

## Review Article

### Antioxidants in Oral Diseases and Future Prospects and their Application in Dentistry

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#### ABSTRACT:

In recent years there is an upsurge in the areas related to newer developments in prevention of disease especially the role of free radicals and antioxidants. Free radicals are unstable chemicals formed in the body during normal metabolism or exposure to environmental toxins such as pollutants in air, food and water. These free radicals further result in oxidative stress. Severe oxidative stress can cause cell damage and death. Free radicals have been implicated in numerous human diseases including atherosclerosis, diabetes mellitus, parkinsonism, immune dysfunction, rheumatoid arthritis as well as various oral diseases like leukoplakia, oral submucous fibrosis and oral cancer. Oxidative stress is also associated with genotoxicity, and as well premature aging. It is a remarkable fact that antioxidants are non-toxic compounds that reduce the incidence of oral cancer. Antioxidant nutrients such as vitamin E, beta-carotene, lycopene and selenium are regularly found to reduce the risk of lung, prostate, stomach, or body cancers as well as pre-cancerous conditions.

**Keywords:** Antioxidant, Periodontal disease, oral cancer, leukoplakia, oral submucous fibrosis.

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#### INTRODUCTION

As the recent trend in nutrition is towards development of healthy food in the form of "functional food", one of the desirable properties in a dietary component is its "antioxidant effect". Antioxidants have gained importance in recent years due to their ability to neutralize free radicals or their actions. Antioxidants are enzymes or other organic molecules that can counteract the damaging effects of reactive oxygen species in tissues. Antioxidants can be both exogenous and endogenous, and synthetic or natural and they can be water soluble or lipid soluble. The term "antioxidant" is often applied to any organic molecule that act against the harmful effects of free radicals (molecules with unpaired electrons).<sup>1</sup>

Free radicals are unstable chemicals formed in the body during normal metabolism or exposure to environmental toxins such as pollutants in air, food and water. These free radicals further result in oxidative stress. Severe oxidative stress can cause cell damage and death. Free radicals have been implicated in numerous human diseases including atherosclerosis, diabetes mellitus, parkinsonism, immune dysfunction, rheumatoid arthritis

as well as various oral diseases like leukoplakia, oral submucous fibrosis and cancer. Oxidative stress is also associated with genotoxicity, and as well premature aging.<sup>2</sup>

It is a remarkable fact that antioxidants are non-toxic compounds that reduce the incidence of cancer.<sup>1</sup> Antioxidant nutrients such as vitamin E, beta-carotene, lycopene and selenium are regularly found to reduce the risk of lung, prostate, stomach, or body cancers as well as pre-cancerous conditions.<sup>3</sup> Food containing these nutrients are similarly effective, as are non-dietary antioxidants such as green tea phenols and various oriental herbal medicines. Antioxidants like lycopene, flavanoids certain minerals like Manganese, Copper, Selenium, Zinc and herbal medicines are also gaining importance in this regard. Scientific experiments, since 19<sup>th</sup> century have documented the antioxidant properties of some spices, herbs and their components. There is growing interest towards natural antioxidants from herbal sources.

Excessive free radicals production and lipid peroxidation underlie the pathogenesis of diseases whose prevalence is increasing day by day. Recent studies have proved

that antioxidants play important preventive role in these diseases as potent scavenger of free radicals and protect our cells against oxidative damage and reduce the risk of developing these certain types of diseases.<sup>4</sup>

One important line of defense is the system of enzymes, including glutathione peroxidases, superoxide dismutases and catalase, which decrease concentrations of the most harmful oxidants in the tissues. Several essential minerals including selenium, copper, manganese and zinc are necessary for the formation or activity of these enzymes. Hence, if the nutritional supply of these minerals is inadequate, enzymatic defenses against free radicals may be impaired.

Natural antioxidants are present in fruits and vegetables and are able to protect living tissue from reactive oxygen species such as superoxide anion and hydroxyl radicals and non free radical species such as hydrogen peroxide and singlet oxygen as well as other radicals and aid in retarding the progress of many chronic disease. The role of antioxidants has attracted much interest with respect to their protective effect against free radical damage that may cause various pathologies in body, premalignant lesions and as well as cancer. Many plant phenols, flavonols etc. other than antioxidant vitamins such as: C, E and carotenoids exert powerful antioxidant effects.<sup>5</sup>

Dietary deficiencies or excesses have shown to be associated with a number of cancers.<sup>1</sup> Many studies reported that the trace elements play a major role as either inhibitory or causative agents of cancers. Copper, zinc, iron and ceruloplasmin a copper containing enzyme with ferroxidase activity, are biologically essential for normal development, growth and function.<sup>2,5</sup>

In recent years there is an upsurge in the areas related to newer developments in prevention of disease especially the role of free radicals and antioxidants. So, this review compiles the pertinent possible role of 'free radicals' in disease and 'antioxidants' in its prevention, especially the current status of the antioxidants in oral diseases and future prospects and their application in dentistry

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## HISTORY OF ANTIOXIDANTS

Secrets of antioxidants and free radicals started to attract interest of researches in the beginning of 20<sup>th</sup> century. Duclaux first demonstrated participation of atmospheric oxygen in oxidation of free fatty acids. Interestingly, the first reports on antioxidants employed for food lipids were about using natural sources. "Antioxidant synergism in food was first reported by Olcott and Mattill, and this was significant in achieving oxidative stability in food by using a combination of antioxidants found in the unsaponifiable fraction of oils. Recently, Ferreira et al. studied the prophylactic effect of topical Vitamin E in head and neck cancer patients for prevention of radiation induced oral mucositis.<sup>6</sup> Around the world a revival is seen in studying the natural antioxidants in foods and the potential health benefits of natural antioxidants in relation to prevention and therapy of oxidative stress and related diseases. The antioxidant defense systems of the human body are complex and various classification systems exists.

