre-malignant condition', 'medical management' and 'treatment'. Relevant articles contributing to the main aim of the article was then reviewed.

A. vera is an ayurvedic medicinal plant that has anti-inflammatory, immunomodulatory, antioxidant and wound-healing properties.[10] Since thousands of years, *A. vera* has been used as a medicinal plant without any reported side effects. It also has antiseptic, antiviral, hypoglycaemic, antibacterial and antifungal properties.[11,12] It is known to strengthen the immune system.

A. vera belongs to the family Asphodelaceae (Liliaceae) and genus Aloe.[11] *A. vera* is a cactus-like plant that grows in dry and hot climates.[12] *A. vera* Barbadensis is the most commonly

used among these species.[11] Commercially used species are *Aloe barbadensis* Miller and *Aloe arborescens*.[12] 'Aloe' is derived from the Arabic word 'Alloeh', meaning 'shining bitter substance'. 'Vera' means 'true'.[13] The plant grows in Africa, Northern America, India, Egypt and Sudan. *A. vera* gel inhibits inflammation by inhibiting cyclooxygenase-induced arachidonic acid pathway.[11]

Mucilaginous gel containing 98-99% water and 1-2% active compounds is secreted by parenchymatous cells in the fresh leaves of *A. vera*.[12] *A. vera* contains several vitamins that include vitamin A, C and E, which have antioxidant properties and help to combat destructive free radicals. Also, these vitamins strengthen the immune system.[13] Vitamin C and E also have wound-healing properties. *A. vera* also contains fatty acids, salicylic acid and hormones such as auxins and gibberellins, all of which result in inflammation reversal. *A. vera* contains polysaccharides, such as acemannan, which has wound-healing and immunomodulating properties. It contains lupeol, which is a sterol, and is antiseptic, analgesic and has anti-inflammatory properties. It also contains salicylic acid, which has analgesic properties.[13] *A. vera* increases blood supply and speeds up healing. Isorabaichromone, feruoylaloesin and p-coumaroylaloesin are aloesin derivatives of *Aloe*, which exhibit potent free radical and superoxide anion activity.[11] *A. vera* is a mannoprotein, containing many amino acids called 'wound-healing hormones'. The polysaccharides contained in the gels of leaves also have gastroprotective and anticancer properties. The sterols in *A. vera* have a strong ability to inhibit inflammation similar to the action of cortisone without any side effects.[14] *A. vera* has been observed to be useful in OSMF, oral lichen planus and burning mouth syndrome.[14-16] Some of the beneficial effects of *A. vera* are outlined in Figure 1.

Sudarshan *et al*., in their preliminary study, observed that *A. vera* significantly reduced burning sensation and improved mouth opening and cheek flexibility when compared to other antioxidants. The authors opined that *A. vera*, in addition to being economical, non-invasive, effective and readily available, has an added advantage of topical usage. The study recruited 10 OSMF patients with mouth opening between 20 and 39 mm. The patients applied *A. vera* gel (5 mg) three times a day on buccal mucosa topically for a 3-month duration. These patients were compared with another group consisting of 10 OSMF patients who took an antioxidant capsule two times a day for 3 months. The antioxidant capsule consisted of mixed carotenoids, beta carotene, vitamin E, vitamin C, copper, zinc, selenium, manganese and chromium. Though some patients initially exhibited nausea, it was usually tolerated by next follow-up. Twenty per cent improvement in mouth opening was observed in the *A. vera* group, that is, 5.1 mm. The reduction in burning sensation was 80%. Also, there was a statistically significant improvement in cheek flexibility and tongue protrusion in the *A. vera* group.[14]

