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ROLE OF FREE RADICALS AND EFFECTIVENESS OF ANTIOXIDANTS IN PATIENTS WITH OSMF AND OLP- A SYSTEMATIC REVIEW.

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ABSTRACT

The aim of the present study is to update the evidence of antioxidants in treating oral premalignant diseases and it's effectiveness; Data sources: automated searches of Medline, Pubmed, and the Cochrane Library were conducted; additional searches of main oral medicine journals were done manually using the keywords oral submucous fibrosis (OSF), Oral leukoplakia (OLP), treatment and antioxidants. Inclusion criteria: Surveys; randomised controlled studies (RCTs), observational studies, or case series reports that encompassed individuals of any age with confirmed diagnosis of OSF and OLP clinically and histopathologically. Types of interventions excluded were treatments with only habit intervention, surgical procedures, medical treatments (i.e. systemic, submucosal injection or topical agents), or physical therapy. 23 studies related to OLP and 15 studies related to OSF, were identified for inclusion. The authors were thoughtful in interpreting their conclusions. Treatment options included oral lycopene, oral lycopene with intralesional corticosteroids or an oral placebo; oral and topical curcumin, oral levamisole; multivitamins and oral beta carotene. Various objective and subjective outcomes improved with antioxidants, whereas some studies showed regression and malignancies. Use of antioxidants show some promise but there are no studies indicating the effectiveness of particular antioxidants or their combinations to be superior. Thus we conclude that current evidence for the benefit of antioxidants to manage OSF and OLP is weak.

KEYWORDS: *Oral submucous fibrosis (OSF), Oral leukoplakia (OLP), Antioxidants, Curcumin, Lycopene.*

INTRODUCTION

The past twenty years have seen an explosion of interest in free radicals, as their pivotal role in both chemistry and biology has come to light. The ability to utilize oxygen has provided humans with the benefit of metabolizing nutrients. Oxygen is a highly reactive atom that is capable of becoming part of potentially damaging molecules commonly called "free radicals." Oral cells are uniquely susceptible to free radical damage because the mucus membranes allow rapid absorption of substances across their surfaces. Direct exposure to noxious substances in the mouth further exacerbates the problem. Alcohol, nicotine from tobacco products, and dental materials such as hydrogen peroxide for bleaching, dental cements, composite fillings, and dental implants all increase free radicals resulting in cell damage[1]. Free radicals have been implicated in the etiology of large number of major diseases. They can adversely alter many crucial biological molecules leading to loss of form and function. Such undesirable changes in the body can lead to diseased conditions[2]. Oral cavity is exposed to lot of carcinogens and is prone to develop precancerous lesions and conditions which may turn to oral cancer. Oral cancer is a disease with high morbidity and mortality, and is the sixth commonest cancer in the world (Parkin et al, 1993)[8]. Its incidence is particularly high in India, some other countries in Asia, and certain places in the Western hemisphere, e.g., parts of France and Brazil. Dietary substitute play a vital role in prevention of oral cancer, potentially malignant

disorders like leukoplakia, lichen planus, oral submucous fibrosis, burning mouth syndrome, dental caries, strengthening the bond strength of orthodontic brackets, aids in bone healing and treating periimplantitis. Oral submucous fibrosis (OSF) is a chronic inflammatory disease, which has been categorised by WHO as one of the potentially malignant disorders (WHO workshop, 2005). Malignant transformation rate of OSMF is 7.6 % over a period of 10 years has been reported[3]. And according to Warnakulasuriyaet al.[4], the new concept of OLP shall acknowledge white lesions with questionable risk of being an OLP. Downer and Petti found an annual oral cancer incidence rate attributable to leukoplakia between 6.2 and 29.1 cases per 100,000 people [5]. Oral leukoplakia and OSF is relatively common oral lesion that, in an erratic proportion of cases, undergoes malignant transformation. Hence**,** leukoplakia and OSF should be considered a severe health problem.