Antioxidants are grouped into two namely; Primary or natural antioxidants and Secondary or synthetic antioxidants.<sup>7</sup>

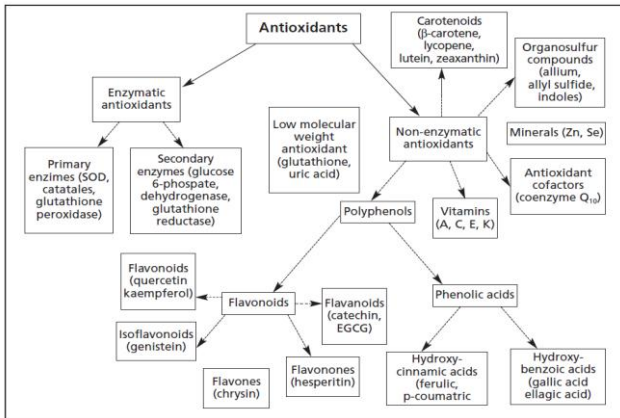
**Primary or natural antioxidants :**

They are the chain breaking antioxidants which react with lipid radicals and convert them into more stable products.

**Secondary or synthetic antioxidants**

These are phenolic compounds that perform the function of capturing free radicals and stopping the chain reactions, the compound

**SUMMARY OF CLASSIFICATION OF ANTIOXIDANT**



**ROLE OF ANTIOXIDANTS IN ORAL CAVITY**

Antioxidants are critical for maintaining optimum health and well-being. The best sources of antioxidants are fruits and vegetables, which provide a variety of antioxidants such as Vitamins A, C, E, and carotenoids.<sup>8</sup> Studies suggest the role of antioxidants in treatment of oral mucosal lesions particularly include oral leukoplakia, oral lichen planus, oral submucous fibrosis, oral cancer and RAS.<sup>10</sup>

The possible therapeutic uses of antioxidants for oral mucosal lesions include the following<sup>8</sup>:

1. Prevention of lesions in high-risk individuals with mucosa that clinically appears normal with no history of either premalignant or malignant lesion.
2. The treatment of premalignant oral lesions.
3. In patients who have had either premalignant or malignant oral lesions that have been successfully treated, in order to prevent recurrence of the treated initial lesion or to prevent the development of another lesions.

The antioxidant potential has been ranked as follows: lycopene > α-tocopherol > α-carotene > β-cryptoxanthin > zeaxanthin = β-carotene > lutein.<sup>9</sup>

In recent years there is an upsurge in the areas related to newer developments in prevention of diseases specially the role of free radicals and antioxidants. So, it will be pertinent to examine the possible role of ‘free radicals’ in various diseases and how ‘antioxidants’ play an important role in their prevention, especially the current status of the subject matter and future prospects.<sup>10</sup>

**ORAL SUBMUCOUS FIBROSIS**

Sushruta, a renowned Indian physician who lived in the era from 2500 to 3000BC, had already recognized it as a mouth and throat melody and had labeled it as ‘Vidhari’. The features of which were described as a progressive narrowing of the mouth, blanching of the oral mucosa, pain and burning sensation on taking food, hypomobility of the soft palate and tongue, loss of gustatory sensation and occasional mild hearing impairment due to the blockage of the Eustachian tube. There has been nearly no change in these symptoms till today. This condition has a reference in modern literature due to the works of Schwartz in 1952. Joshi was the first to describe this condition in India in 1952 and he coined the name ‘oral submucous fibrosis’.<sup>11</sup>

Oral submucous fibrosis is a chronic progressive scarring disease of oral cavity and oropharynx characterized by epithelial atrophy and juxta epithelial inflammatory reaction with progressive fibrosis of the lamina propria a deeper connective tissue. The resulting stiffness of the oral mucosa then causes a progressive decrease in mouth opening.<sup>12</sup> A variety of etiologic factors including capsaicin, betel nut alkaloids, hypersensitivity, autoimmunity, genetic predisposition and chronic iron and vitamin B-complex deficiency have been suggested by various authors, the most common of which is chewing areca nut. Excessive use of areca nut may cause fibrosis due to increased synthesis of collagen and induce the production of free radicals and reactive oxygen species, which are responsible for high rate of oxidation/peroxidation of polyunsaturated fatty acids which affect essential constituents of cell membrane and might be involved in tumorigenesis.<sup>9</sup>

It is known that the process of carcinogenesis occurs by generation of Reactive Oxygen Species, which act by initiating lipid peroxidation (LPO). Prevention against LPO mediated damage is done by antioxidants and it has also been reported that oral premalignant lesions can be successfully treated by antioxidant supplementation which led many clinicians to consider antioxidants in the treatment of OSMF.<sup>13</sup>