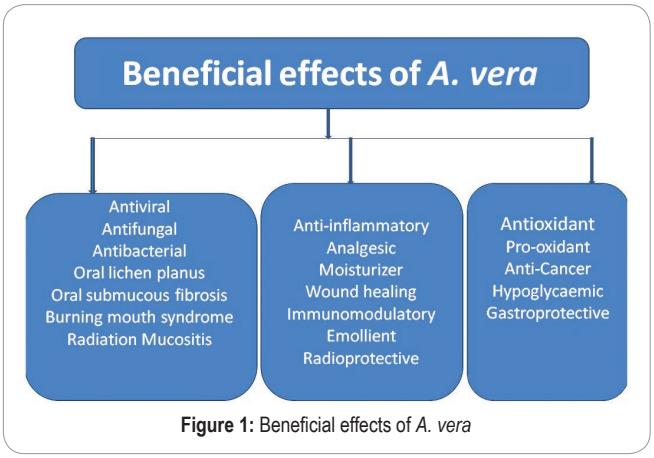

Figure 1: Beneficial effects of *A. vera*

Patil *et al*. compared the efficacy of *A. vera* and oxitard in the treatment of OSMF. Sixty OSMF patients were administered topical 5 mg *A. vera* gel three times a day for 3 months. Another group consisting of 60 OSMF patients was administered two capsules of oxitard twice daily for 3 months. The authors observed significant improvement in pain, difficulty in swallowing and speech, mouth opening and tongue protrusion in the oxitard group. Ten patients in the *A. vera* group exhibited decrease in size of the lesion greater than 2.5 cm. Twenty-one patients showed moderate change in size of the lesion, that is, 1.5-2.5 cm. Nineteen patients showed mild change, that is, 0-1.5 cm. *A. vera* has the added advantage of being economical. The authors opined that oxitard is superior to *A. vera* in OSMF management.[17]

Patil *et al*. compared the efficacy of *A. vera* and spirulina in the management of OSMF. Twenty-six OSMF patients were administered topical *A. vera* gel (5 mg) three times a day for 3 months. Another group consisting of 60 OSMF patients was administered spirulina (500 mg) in two divided dose for 3 months. The authors observed significant increase in mouth opening and clinical improvement in ulcer/erosions/vesicles in the OSMF patients receiving spirulina compared with *A. vera*. Also, *A. vera* and spirulina were equally effective in reducing burning sensation and pain.[10]

Singh *et al*. compared the effectiveness of *A. vera* gel (Forever *A. vera* gel™ by Forever Living) plus physiotherapy to antioxidant capsules plus physiotherapy in OSMF patients. *A. vera* improved all the parameters, that is mouth opening, tongue protrusion, burning sensation and cheek flexibility. The authors concluded that *A. vera* is a soothing, simple, safe mode of treatment in OSMF. The analgesic property of *A. vera* with physiotherapy exercises exhibited superior results when compared to antioxidants. In the study, 20 patients were assigned to *A. vera* gel plus physiotherapy group. Another 20 patients were assigned to Antoxid™ (Dr. Reddy's product) plus physiotherapy group. Antoxid capsule is a soft gelatin capsule commercially manufactured by Dr. Reddy's. It consists of beta carotene (10 mg), zinc sulphate monohydrate (27.45 mg), monohydrated selenium dioxide (0.07 mg), manganese (2 mg) and copper (1 mg).[18] In the study, the *A. vera* gel group exhibited 93.8% reduction in burning sensation, while the antoxid group exhibited 71.2% reduction. The *A. vera* gel group exhibited significantly higher average post-treatment percentages in mouth opening and tongue protrusion when compared to the antoxid group.

However, there was no significant difference between the groups in terms of post-treatment cheek flexibility. *A. vera* gel group exhibited 80.8% improvement in cheek flexibility when compared to 61.4% in the antoxid group.[7]

Alam *et al*. studied the efficacy of the *A. vera* gel as an adjuvant to submucosal local injection of hyaluronidase diluted with dexamethasone, 2% lignocaine and 1:80,000 adrenaline and with surgical excision of fibrotic bands with or without grafts. Sixty patients were recruited for the study. Thirty patients with grade I and II received medical management. And the remaining 30 patients with grade III and IV received surgical management. The patients were also put on lycostar once daily during treatment and up to 6 months after treatment. Patients were also prescribed physiotherapy for increasing mouth opening, 4-5 times a day on regular basis. Each of the medicinal and surgical group was further randomly divided into group A that received topical *A. vera* gel twice a day and group B with no *A. vera* gel instructions. Both group A and group B contained equal number of patients. *A. vera* had potent effects in reducing burning sensation both in medicinal and in surgically treated groups. *A. vera* gel significantly increased mouth opening in medicinal group and maintained the mouth opening in surgically treated group that could otherwise decrease without it. *A. vera* also increased tongue protrusion both in medicinal and in surgically treated groups. *A. vera* exhibited the tendency to increase cheek flexibility. The authors concluded that *A. vera* can be useful as an adjunct to surgical and medicinal modes of OSMF management.[19]