DISCUSSION

Free radiclals

Free radicals are an unstable atom or molecule that contains one or more unpaired electrons in their valence shell (Fig 1)[12]. The first free radical identified, was triphenylmethyl radical by Moses Gomberg in 1900 at the University of Michigan[6]. Free radicals are produced during, Normal cellular activities like liver detoxification, Immune reactions and ETC (electron transport chain) reactions, or in Pathological events like ionizing radiation, toxic chemicals and tissue ischemia or they are produced in Disease conditions[7]. At low or moderate levels of concentration, ROS (reactive oxygen species) participate in the biosynthesis of molecules. At high concentrations; they generate oxidative stress and nitrosative stress that can damage all cell structures[8].

Oxidative stress

In a biological context, reactive oxygen species (ROS) and reactive nitrogen species (RNS) are formed as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling and homeostasis[9]. However, during environmental stress (e.g., UV or heat exposure), ROS levels can increase dramatically opposing body's antioxidant defense mechanisms leading to Oxidative stress. Cellular constituents of our body are altered in oxidative stress conditions, resulting in various diseases. This can be effectively neutralized by enhancing cellular defense in the form of antioxidants[10]. The generation of ROS begins with rapid uptake of oxygen, activation of NADPH oxidase, and the production of the superoxide anion radical ($O_2^{\cdot -}$)[11].

Antioxidant

Today, the entire world is suffering a rise in chronic health complications. Diets rich in fruits and vegetables have protective effect against a variety of diseases. The primary nutrients provide protection afforded by fruit and vegetables are the "Antioxidants"[8]. An antioxidant is a molecule which inhibits the oxidation reaction; terminate the chain reaction caused by free radicals of oxidation reaction, preventing cell damage or death of the cells. Ideal antioxidants have no harmful effects, are effective in low concentration, are fat soluble, readily available and do not contribute to objectionable flavor, odor or color to the fat[9].

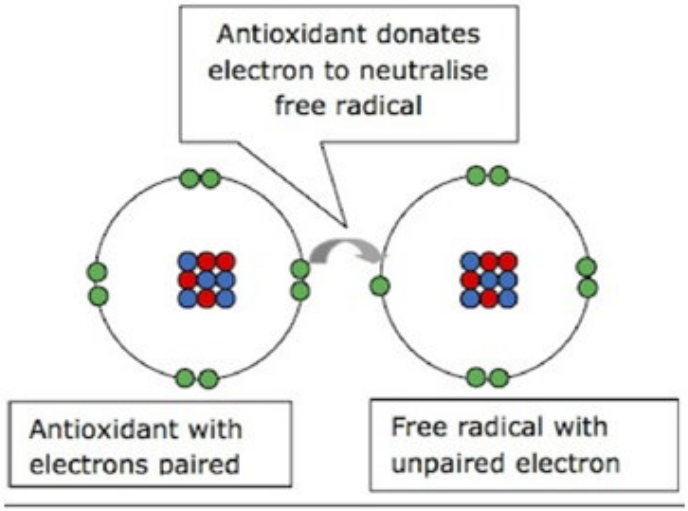

Figure 1
Formation of Free Radicals

Mechanism of action

Reactive oxygen species can cause tissue damage by a variety of different mechanism which include[13,14]

- DNA damage
- Lipid peroxidation (through activation of cyclogenase
- and lipooxygenase pathway)
- Protein damage, including gingival hyaluronic acid and proteoglycans
- Oxidation of important enzymes, e.g. Antiprotease such as;antitrypsin
- Stimulation of pro inflammatory cytokine release by
- Monocytes and macrophages by depleting intracellular thiol compounds and activating nuclear factor.