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**ROLE OF ANTIOXIDANTS IN MANAGEMENT OF OSMF**

Selvam et al. in 2013 evaluated role of Lycopene in management of OSMF. Group A patients were given oral Lycopene capsules 16 mg, one capsule/day along with bi-weekly intralesional injections of Dexamethasone 1.5 ml & Hyaluronidase 1500 IU mixed with lignocaine. Group B patients were given oral antioxidant capsules, one capsule/day along with bi-weekly intralesional injections of Dexamethasone 1.5 ml & Hyaluronidase 1500 IU mixed with lignocaine. Results indicated that lycopene is more efficacious than other antioxidants when used in combination with intralesional steroids to treat OSMF.<sup>9</sup>

A study conducted by Gowda et al. on 12 patients with OSMF. After the clinical examination, investigation and

biopsy confirmed the diagnosis as oral submucous fibrosis, each patient was given the commercially available antioxidant, LycoRed (capsule containing 100% natural lycopene with zinc, selenium and added phytonutrients. Deepa Das et al., found that turmeric dispensed in the form of curcumin and turmeric oil was effective in the treatment of OSMF which was evident by the positive changes observed in the histopathological examination after treatment along with the significant improvement in clinical signs and symptoms.<sup>14</sup> Turmeric has been found to inhibit many disease processes through their anti inflammatory, antioxidant and anticancer properties. Curcuminoids isolated from turmeric, has been found to have effective antioxidant, DNA-protectant and antimutagen action. Turmeric given in any form, i.e., alcoholic extracts of turmeric, turmeric oil and turmeric oleoresin is found to be effective in decreasing the number of micronucleated cells both in exfoliated oral mucosal cells and in circulating lymphocytes.<sup>13</sup>

### **ROLE OF ANTIOXIDANTS IN THE MANAGEMENT OF ORAL LEUKOPLAKIA**

Leukoplakia is the most common pre-cancerous lesion in the oral cavity. OL has an annual malignant transformation rate of 0.1% to 17%. Oral leukoplakia once diagnosed, the patient is advised to discontinue the habit after proper counselling of the risk of leukoplakia turning into malignancy and is supported with mainly antioxidants in mild cases. . Recurrence of OL after surgical treatment has been reported in 10%–35% of cases.<sup>15</sup> Tobacco smoke contains nitrous oxide radicals, which are carcinogenic. Lycopene exhibits the highest physical quenching rate constant with singlet oxygen. Lycopene increases the expression of the gene encoding connexin-43, a gap junction protein, effect being independent of provitamin- A or antioxidant properties.<sup>16</sup>

A study conducted by M. Singh et al., with a supplement of Lycopene in dosage of 8 mg and 4 mg on 58 patients with oral leukoplakia. The patients receiving lycopene supplementation in both 8 and 4 mg regimens showed highly significant difference in the response as compared to the placebo group According to Liede et al., a diet supplemented with beta-carotene can prevent changes in the oral mucosa, especially in smoker patients, who present low serum levels of vitamin C and beta carotene when compared to nonsmokers. In another study, 23 patients with OL were treated with beta-carotene, in oral doses of 90mg/day, for three cycles of 3 months each. Of 18 patients who completed the study, 6 (33.3%) showed complete clinical response. No significant clinical signs of toxicity were detected in any of the patients.<sup>17</sup>

T. J. Barth et al. in 1997, conducted study on 24 patients with leukoplakia and supplemented them with Beta-carotene, vitamin E, and L-AA. In 97.5% of patients, dysplasias were diminished by use of antioxidant combinations and more evidently in patients with cessation of habit.<sup>18</sup>

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Kaugars et al. implemented retinoic supplementation in various dosages for OL treatment. Fifty percent of patients had complete or partial clinical resolution of OL, but with side effects such as dizziness and headache. Some patients ceased treatment due to its side effects. On the other hand,

during the assessment of 13-cRA topical use (0.1% isotretinoin gel) for 4 months, in 9 patients with OL, 20% showed complete clinical response to treatment and no patient reported adverse effects.<sup>15</sup>

Tea is a rich source of polyphenolic flavonoids which exhibit potent antioxidant activity in vitro and in-vivo. Clinically, oral lichen planus (OLP) presents in various forms such as reticular, papular, plaque like, atrophic, erosive and bullous, of which erosive and atrophic forms are usually symptomatic and need therapeutic interventions. . A study done on erosive vulval LP tissues showed increased oxidative stress and decreased antioxidant enzyme expression.<sup>19</sup>

The management of oral lichen planus should therefore address both the transformation rate as well as the patient symptoms. Use of lycopene, as a potent antioxidant in the management of various systemic and oral diseases including cancer and precancerous lesions has been reported in the literature. Supplementing with 8 mg/day of lycopene for 8 weeks showed favorable results in OLP patients. In a study, 15 OLP patients treated with Lycopene 8 mg/day and another 15 with an identical placebo. The doses of lycopene used vary in the range of 6–60 mg/day.

In the study, patients in both lycopene and placebo groups showed a significant reduction in the burning sensation at the end of the treatment (84% and 67%, respectively). However, this reduction in burning sensation was higher in lycopene group than in the placebo group.<sup>20</sup> Previous studies revealed that side effects were common and troublesome with marginal improvement. . Studies to date indicate that higher dosages of curcumin (up to 6,000 mg/ day) helped a significant number of OLP patients control their symptoms. Minimal side effects like diarrhea and gastrointestinal discomfort may occur, which are usually dose related.