Anuradha *et al*., in their study comprising of 74 OSMF patients, compared the effect of *A. vera* gel plus juice with intralesional injection of hydrocortisone plus antioxidant supplement. Patients were divided into two groups. Group A patients drank 30 ml of *A. vera* juice twice daily before food and applied 5 mg of *A. vera* gel over the lesion three times per day for 3 months. Group B patients were administered intralesional injections of hydrocortisone acetate (25 mg/ml) and hyaluronidase (1500 IU) weekly for 6 weeks. They were also additionally prescribed Cap SM Fibro twice daily for 3 months. Both groups exhibited significantly reduced burning sensation and increased interincisal mouth opening, cheek flexibility and tongue protrusion. *A. vera* induced rapid reduction in burning sensation.[20] Table 1 outlines various clinical studies that researched *A. vera* in the management of OSMF.

A. vera exerts anti-inflammatory effects by reducing leukocyte adhesion and levels of tumour necrosis factor (TNF)-alpha. *A. vera* possesses carboxypeptidase that inactivates bradykinins and thus exhibiting an anti-inflammatory effect. It improves wound healing by increasing blood supply, which in turn increases oxygenation. *A. vera* has soothing and cooling

Table 1: Clinical studies done with *A. vera* in the management of oral submucous fibrosis

Sl. No.	Authors	Samples	Therapeutic agents	Duration	Results pertaining to the use of *A. vera* in OSMF patients
1	Sudarshan *et al*. 2012[14]	20	*A. vera* gel (5 mg), antioxidant capsule	3 months	Mouth opening – 20%, reduction in burning sensation – 80%, statistically significant improvement in cheek flexibility and tongue protrusion.
2	Patil *et al*. 2014[17]	120	*A. vera* gel (5 mg), oxitard capsules	3 months	Decrease in size of the lesion greater than 2.5 cm = 10 patients, moderate change in size of the lesion = 21 patients, mild change = 19 patients.
3	Patil *et al*. 2015[10]	86	*A. vera* gel (5 mg), spirulina (500 mg)	3 months	*A. vera* reduced burning sensation and pain. Also, improvement was seen in mouth opening, ulcer/erosion/vesicles.
4	Singh *et al*. 2016[7]	40	*A. vera* gel+ physiotherapy, antioxidant capsule+ physiotherapy	3 months	*A. vera* improved mouth opening, tongue protrusion, burning sensation and cheek flexibility. Reduction in burning sensation – 93.8%, cheek flexibility – 80.8%.
5	Alam *et al*. 2013[19]	60	*A. vera* gel, hyaluronidase, dexamethasone, 2% lignocaine, 1:80,000 adrenaline, surgical excision of fibrotic bands with or without grafts, lycostar, physiotherapy.	*A. vera* gel was applied by part of both medical and surgical group for a period of 6 months.	*A. vera* reduced burning sensation and increased mouth opening, cheek flexibility and tongue protrusion.
6	Anuradha *et al*. 2017[20]	74	5 mg *A. vera* gel + 30 ml *A. vera* juice, 25 mg/ml hydrocortisone, 1500 IU hyaluronidase + antioxidant supplement	3 months	*A. vera* significantly reduced burning sensation and increased interincisal mouth opening, cheek flexibility and tongue protrusion.

properties. This property of *A. vera* reduces pain and burning sensation in OSMF patients. Patients usually will attempt to open mouth when pain subsides or get reduced. *A. vera* contains several antioxidants, such as vitamins like beta carotene, vitamin A, vitamin C and vitamin E, along with several minerals such as zinc, iron and selenium. Antioxidants help boost the immune system and combat free radicals in the body. When there is ongoing inflammation, as seen in OSMF, pain and vasodilation is seen because of bradykinins. Hydrolysis of bradykinin reduces pain and vasodilation and produces an analgesic effect. So, hydrolysis of bradykinin by *A. vera* could be the possible reason for reducing pain and improvement in mouth opening in patients with OSMF.[7]