Mechanisms by which antioxidants may offer protection

→ Prevention of formation of free radicals
→ Interception of free radicals
→ Facilitating the repair
→ Providing a favourable environment

Saliva is the considered oral cavity's first level of defense system against oxidative stress. In healthy individuals, the total antioxidant capacity of saliva is sufficient to maintain homeostasis by neutralizing mild oxidative damage. When that equilibrium is disturbed by an overabundance of ROS, the introduction of additional antioxidants is needed to return the oral cavity to a balanced state. Antioxidants are accessible from different sources, including vitamins, minerals, enzymes and hormones, as well as food and herbal supplements. Nowadays, dental manufacturers have started incorporating antioxidant formulations into toothpastes, mouth rinses/mouthwashes, lozenges, fluoride gels, dentifrices, oral sprays, and other dental products for the control of gingival and periodontal diseases[12]. This review will give an update on various antioxidants, their role in treating the oral premalignant lesions Leukoplakia (Table 1, 2 and 3) and OSF (Table 4, 5 and 6).

RESULTS

A total of twenty three studies related to leukoplakia and antioxidants were considered, among which four studies shows treatment using lycopene, three studies shows treatment using Vitamin A, seven with Beta Carotene, and other eight by combination and 13-cRA. Among all the studies, lycopene shows complete resolution and promising results. Malignancies and recurrences were reported in patients treated with beta carotene, isotretinoin, vitamin A and vitamin C[17, 22 and 23]. There was one study using lycopene and Biocrush 250 mg[30], which shows complete remission of the lesion. Biocrush (Tabin-daingmya-nan) an herbal medicine which was used in Myanmar for treating Leukoplakia, but its efficacy needs further studies. Some studies[22] do not recommend the combination of beta-carotene with vitamin C for the chemoprevention of oral cancer. The database of most review and studies suggest that, Beta-carotene with ascorbic acid or alpha-tocopherol is attractive because of a lack of side effects, but the range in reported values for lesion improvement has been broad and the clinical improvement typically takes several months. Topical bleomycin, systemic 13-*cis*-retinoic acid, vitamin A and beta-carotene caused adverse effects of varying severity[52, 53]. Recent Cochrane review shows that none of the treatment was effective in preventing Cancer development, which was measured in studies of three treatments: systemic vitamin A, systemic beta carotene and topical bleomycin.. The one and only thing to be considered is, regardless of response to therapy, long-term follow-up is necessary[54]. Fifteen studies of OSF treated with antioxidants were selected, among which five studies shows treatment using turmeric (curcumin), four using Lycopene and six using vitamins and other antioxidants. It is evident from the studies that curcumin and lycopene holds good promise in the treatment of OSF in future and that neither has any adverse effect (Table 4 and 5). A Cochrane review was done in 2008 to assess the effectiveness of lycopene in conjunction with intralesional injections of a steroid, and pentoxifylline in combination with mouth stretching exercises along with heat application. But they provided a limited amount of unreliable data, which was due to poor methodology quality[55]. Some reviews raised the point that cessation of areca nut use alone has not been studied and a minority of studies includes advice to quit the habit[56]. El Khoury E has stated Curcumin conjugated silver nano particles show anti-bacterial activity. Hence these curcumin conjugated nano particles can be used as an anti-cancer agent[57]. Concerns were expressed regarding the small sample size, insufficient follow up, uncertain success rates of using antioxidants and lack of adequate evaluation of antioxidants prior to marketing, which demands the need for consistency in conducting and reporting the clinical trials[58, 59].