Turmeric and its ingredients curcumin are being studied as chemo preventive agent that inhibits the development of oral cancer. Curcumin and essential oil of turmeric have been found to inhibit many diseases processes through their ant inflammatory, antioxidant and anticancer properties. Green tea (epigallocatechin-3-gallate) is known to have possessing anti-inflammatory and chemopreventive properties.

### **ROLE OF ANTIOXIDANTS IN THE MANAGEMENT OF LICHEN PLANUS**

Lichen planus (LP) is an autoimmune, chronic, inflammatory disease that affects mucosal and cutaneous tissues. Oral lichen planus (OLP) occurs more frequently than the cutaneous form and tends to be more persistent and more resistant to treatment. Its predisposing factors are :

- 1) Stress
- 2) Genetics
- 3) Hepatitis C virus infection

Clinically, oral lichen planus (OLP) presents in various forms such as reticular, papular, plaque like, atrophic, erosive and bullous, of which erosive and atrophic forms are usually symptomatic and need therapeutic interventions. The pathogenesis has been extensively studied and the disease appears to be a result of a cell-mediated immune reaction in which Langerhans cells, keratinocytes and activated T lymphocytes are involved.<sup>20</sup>

The role and importance of oxidative stress has been suggested in the pathogenesis of LP. A study done on erosive vulval LP tissues showed increased oxidative stress and decreased antioxidant enzyme expression.<sup>19</sup>

The management of oral lichen planus should therefore address both the transformation rate as well as the patient symptoms. Care and management of such patients challenges even the most experienced clinician.

Use of lycopene, as a potent antioxidant in the management of various systemic and oral diseases including cancer and precancerous lesions has been reported in the literature. Supplementing with 8 mg/day of lycopene for 8 weeks showed favorable results in OLP patients. Burning sensation was reduced by 84% and lowered oxidative stress in a placebo-controlled trial.<sup>21</sup> In a study, 15 OLP patients treated with Lycopene 8 mg/day and another 15 with an identical placebo. The doses of lycopene used vary in the range of 6–60 mg/day. LP is a chronic condition and various studies have reported longer duration of treatment, ranging from 2 to 32 weeks, and most of the studies, using retinoids, have used the medications for 8 weeks.[1-4] in this study use 8 mg/day of lycopene was given for a period of 8 weeks. Relief from the symptoms or burning sensation is an important goal in the management of OLP. In the study, patients in both lycopene and placebo groups showed a significant reduction in the burning sensation at the end of the treatment (84% and 67%, respectively). However, this reduction in burning sensation was higher in lycopene group than in the placebo group.<sup>20</sup>

Retenoids have also been tried for the treatment of OLP. Previous studies revealed that side effects were common and troublesome with marginal improvement. In a study by Ferguson et al. Etritinate was found to have minimal value in the management of erosive OLP when used in dose of 25-75 mg for 8 weeks, with side effects such as pruritis, cheilitis, desquamation of hands and feet and paronychia. Meirgrosky et al. in their study noted that when Etritinate was used in the dose of 75 mg/day for 2 month it was effective in treating oral symptomatic lichen planus only for the duration of its use, discontinuation resulted in recurrence of signs and symptoms.<sup>21</sup>

Curcuminoids are components of *Curcuma longa* (turmeric) known to have anti-inflammatory properties. Studies to date indicate that higher dosages of curcumin (up to 6,000 mg/day) helped a significant number of OLP patients control their symptoms. Minimal side effects like diarrhea and gastrointestinal discomfort may occur, which are usually dose related. Whereas smaller doses of curcumin (< 2,000 mg/day) have failed to provide relief. The extract of curcumin plant have been a major ingredient of medicine since the time immemorial. It has been attributed a number of medicinal properties in the traditional systems of the medicine. Turmeric and its ingredients curcumin are being studied as chemo preventive agent that inhibits the development of oral cancer. Curcumin and essential oil of turmeric have been found to inhibit many diseases processes through their ant inflammatory, antioxidant and anticancer properties. So, it can be used as a herbal method to minimize lichen planus.<sup>22</sup>

Green tea (epigallocatechin-3-gallate) is known to have possessing anti-inflammatory and chemopreventive properties. It is known to reduce the incidence of OLP by regulating the factors which are involved in the etiopathogenesis of the disease. Green tea is known to inhibit T-cell activation, migration, proliferation, antigen presentation and control other inflammatory mediators.<sup>23</sup>

*Ocimum Sanctum* (Tulsi) has a unique property to act on blood and skin tissue and bring about desired immunomodulation and is used as an Ayurvedic medicine to treat cases of lichen planus.<sup>24</sup>

But the exact role of antioxidants in the treatment of lichen planus is not yet clear and it has been studied as an adjuvant in most of the studies

#### ANTIOXIDANTS IN THE MANAGEMENT OF APHTHOUS STOMATITIS

Recurrent aphthous ulceration or recurrent aphthous stomatitis is the most commonly known oral mucosal disease with a prevalence of up to 25% in the general population and 3-month recurrence rates as high as 50%. Popularly referred to as mouth ulcers or canker sores, aphthous ulcers are round or oval with a yellow or grey floor surrounded by an erythematous halo of inflamed mucosa. They can cause considerable pain and may interfere with eating, talking and swallowing. Aphthous ulcers can be classified into three different types: minor, major and herpetiform.<sup>25</sup>