A. vera contains magnesium lactate that inhibits histidine decarboxylase. This results in the inhibition of formation of histamine from histidine in mast cells. Salicylates are by-products of amodin, aloe-emodin and aloin. Peptidase bradykinin extracted from *A. vera* is responsible for the breakdown of bradykinin and thereby reduces pain. *A. vera* increases the production of dermatan sulphate and hyaluronic acid in granulation tissue of healing wound. *A. vera* also stimulates fibroblasts that produce collagen and elastin fibres responsible for conferring elasticity to skin.[20]

However, it is also observed that *A. vera*, in addition to increasing collagen production and fibroblastic activity, also modifies the collagen composition and increases collagen cross linking. Increased fibrosis in OSMF is due to increased cross linking of collagen.[20]

Areca nut contains high levels of copper that causes fibrosis through upregulation of lysyl oxidase.[21,22] Copper levels in saliva increases within 5-30 min after chewing areca nut. In OSMF, there is an increased production of highly cross-linked insoluble collagen type I and decrease in more soluble procollagen type III and collagen IV. Also, copper content in buccal epithelial cells in OSMF patients are observed to be more than those of healthy patients with or without areca nut chewing habit.[22] Copper has been reported to induce p53 aberrations in OSMF tissues, resulting in squamous cell carcinoma.[23]

Aloe emodin of *A. vera* is reported to induce apoptosis in cancer cell lines. *A. vera* also has pro-oxidant properties, especially in the presence of copper. In the presence of copper ions, aqueous extract of *A. vera* causes DNA degradation by the generation of reactive oxygen species, such as superoxide anion and hydroxyl radicals, in a dose-dependent fashion. Aloe emodin has antioxidant properties at a concentration of 200-400 μM. But it exhibits pro-oxidant effect on DNA at higher concentrations of 1.25-2.5 mM. In OSMF, patients usually have high local copper levels in saliva and OSMF tissues. So, *A. vera* may be hypothesised to theoretically confer anticancer benefits to patients suffering from pre-malignant conditions like OSMF, due to its pro-oxidant properties at higher concentrations.[24] Future clinical, *in vivo* and *in vitro* research studies should be attempted in this direction.

Adverse Effects and Contraindications

Side effects of topical *A. vera* include allergic reactions. Allergic reactions may be due to anthraquinones-aloin and barbaloin. Allergy may be in the form of redness, burning and stinging sensation. Contraindications of oral *A. vera* include pregnancy where it can theoretically cause uterine contractions in mothers and gastrointestinal distress in nursing infants. Oral administration of *A. vera* can cause abdominal cramps and low potassium levels.[13]

Conclusion

Topical *A. vera* appears to be useful in the management of OSMF as evidenced from before-mentioned studies in the literature. Along with completely quitting deleterious habits and adopting oral physiotherapy exercises, *A. vera* is promising in the management of OSMF. However, *A. vera* also appears to exhibit increased fibroblastic activities. Hence, more *in vitro* studies are required to exactly conclude the usefulness of *A. vera* in the management of OSMF.