Table 1
Studies showing management of Oral leukoplakia with Beta-Carotene

Author and Year	No. of patients and Dosage	Results	Adverse effects and Malignant transformation
Beta-Carotene			
H. S. Garewal, et al - 1990[15]	24 patients treated with beta-carotene at a dose of 30 mg/day for six months.	Only 2 patients (8.3%) presented a complete clinical response and 15 patients (62.5%) had partial clinical response	
S. Toma, et al - 1992[16]	23 patients treated with beta-carotene, in oral doses of 90 mg/day, for three cycles of 3 months each	Of 18 patients who completed the study, 6 (33.3%) showed complete clinical response. 5% Recurrence	
G. E. Kaugars, et al -1994[17]	79 patients, 30 mg of betacarotene, 1000 mg of L-AA [L-ascorbic acid] and 800 IU of AT [alpha tocoferol] per day for 9months.	55.7% showed reduction in the size. Clinical improvement was observed in 90% of the patients who had reduced risk factors, compared with 48.8% of improvement in those who did not.	Squamous cell carcinoma developed in seven patients (8.9%)
Sankaranarayanan, et al - 1997[18]	Out of 110 patients 55-treatment 55-placebo 360 mg beta-carotene per week during 12 months.	Complete resolution of OL. 8 out of 15 (54%) of the patients who had a complete response presented recurrence	Observed in 5 patients, 3 with headache and 2 developed muscular pain.
T. J. Barth et al 1997 [19].	24 Beta-carotene, vitamin E, and L-AA	In 97.5% of patients, dysplasias were diminished by use of antioxidant combinations and is more evident in patients with cessation of habit.	
Garewal, et al – 1999[20]	50 patients treated with beta-carotene at a dose of 60 mg/day, for six months.	Only 2 patients (4%) demonstrated a complete clinical response. Relapses were found in 4 patients.	
Nagao, et al-2000[21]	48 cases detected with oral leukoplakia (38 male:10 female) examined the fasting serum levels of retinol, alpha-tocopherol, zeaxanthin and lutein, cryptoxanthin, lycopene and carotenoids (alpha-carotene and beta-carotene) by high-performance liquid chromatography	Logistic regression analysis with leukoplakia as the dependent variable showed that high serum levels of beta-carotene were related to low risk of oral leukoplakia	
J. Jack Lee, et al - 2000[22]	70 patients, Phase 1: 3 months Phase 2: 9 months. Phase1: isotretinoin (1.5	9/26 (34.6%), 11 /33 (33.3%), and 2/11 (18.2%) developed cancer in 3 groups	

	mg/kg) Phase 2: low dose isotretinoin (0.5 mg/kg/day) or β-carotene (30 mg/day).	with low dose isotretinoin, β-carotene, and induction.	
Toru Nagao et al - 2015[23]	46 participantswere allocated randomly either to an experimental arm 10 mg /day of beta-carotene and 500 mg/day of vitamin C or placebo arm 50 mg/day of vitamin C. 5-year follow-up period as a secondary endpoint.	The overall response rate at a time of 1-year observation including CR (complete remission) and PR (partial remission) in the experimental arm was 17.4% (95% CI: 1.9–32.9%) and 4.3% (95% CI: 0–12.7%) for the placebo arm.	Two subjects in the experimental arm and three in the control arm developed oral cancer

Table 2
Studies showing management of Oral leukoplakia with Vitamin A

Vitamin A			
Joel B. Epstein, et al-1999[24]	26 (17 men and 9 women) Topical 0.05% Vitamin A (tretinoin) acid gel 4 times a day	27% of the patients had a complete clinical remission. Recurrence in 40% patients with complete remission. The mean duration of the application of vitamin A acid gel was 3.5 years in the patients with clinical improvement and 1.5 years in those with no such improvement	Lichenoid reaction: 35% Sensitivity: 19%. In 4 patients the post treatment dysplasia was increased at a mean period of 1.5 years
Piattelli, et al-1999[25]	10 patients (6 male, 4 females). Patients were randomly assigned either topical 0.1% isotretinion gel or placebo for 4 months	9 patients completed the study and all of them receiving active drug showed improvement in oral lesions and the patients receiving placebo showed no virtual change. One patient showed complete resolution of lesion, whereas rest 8 showed partial resolution	Only one patient showed bcl-2 positivity
G. A. Scardina, et al - 2006[26]	Forty patientswere randomly divided into two groups and the drug was administered topically at 0.05% and 0.18% of isotretinoin concentrations for 3 consecutive months	Clinical resolution was 85% in the 0.18% of isotretinoin concentrations group	No adverse topical and systemic reactions in 10 years follow up.