The ideal treatment of aphthous ulcers would improve ulcer healing by stimulating mucosal cell growth and removing bacterial cells that otherwise retard the healing process. Phytogetic agents (phytochemicals from fruits and vegetables) have traditionally been used by herbalists and indigenous healers for the prevention and treatment of peptic ulcer.<sup>26</sup>

Quercetin is an important dietary flavonoid and from whole onion and apple extracts. The uptake of quercetin aglycon and quercetin 3-glucoside were recently found to accelerate cutaneous lesion healing in rats when applied topically once daily. Calvo et al (2007) showed that single oral administration of quercetin (250mg/kg/once daily) potently stimulates gastric epithelial cell proliferation that contributes to the accelerated healing of gastric ulcers. Topical application of quercetin to minor mouth ulcers produced complete healing in 35% of patients between 2 and 4 days, 90% between 4 and 7 days, and all patients treated with quercetin experienced complete ulcer healing in >7 days.<sup>27</sup>

Curcumin (diferuloyl methane), the yellow pigment in turmeric is the major antioxidant and anti-inflammatory substance in turmeric. (Thapliyal et. al, 2002). Studies showed that curcumin could down regulate the expression of interleukin (IL)-6 protein, TNF, and various other chemokines which could suppress inflammation through multiple pathways (Aggarwal et. al, 2009).<sup>28</sup>

*Ocimum Sanctum* at a dose of 100mg/kg was found to act as antiulcer agent. Antiulcer effect of *Ocimum Sanctum* may be due to its cytoprotective effect rather than anti-secretory properties. So, it possess anti-ulcerogenic property as well as ulcer healing properties and can be used against peptic ulcer.<sup>10</sup>

#### ANTIOXIDANTS IN MANAGEMENT OF PERIODONTAL DISEASES

Periodontal diseases, the most prevalent disease throughout the world<sup>29</sup>, are predominantly caused by gram-negative, anerobic bacteria present on the tooth root surfaces as a biofilm.<sup>29</sup> The periodontal complex comprises alveolar bone, periodontal ligament, root cementum, and the overlying gingival tissues. Periodontitis is regarded as "an inflammatory lesion, mediated by complex host-parasite interactions, that leads to the loss of connective tissue

attachment to root surface cementum and adjacent alveolar bone".<sup>31</sup>

Inflamed periodontal tissue produces significant amounts of pro-inflammatory cytokines, mainly IL-1, IL-6, PGE<sub>2</sub> and tumor necrosis factor alpha (TNF- $\alpha$ ), reactive oxygen species enzymes, proteins, host cells, ions, hormones, and markers of oxidative stress and antioxidant.<sup>30</sup> Reactive oxygen species (ROS) play crucial roles in normal physiological processes including response to growth factors, the immune response, and apoptotic elimination of damaged cells, but are also highly toxic and destructive when generated during the respiratory burst as it represents an important pathogenic mechanism for tissue damage and diseases associated with phagocytic infiltration.

The inflammatory and immune responses to the bacteria and also viruses that colonize the periodontal and associated tissues involve the systemic circulation and ultimately the peripheral systems of the body. This creates a complex bi-directional series of host - microbial interactions involving cellular and humoral factors and networks of cytokines, chemokines, and growth factors.<sup>30</sup> According to Haffajee, et al.,<sup>32</sup> the primary etiological agent is specific which consists predominantly gram-negative anaerobic or facultative bacteria within the subgingival biofilm, but the majority of periodontal tissue destruction is caused by an inappropriate host response to those microorganisms and their products.

Prevention of gingivitis and periodontitis is based on the control of their causal and risk factors (as defined by an attribute that is causally related to its pathogenesis). The most widely accepted risk factor is the periodontal biofilm that forms on the teeth in the absence of effective oral hygiene. Antioxidant therapy is emerging as a promising new paradigm as prophylactic and therapeutic agents. These are those agents which scavenge free radicals or ROS and prevent the damage caused by them.<sup>33</sup> Inflammatory stimulation by periodontal pathogens increases the production of crevicular fluid and induces the chemotaxis of polymorphonuclear leukocytes, which, in order to inactivate periodontal pathogens, release singlet oxygen and hypochlorous acid into the crevicular fluid.<sup>34</sup> Polyphenols have an in vitro antibacterial activity against periodontal pathogens. Catechin, an active ingredient in green tea, is known for the improvement of periodontal disease. Green tea catechin has been reported to be therapeutic for prevention of periodontal disease for its inhibitory effect on collagenase activity. Takada et al. studied the effect of locally delivered slow-release green tea catechin on black-pigmented, Gram-negative anaerobic rods (BPR), which have been associated with various forms of destructive periodontal disease. Resting bacterial cells from *P. gingivalis*, *P. intermedia*, and *P. nigrescens* were killed by green tea catechin within 120 minutes. The antibacterial effects of green tea catechin on BPR showed bactericidal action in this study.<sup>35</sup>