References

1. Ekanayaka RP, Tilakaratne WM. Oral submucous fibrosis: review on mechanisms of malignant transformation. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:192-99.
2. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. Oral Surg Oral Med Oral Pathol 1966;22:764-79.
3. Wollina U, Verma SB, Ali FM, Patil K. Oral submucous fibrosis: an update. Clin Cosmet Investig Dermatol 2015;8:193-204.
4. Tilakaratne WM, Ekanayaka RP, Warnakulasuriya S. Oral submucous fibrosis: a historical perspective and a review on etiology and pathogenesis. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:178-91.
5. Dwivedi S, Aggarwal A, Dev M. All in the name of flavour, fragrance and freshness: commonly used smokeless tobacco preparations in and around a tertiary hospital in India. Indian J Med Res 2012;136:836-41.
6. WHO SEARO 2004. Report on oral tobacco use and its implications in south-east Asia. [Cited 2017 May 25]. Available from: http://searo.who.int/tobacco/topics/oral_tobacco_use.pdf.
7. Singh N, Hebbale M, Mhapuskar A, Ul Nisa S, Thopte S, Singh S. Effectiveness of aloe vera and antioxidant along with physiotherapy in the management of oral submucous fibrosis. J Contemp Dent Pract 2016;17:78-84.
8. Subapriya R, Kumaraguruparan R, Nagini S, Thangavelu A. Oxidant-antioxidant status in oral precancer and oral cancer patients. Toxicol Mech Methods 2003;13:77-81.
9. Warnakulasuriya S, Kerr AR. Oral submucous fibrosis: a review of the current management and possible directions for novel therapies. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:232-41.
10. Patil S, Al-Zarea BK, Maheshwari S, Sahu R. Comparative evaluation of natural antioxidants spirulina and aloe vera for the treatment of oral submucous fibrosis. J Oral Biol Craniofac Res 2015;5:11-15.
11. Sujatha G, Kumar GS, Muruganandan J, Prasad TS. Aloe vera in dentistry. J Clin Diagn Res 2014;8:ZI01-2.
12. Nair GR, Naidu GS, Jain S, Nagi R, Makkad RS, Jha A. Clinical effectiveness of aloe vera in the management of oral mucosal diseases – a systematic review. J Clin Diagn Res 2016;10:ZE01-7.

13. Mangaiyarkarasi SP, Manigandan T, Elumalai M, Cholan PK, Kaur RP. Benefits of aloe vera in dentistry. J Pharm Bioallied Sci 2015;7:S255-9.
14. Sudarshan R, Annigeri RG, Sree Vijayabala G. Aloe vera in the treatment for oral submucous fibrosis – a preliminary study. J Oral Pathol Med 2012;41:755-61.
15. Choonhakarn C, Busaracome P, Sripanidkulchai B, Sarakarn P. The efficacy of aloe vera gel in the treatment of oral lichen planus a randomized controlled trial. Br J Dermatol 2008;158: 573-77.
16. Lopez-Jornet P, Camacho-Alonso F, Molino-Pagan D. Prospective, randomized, double-blind, clinical evaluation of Aloe vera Barbadensis, applied in combination with a tongue protector to treat burning mouth syndrome. J Oral Pathol Med 2012;42:295-301.
17. Patil S, Halgatti V, Maheshwari S, Santosh BS. Comparative study of the efficacy of herbal antioxdants oxitard and aloe vera in the treatment of oral submucous fibrosis. J Clin Exp Dent 2014;6:e265-70.
18. CIMS. ANTOXID. [Cited 2017 May 25]. Available from: http://www.mims.com/india/drug/info/antoxid/antoxid%20soft-gelatin%20cap.
19. Alam S, Ali I, Giri KY, Gokkulakrishnan S, Natu SS, Faisal M, *et al*. Efficacy of aloe vera gel as an adjuvant treatment of oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;116:717-24.
20. Anuradha A, Patil B, Asha VR. Evaluation of efficacy of aloe vera in the treatment of oral submucous fibrosis – a clinical study. J Oral Pathol Med 2017;46:50-55.
21. Rooban T, Saraswathi TR, George A, Joshua E, Ranganathan K. Cytological study of copper in oral submucous fibrosis. Indian J Dent Res 2004;15:129-32.
22. Sharma A, Sahni P, Nayak MT, Singhvi A, Kumar R. Identification of the pattern of copper as an etiological factor in oral submucous fibrosis: a cytological study. J Exp Ther Oncol 2014;10:317-23.
23. Trivedy CR, Warnakulasuriya KA, Peters TJ, Senkus R, Hazarey VK, Johnson NW. Raised tissue copper levels in oral submucous fibrosis. J Oral Pathol Med 2000;29:241-48.
24. Naqvi S, Ullah MF, Hadi SM. DNA degradation by aqueous extract of Aloe vera in the presence of copper ions. Indian J Biochem Biophys 2010;47:161-65.

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