Table 3
Studies showing management of Oral leukoplakia with Lycopene and other vitamins.

Lycopene			
Gupta, et al - 1998[27]	An interviewer-administered food frequency questionnaire Among 5018 male tobacco users, 318 were diagnosed as cases	A protective effect of tomato(contains lycopene) and ascorbic acid consumption was observed in leukoplakia	

Singh, et al-2004[28]	58 Group 1: 20 Group 2: 20 Group 3: 18 3 months Systemic Lycopene Group 1:4mg Group 2: 8 mg Group 3: Placebo	80%, 66.25% and 12.5% clinical resolution in 3 groups respectively.	Recurrence & Malignant transformation not reported
Zakrzewska JM-2005[29]	58 patients received either 8 mg oral lycopene in two doses daily (n = 20), 4 mg oral lycopene in two doses daily (n = 18) or placebo capsules (n = 18), for a 3-month period.	The response, assessed histologically, after the 8-mg lycopene treatment was significantly better than that from 4 mg lycopene. Patients taking 4 mg lycopene also responded significantly better than those in the control group. There was no significant difference in patients taking 8 mg lycopene compared to those taking 4 mg clinically in 5 month duration	
Win Pa PaAung, et al -2013[30]	72 patients were treated with 10 mg and 500 mg lycopene twice a day for 3 months, with Biocrush 250 mg, bd.	totally eradication of white patch area was seen within a month	No toxicity. Or side effects encountered.
Others			
Hong – 1986[31].	44 patients 24 treatment 20 placebo 13-cis-retinoic acid 1 to 2 mg per kilogram of body weight per day for 3 months	Follow up for 9 months Clinical resolution 67% versus 10 % in Placebo. Reversal of dysplasia in 54% versus 10% in placebo Relapse occurred in 9 of 16 patients in two to three months	Two patients: Cheilitis, facial erythema, and dryness and peeling of the skin, conjunctivitis and hypertriglyceridemia
S. Toma. P. E, et al -1992[32].	16 patients for 6 months treated with Oral 13-cis-retinoic Acid. The initial dose, given for 3 months, was 0.2 mg/kg/day, increasing by further 0.2 mg/kg/day in successive 3 month cycles. The maximum dosage reached 1.0mg/kg/day	Fourteen of the patients completed the trial and there was one complete response obtained at 0.4 mg/kg/day. After the retinoic acid treatment was stopped, patients were followed-up for 12 months; 2 patients showed regression of the responses after 6 and 9 months	
Benner SE, et.al 199[33].	43 patients treated orally with alpha-	Patient's recorded drug calendars, as well as serum	

	tocopherol (400 IU) twice daily for 24 weeks. Follow-up was performed at 6, 12, and 24 weeks after the start of treatment to assess toxicity and response, and serum alpha-tocopherol levels	drug levels, indicated excellent patient compliance	
I. W. Dimery, et al 1997[34].	7 patients treated with 13-cRA (10 mg/day) plus an escalating dose (beginning at 800IU/day, until 2000 IU/day) for 4 months	71% complete resolution	
Sankaranarayanan, et al. 1997[35].	105 patients 50 treatment 50 placebo Systemic Isotretinoin 300.000 IU given for 12 months	52% clinical resolution. 67% recurrence. Malignant transformation not reported	headache, muscular pain, dry mouth
FaustoChiesa, et al 2005[36].	170 [surgically operated cases with histologically proved non carcinoma cases [121 males,49 females] 84-treated 86-control 12 months 4-HPR 200 mg/day [100 mg twice a day]	43 completed treatment at full dosage with 90% compliance. 15 recurrence and 10 new lesions in control and 15 recurrence and 4 new lesions in 4-HPR treated cases.	9 out of 43 had mild adverse effects 14 with major effects: hematologic toxicity in 7, cutaneous toxicity in 6 and gastric toxicity in one. Malignant transformation was reported in both groups.