Vitamin C is a major constituent of collagen, which not only preserves the integrity of tissues but also supports the body's resistance to invading microbes. Vitamin C, an important aqueous antioxidant, is essential for collagen formation and healing of wounds, and is shown to improve resistance to infection. Vitamin C deficiency also makes capillaries fragile and susceptible to rupture. Bleeding and swelling of the gingiva is the chief symptom of scurvy, which is readily reversed by administration of vitamin C. Vitamin C consists

of a number of vitamers that have vitamin C activity in animals including ascorbic acid and its salts and many oxidized forms of the molecule like dehydro-ascorbic acid. Ascorbate and ascorbic acid, both are present naturally in the body when any of these is introduced into cells as the forms interconvert according to pH. In at least eight enzymatic reactions, Vitamin C is a cofactor including various collagen synthesis reactions. When these synthetic reactions become dysfunctional, they cause the most severe symptoms of scurvy. Although various infections and systemic diseases cause gingival bleeding, a vitaminosis C does not cause commonly encountered periodontal disease, but it will aggravate the already established periodontitis. So, Vitamin C should not be used for cure or prophylaxis of periodontitis in healthy well-nourished individuals.<sup>36</sup>

Maserejian et al. reported the positive effects of vitamin C rich fruits and vegetables in decreasing the risk of oral premalignant lesions. The risk of oral premalignant lesions was significantly reduced with higher consumption of fruits, particularly citrus fruits and juices.

The role of vitamin C are

1. Vitamin C increases the body's ability to fight invading bacteria and other toxins that contribute to gum disease.
2. Vitamin C is the antioxidant that protects the body from free radical damage and boosts the immune system.
3. Vitamin C helps build and repair bodily tissue and promotes wound healing.
4. The body uses vitamin C to help metabolize fats and cholesterol, absorb iron, and synthesize amino acids and collagen.

Vitamin E is an antioxidant and it prevents the activity of harmful free radicals, which oxidize and damage tissues. Vitamin E can help to control periodontal disease is through its ability to prevent inflammation.

Turmeric is considered a safe, nontoxic, and effective alternative for many conventional drugs due to its distinguished therapeutic properties and multiple effects on various systems of the body. Generally considered safe, but may cause gastric irritation, stomach upset, nausea, diarrhoea, allergic skin reaction, and antithrombosis activity interfering with blood-clot formation. Tulsi leaves dried in sun and powdered can be used for brushing teeth. It can be mixed with mustard oil to make a paste and used as toothpaste. This can be used for massaging gingival to treat various gingival and periodontal problems. This is also used to cure halitosis.<sup>10</sup>

Waghmare et al. concluded that chlorhexidine gluconate as well as turmeric mouthwash can be effectively used as an adjunct to mechanical plaque control methods in prevention of plaque and gingivitis. Turmeric mouthwash prepared by dissolving 10 mg of curcumin extract in 100 ml of distilled water and 0.005% of flavouring agent peppermint oil with pH adjusted to 4 is found to be as effective as most widely used chlorhexidine mouthwash. Though chlorhexidine gluconate has been found to be more effective when antiplaque property was considered. The effect of turmeric observed may be because of its anti-inflammatory action.<sup>37</sup> Green tea polyphenols are responsible for its antioxidant activity either directly by scavenging of reactive oxygen and nitrogen species and chelating redox-active transition of metal ions like iron and copper or indirectly by

inhibition of pro oxidant enzymes, redox sensitive transcription factors, and induction of antioxidant enzymes.<sup>38</sup> It has been acknowledged for many years that nutritional intake can impact upon the levels of inflammation seen in a number of diseases, and this is no less the case in periodontitis. Oxidative stress is a key driver of chronic inflammation and as a result has a central role in the pathogenesis of periodontitis and a wide range of chronic inflammatory diseases. Many studies has shown role of various antioxidants in controlling and alleviating periodontal diseases.

**ANTIOXIDANTS IN MANAGEMENT OF ORAL CANDIDIASIS**

Cinnamon is a powerful **antioxidant**. Studies have also shown Tea tree oil drops in warm water and allow it to gargle is good for oral candidiasis. Antioxidant properties of essential oil of *Ocimum Sanctum* (holy basil, Tulsi) and its two main components i.e. eugenol and linalool have shown promising results against *C.albicans*.<sup>39</sup>

**ANTICARIOGENIC EFFECT OF ANTIOXIDANTS**

Dental caries is a single most common biofilm dependant oral infectious disease worldwide.

Surface adsorbed GTases increase the synthesis of structurally distinct glucans, which provide enhanced s. mutans binding to apathetic surface. Thus one way to prevent dental caries is by inhibiting the growth and adherence of s. mutans to tooth surface.

Coffee extracts are extremely rich in polyphenols, which suggest that they can inhibit the tooth demineralization process. The inhibition of tooth demineralization after the biofilm formed on dental fragments was observed by Antonio et al.<sup>40</sup>

Dental caries are induced by oral microflora. Among hundreds of microorganisms in the oral cavity, only the cariogenic streptococci, especially Streptococcus mutans, play an important role in causing dental caries (Hamada and Slade, 1980). Several green tea polyphenols have preventative effects on dental caries (Sakanaka et al., 1989, 1990, 1992). Raw food, alkaline diet of fresh alkaline forming fruits, vegetables and green fruits and vegetables high in chlorophyll (spring greens, lettuce, wheat grass juice, kale, collards, etc.) in the diet as well helps in preventing risk of dental caries.