Table 4
Studies showing management of Oral submucous fibrosis with Curcumin

Author and Year	No. of patients and Dosage	Results
Curcumin		
Deepa DA et al, 2010[37].	48 patients were called every 15 days for 3 months during treatment and followed up for 6 months Grp I: curcumin capsules GrpII:turmeric oil Grp III: multinal tablets (control grp)	Burning sensation improvement was statistically significant in grp I and II. Curcumin showed quicker results whereas turmeric oil had long term effect on follow up evaluation Grp III showed minimal improvement.
N Agarwal et al, 2014[38].	30 subjects Group A: >35 mm Group B: Between 30 and 35 mm Group C: Between 20 and 30 mm Group D: <20 mm Turmix (curcumin 300 mg and piperine 5 mg)	An improvement of 82.50% (33), 83.33% (5), 66.10% (39), and 71.67% (43) was seen in groups A, B, C, and D, respectively. An improvement of in mouth opening of group A -10.4 mm group B, - 1.4 mm group C, - 2.3 mm group D -6.5 mm

M Yadav et al, 2014[39].	40 patients randomly divided into 2 groups. First group: treated with weekly intralesional injection of 4 mg Dexamethasone & 1500 I.U Hyaluronidase. Second group:by oral administration of two Curcumin tablets (Turmix 300 mg) per day for 3 months each	Complete resolution of burning sensation was noted with turmix. The mean increase in interincisal distance was 3.13 mm and 1.25 mm respectively in groups 1 &2.
V K Hazarey et al, 2015[40].	30 patients Two groups: 15 patients in each group. Test group: Longvida (curcumin) lozenges of 2g daily Control group: Tenovate ointment (clobetasol propionate (0.05%) along with mouth exercises for 3 months duration and follow-up was done for 6 months.	The test group showed 5.93 (±2.37) mm, increase in mouth opening compared to control group. In relation to VAS scale with spicy and normal food the average reduction was 64 and 77 as compared to 34 and 64 respectively in control group.
F Karjodkar et al, 2016[41].	129 patients treated for 3 months Grp I - 20 :Turmeric oil(100mg)+Turmeric extract(500mg) 6 tabs/day 3.6 gms, GrpII- 20: Oleoresin(120mg)+Turmeric extract(600mg) 5 tabs/day 3.6 gms GrpIII -20: Oleoresin of turmeric (50mg)+250mg of mixture of betel leaf extract+ catechu extract 6 tabs/day 0.3gms GrpIV -24: Turmeric extract + Betel leaf extract+ Catechu+ Cinnamic acid(500mg) 3 tabs/day 1.5gms Grp V- 10: Betel leaf extract(150mg) 2tabs/day 0.3gms Grp VI-10: Catechu extract(150mg) 2tabs/day 0.3gms GrpVII- 25: Turmeric extract(500mg) 3tabs/day 1.5gms	The most significant response to relief in burning sensation was within Group III Only 1 patient showed oral opening improvement of more than 15 mm Group VII (Turmeric extract (500mg) showed the most statistically significant difference between micronuclei count before and after treatment.

Table 5
Studies showing management of Oral submucous fibrosis with Lycopene

Lycopene		
Kumar et al, 2007[42].	83 participants group A, n = 21: 16 mg of lycopene daily in 2 equally divided doses group B, n = 19:16 mg of lycopene daily in 2 equally divided doses and were given intralesional injections of betamethasone (2 1-mL ampules of 4 mg each) twice weekly group C, n = 18:placebo capsules 58 patients completed the trial	Objective measurement of mouth opening was reported to be significantly improved with an average increase of 3.4mm, 4.6mm and 0mm for groups A, B and C, respectively. Complete relief from burning sensations within 2 weeks, whereas only one patient from the placebo group reported a similar improvement.
Gowda BB et al, 2011[43].	12 adult patients Group1: Very early case Group 2: Early cases (7 patients) Group 3: Moderately advanced cases (5patients) Each patient was given lycored twice daily for 3 months, where each	Subsequently, a definite reduction in the burning sensation and an increase in the mouth opening were noted

	capsule contained 2000 µg of lycopene. The responding patients continued to take lycopene for an additional 3 months.	
Selvam NP et al, 2013[44].	45 patients divided into 3 groups consisting of 15 cases each followed up to 3 and 6 months Group A: oral lycopene 16 mg/day with biweekly intralesional steroids and hyaluronidase Group B: oral antioxidant capsules with biweekly intralesional steroids and hyaluronidase Group C: biweekly intralesional steroids and hyaluronidase alone.	The results were statistically significant between Group A and C and Group B and C. There was significant increase in mouth opening among all the 3 groups.
R K C Kopuri et al, 2016[45].	30 study subjects Group A: lycopene 8 mg/day in 2 divided doses prescribed for 3 months. Group B: curcumin 800 mg/day in 2 divided doses prescribed for 3 months	There were improvements in both the groups, but significant improvements were observed in Group A.

Table 6
Studies showing management of Oral submucous fibrosis with vitamins and other antioxidants

Vitamins and others		
Maher R et al, 1997[46].	117 subjects Combination of micronutrients (vitamins A, B complex, C, D, and E) and minerals (iron, calcium, copper, zinc, magnesium, and others) were prescribed for one to three years	Significant improvement in symptoms, notably intolerance to spicy food, burning sensation, and mouth opening, was observed at exit
S. Gupta et al, 2004[47].	34 patients Treated with "antoxid" tablets. 1 tablet thrice daily for 6 wks. Each tablet contains beta-carotene 50 mg, Vitamin A palmitate 2500 IU, Vitamin E acetate 10 IU along with Vitamin C, zinc manganese and copper.	Decrease in mean MDA level and the increase in levels of beta-carotene were found to be statistically significant. There was increase in mouth opening and tongue protrusion measurement.
Jirge et al 2008[48].	45 participants Group I: oral levamisole 50 mg three times daily Group II: oral 2 capsules of antoxid daily for six weeks Group III: oral levamisole and antoxid.	improvement of mouth opening of 7.1%, 6.7% and 8.0% in groups I, II and III, respectively with reduction in burning sensations in all study groups
R Mehrotra et al, 2013[49].	64 patients Vitamin A or carotinoids Se, Zn. Fe and B Complex vitamin, Mn, Cu, Vitamin C were given and followed up for 3months	Among 64 cases of oral submucous fibrosis 36 cases improved on therapy (56.25%) No patient got complete cure by therapy and there were 16 cases who failed on therapy (25%).
P Shetty et al, 2013[50].	40 patients Group A:spirulina 500 mg twice daily and biweekly intralesional steroid injection of Betamethasone 4 mg/ml for 3 months	Both the groups showed statistically significant reduction in burning sensation. Mouth opening and burning sensation was found to be statistically very highly

	Group B: placebo capsules twice daily and biweekly intralesional steroid injection of Betamethasone 4 mg/ml for 3 months.	significant in favor of the spirulina group
Shwetha V et al, 2016[51].	60 subjects Capsule Oxitard was administered to all patients at a dose of 2 capsules twice daily for a period of 3 months	Clinical improvement in mouth opening and symptoms of burning sensation as measured by the VAS scale following oxitard therapy was significant.

CONCLUSION

According to the present review, most authors support the safety and effectiveness of using antioxidants over the oral lesions, due to its scavenging effect on free radicals. But there is much debate regarding the dosage, regime and tolerance rate of antioxidants, which requires further research. Hence we conclude that more studies are necessary in the field of dentistry, considering the following points

1. Evaluation of the combination of conventional surgical excision and the administration of postoperative antioxidants should be done.
2. Most effective combinations and the exact dosage of antioxidants with least or no adverse effects need to be studied

CONFLICT OF INTEREST

Conflict of interest declared none

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