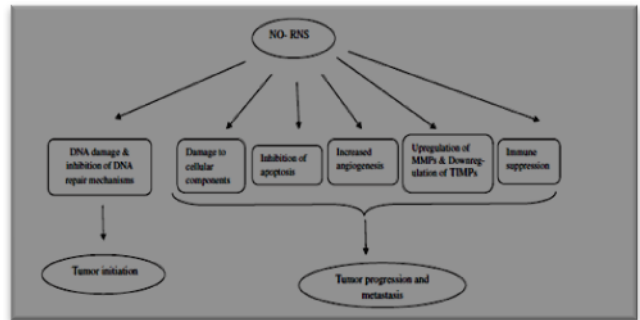
**ANTIOXIDANTS IN MANAGEMENT OF ORAL CANCER**

Tobacco (smoking and smokeless) use and excessive consumption of alcohol are amongst the major risk factors for oral cancer.<sup>41,42</sup> Tobacco consumption exposes the oral epithelium to toxic oxygen and nitrogen free radicals that can affect host antioxidant defence mechanisms. Elevated levels of ROS and Reactive Nitrogen Species (RNS) and lowered antioxidants are found in oral precancer and cancer. Development of cancer in humans is a multistep process. radicals and non-radicals are collectively known as ROS.

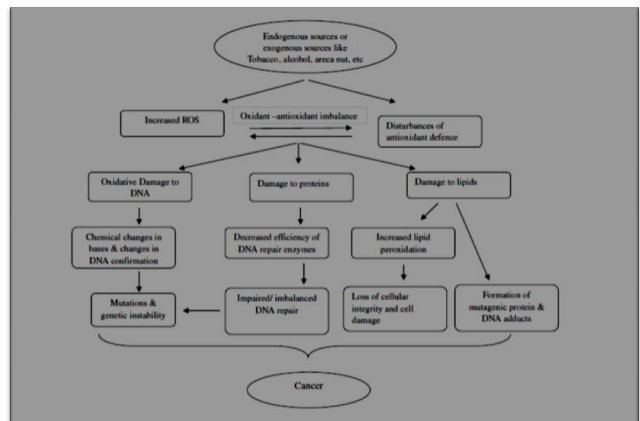
Under pathological conditions, much larger amounts of free radicals are formed than normal. To mitigate their harmful effects, antioxidant defense mechanisms act at different levels.<sup>43</sup>

Oxidative stresses induced by free radicals cause DNA damage, which, when left unrepaired, can lead to base mutation, single- and double-strand breaks, DNA cross-linking, chromosomal breakage, and rearrangement. This damage may be limited by dietary antioxidants in fruits and vegetables through modulation of detoxification enzymes, scavenging of oxidative agents, stimulation of the immune system, hormone metabolism, and regulation of gene expression in cell proliferation and apoptosis.<sup>1</sup>

**Mechanism of action of RNS in Oral Cancer<sup>43</sup>**



**Mechanism of action of ROS in Oral Cancer.<sup>43</sup>**



Strategies in biology designed to evade oxidative stress are prevention, interception, and repair of free radicals or their damage by antioxidants. Three major classes of antioxidant enzymes, superoxide dismutases, catalases and glutathione (GSH) peroxidises are important detoxifying compounds. The additive and synergistic effects of phytochemicals in fruits and vegetables are responsible for their potent antioxidant and anticancer activities.

Studies on the blood levels of micronutrients in high risk populations have found deficiencies of multiple micronutrients. The mechanism of action of these antioxidants suggests a synergistic role.<sup>47</sup>

The following conclusions assist in appreciating of the role of antioxidants in the development, treatment, and even prevention of oral cancer.<sup>45,46</sup>

- i. Oxidative DNA damage, a vital phenomenon for carcinogenesis of oral squamous cell carcinoma, occurs due to the interaction of oxidative stress and total antioxidant capacity.
- ii. Elevated oxidative stress markers correlated positively with recurrent squamous cell carcinoma of the oral cavity and a poor prognosis compared to patients staying in complete remission.

iii. The oxidized proteins and DNA found in the saliva of oral cancer patients demonstrates a direct link among salivary free radicals, antioxidants, and oral squamous cell carcinoma.

Non-enzymatic antioxidants like alpha-tocopherol is probably the most efficient compound in lipid phase. It maintains a steady state of peroxy-radical reduction in the cellular membranes. Carotenoids and oxy-carotenoids can efficiently intercept hydroxyl radical. Antioxidants show promise in cancer therapy by their palliative action, reducing painful side effects associated with treatment. Examples of dietary antioxidants are vitamins A, C and E, selenium and flavonoids such as quercetin and genistein. In several *in vitro* and animal studies the hypothesis has been tested that antioxidants benefit patients receiving chemotherapy. On the one hand, antioxidants might protect cancer cells against the oxidative damage induced by chemotherapy, which would mitigate against their use.

Antioxidants nutrients such as vitamin E, vitamin C, vitamin A, and Beta-carotene are involved in detoxification of the Reactive oxygen species (ROS). Vitamin E, A, and Beta-carotene are lipophilic antioxidants whereas vitamin C is hydrophilic antioxidant. Vitamin E function as a free radical chain breaker particularly it interferes with the propagation step of lipid peroxidation. The vitamin A and Beta-carotene have actions by quenching both singlet oxygen and other free radicals generated by photochemical reactions (Peerapatdit et al., 2006).<sup>47</sup>

Kucuk et al. (2002) conducted a clinical trial to investigate the biological and clinical effects of lycopene supplementation in patients with localized prostate cancer.

This study suggested that lycopene may have beneficial effects in prostate cancer. Epidemiological studies have provided evidence that high consumption of lycopene effectively lowers the risk of reactive oxygen species (ROS) mediated diseases such as cardiovascular diseases and cancer. In addition to its antioxidants properties, lycopene shows an array of biological effects including cardio protective, anti-inflammatory, anti-mutagenic and anti-carcinogenic activities. The cancer activities of lycopene have been demonstrated both *in vitro* and *in vivo* tumor models (Blot et al., 1993).<sup>7</sup>

#### **Mechanism of action of various antioxidants against oral cancer :**

Beta-carotene:

- i. Anti-oxidant and free radical scavenging.
- ii. Inhibition of cancer cell growth.

Vitamin C :

- i. Inhibits nitrosamine formation.
- ii. Blocks formation of mutagens.

Vitamin E :

- i. Free radical scavenging.
- ii. Inhibition of cancer cell growth/differentiation.
- iii. Inhibits mutagenicity and nitrosamine formation.
- iv. Inhibition of DNA and RNA, protein synthesis in cancer cells.

A number of animal studies have shown that curcumin is effective in inhibiting carcinogenesis in the skin, colon, stomach mammary gland and oral cavity.

**Flavonoids:** It has been stated that flavonoids, as antioxidants, can inhibit carcinogenesis..

#### **LIMITATION OF ANTIOXIDANT**

**Polyphenols :** Among their many biological activities, the predominant polyphenols in green tea EGCG, EGC, ECG, and EC and the theaflavins and thearubigins in black teas have antioxidant activity. These chemicals, especially EGCG and ECG, have substantial free radical scavenging activity and may protect cells from DNA damage caused by reactive oxygen species. Tea polyphenols have also been shown to inhibit tumor cell proliferation and induce apoptosis in laboratory and animal studies. In other laboratory and animal studies, tea catechins have been shown to inhibit angiogenesis and tumor cell invasiveness. Although many of the potential beneficial effects of tea have been attributed to the strong antioxidant activity of tea polyphenols, the precise mechanism by which tea might help prevent cancer has not been established.<sup>48,49</sup>

Prevention is a more effective strategy than treatment.

It has been seen that association of antioxidant vitamins for the treatment of cancer is still a controversial issue. Numerous lines of evidence suggest a potential role for antioxidants in preventing oral cavity malignancy.

#### **TOXICITY OF ANTIOXIDANTS AND THEIR METABOLITES**

Many antioxidants are considered to be free of side effects at commonly used dosages.

##### **Adverse effects of Vitamin C :**

Toxicity associated with high doses of water-soluble antioxidants such as ascorbic acid are less of a concern, as these compounds can be excreted rapidly in urine. Large doses of vitamin C (ascorbic acid) may be associated with the inhibition of ovarian steroidogenesis and increased probability of abortion. Large doses of vitamin C may cause diarrhea, nausea, and stomach cramps.

##### **Adverse effects of Lycopene :**

High intakes of lycopene rich foods or supplements may result in a deep orange discoloration of the skin known as lycopenodermia.

##### **Adverse effects of Zinc :**

Zinc toxicity can occur in both acute and chronic forms. Acute adverse effects of high zinc intake include nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, and headaches. Intakes of 150–450 mg of zinc per day have been associated with such chronic effects as low copper status, altered iron function, reduced immune function, and reduced levels of high-density lipoproteins.

##### **Adverse effects of Copper :**

Water containing copper concentrations greater than 6 mg/L is associated with gastrointestinal symptoms (nausea and vomiting).<sup>50</sup> Children and individuals with Wilson's disease, a hereditary syndrome that results in an accumulation of copper in the brain, liver, kidneys, and eyes, should not take copper supplements. Because high intakes of zinc and iron can impair absorption of copper, zinc has been used to decrease copper in people suffering from of Wilson's disease.

#### **Conclusion**

Low level of antioxidant cause oxidative stress and may damages cells. As oxidative stress play major role in pathogenesis of many diseases of oral cavity including oral cancer and oral lichen planus<sup>43,51</sup> Antioxidants can protect against the damage induced by free radicals acting at various



levels. The focus should not be on treating various diseases with antioxidants, but on the intake of a balanced diet with emphasis on antioxidant-rich fruits, vegetables, nuts, whole grains as has been recommended for the general population. Therefore, further studies should be conducted to know the beneficial role of antioxidant in the oral cavity, as we know it change the scenario the treatment related to non cure diseases i.e oral cancer and periodontium. New antioxidant products are emerging onto the marketplace almost daily. Novel therapies exist to increase antioxidant absorption directly into the oral tissue and improve clinical outcomes, and adjunctive dietary supplements have the potential to improve body's immune system. Supplements are available that will activate the body's antioxidant production within the cells, and turn down the pro-inflammatory genes. Hence, the judicious use of antioxidants may be useful to prevent free radical-related disorders. However, the repair of existing critical structural damage may be beyond the possibilities of antioxidants, but the beneficial effects of antioxidants cannot be underestimated.

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