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Antioxidants in Oral Mucosal Diseases: A Scoping Remedy

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ABSTRACT

The oral cavity is harboured by many microorganisms which is in contact with various external substances like food, drinks, medications, alcohol, nicotine substances. Since the oral cavity is delicate, it has a tendency to get alter morphologically and biologically by these substances. The process of alteration is initiated by the events of metabolic activities followed by free radical oxidants formation. It is necessary to focus on the maintenance of oxidants and antioxidants balance since disruption of balance may lead to disease progression. Oral potentially malignant disorders and ulcerative lesions burdens the patients with severe symptoms and fear of malignant potential. In the dental field, the use of antioxidants becoming more frequent in these conditions. The properties of antioxidants have been studied based on mechanism, control of disease progression, and protection of oral mucosa. This article focuses on the relation between free radical formation and oral disease progression, the role of antioxidants for the disease management specifically.

Keywords:
Antioxidants, oxidative stress, disease progression, Potentially malignant disorders (PMD), Oral cancer

Introduction

In general, the human system generates free radicals as metabolic by-products and are actively eliminated. Free radicals are atoms or molecules containing one or more unpaired electrons [(1)]. These are highly reactive and can function as oxidizing or reducing agents by removing or donating electrons from other molecules. The optimum balance between production and elimination of these reactive free radicals is well maintained by antioxidant defence system. The remarkable fact is that the normal human metabolic activity is altered by certain lifestyle changes like poor dietary practices, lack of optimal diet, lack of proper sleep and exercise, habit of smoking and alcohol. This may lead to a high degree of changes in metabolism and excess free radical formation. These excess free radicals can cause harmful chain reactions corresponding to cell damage or cell death and even carcinogenesis. To counteract the effects of free radicals, the human body is endowed with adequate inbuilt antioxidant mechanisms in each cell. Antioxidants are also made available for therapeutic use

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in the form of vitamin supplements, topical gels, dried, fresh and herbal paste.

Free radicals in biologic system

Free radicals are produced in the body during several biological processes like oxidative metabolic transformation, mitochondrial respiratory chain, oxygen burst (respiratory burst) duringphagocytosis, eicosanoid synthesis, enzymatic reactions (oxygenase's, oxidases), and xenobiotic metabolism (redox-cycling). The external sources capable of producing free radicals are radiation (ionizing, ultraviolet, and electromagnetic), tobacco, alcohol, Endocrine disturbances, Infections, inflammations, photo-oxidation, and chemicals (pesticides, and insecticides)(1).
Based on the chemical structure the free radicals are classified as reactive oxygen species (ROS) and reactive nitrogen species (RNS). The majority of free radicals are reactive oxygen species and known to be superoxide, hydroxyl radical, peroxyl radical, singlet oxygen, and hydrogen peroxide. The RNS are nitric oxide, peroxynitrite, nitrogen dioxide, and peroxynitrous(1). Free radical toxicity leads to various molecular damage including oxidative DNA damage, lipid peroxidation, protein damage including gingival hyaluronic acid and proteoglycans.

Oxidative Stress and Disease Progression

The imbalance between the free radicals and antioxidants produced within the body is referred to as oxidative stress. The impact of this imbalance in general health accelerates aging process and leads to the development of degenerative changes.Since mouth is the mirror of general health, the oral health can also be affected by oxidative stress. The presence of autoimmunity or chronic inflammation also has a vulnerable effect of inducing oxidative stress. Micronutrients are known to be essential in cell growth and development. The deficiency states of certain micronutrients have strong potential in triggering oxidative stress. The long term oxidative stress cause disease progression in any part of the body. The association between factors inducing the oxidative stress, the type of free radical generated and oral disease progression are crucial to understand. These helps in selecting appropriate antioxidant for the treatment of potentially malignant disorders, oral mucosal lesions and oral cancer.

Antioxidants

According to WHO a biologic antioxidant is defined as *"A substance present in low concentrations compared to an oxidizable substrate (Ex: Proteins, lipids, carbohydrates, and nucleic acids) that significantly delays or inhibits oxidation of a substrate. Antioxidants may be considered as the scavengers of free radicals"*(2).

Classification of antioxidants

A well-balanced diet and proper immune system are essential in maintaining the antioxidant status of the body. The antioxidants are classified based on the source of availability to the body. Molecules known to be the metabolic by-products and have the potential in scavenging free radicals are called as endogenous antioxidants. The exogenous antioxidants are the class of antioxidants which are not found in the body naturally but are required to be supplemented

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for the proper metabolism and to protect against oxidants.

The classification of antioxidants based on the availability to the body is illustrated in Table no.1&2(3).

Table 1.Exogenous Antioxidants

Exogenous antioxidants	Subclass
Carotenoids	Beta-carotene , lycopene, leutin, zeaxanthin
Flavonoids	Quercetin,chrysin, catechin, cyanidin,genistein
Phenolic acids	Garlic acid, ellagic acid, ferulic acid, p-coumaric acid
Vitamins	Vitamins A,B, C,E,K
Minerals	Selenium, iron, magnesium, copper, zinc

Table 2.Endogenous Antioxidants

Endogenous antioxidants	Subclass
Thiols	Uric acid NADPH&NADH Bilurubin
Metal binding proteins	Albumin,Ceruloplasmin ,Transferrin, Ferritin ,Myoglobin
Hormones	Melatonin
Others	Glutathione, N-acetyl cysteine, Alpha lipoic acid

Mechanism of action of antioxidants

Antioxidants provides a sophisticated free radical scavenger environment to the body. To protect the cells, from free radicals the antioxidants acts by the following highly potential mechanisms(3).

1. **Chain breaking mechanism**
   - Inhibition of oxidation processes by scavenging free radicals. Ex: Vitamins A, C, E, albumin, bilirubin, ubiquinol and flavonoids
2. **Preventive mechanism**
   - Antioxidant chelates the transititon metal or scavenges the free radical and decomposes it- Ex:Cerruloplasmin, lactoferrin, hepatoglobin, transferrin, lactoferrin, citric acid
   - Quenching of reactive oxygen species – Ex: Carotenoids
   - Decomposition into nonradical product - Ex: Glutathione peroxidase
3. **Synergistic mechanism**
   - Two antioxidants are combined for enhanced action. Ex: combining the tocopherol with chain breaking ability and citric acid which has the metal chelating activity,

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increases the efficacy.

Antioxidants in oral mucosal lesions

Many studies like laboratory, animal model systems, epidemiologic surveys, and clinical intervention trials are performed to evaluate the significance of antioxidants in the treatment of oral diseases. These studies interpret and expands the evidences in the therapeutic value of antioxidants for certain oral diseases like oral potentially malignant disorders (PMD), recurrent aphthous stomatitis, candidiasis, and oral cancer. The possible therapeutic uses of antioxidants for oral mucosal lesions include the following (4):

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

Oral lichen planus (OLP) and lichenoid reactions represent T cell-mediated altered keratinocyte antigen expression with the release of various cytokines. This inflammatory process triggers the production of ROS & RNS and resulting in cellular apoptosis in the basal epithelium(5). As evidence of oxidative stress, patients with OLP have high levels of lipid peroxidation products such as Malondialdehyde (MDA) and 4-hydroxy-2-nonenal (5). The management of OLP patients with antioxidants is considered to reduce the transformation rate of the condition and burning sensation. Lycopene, a prominent carotenoid, has the unique feature of getting bound to chemical species that react to oxygen, thus being the most efficient biological antioxidizing agent. Supplementing with 8 mg/day of lycopene for 8 weeks showed favourable results in OLP patients and burning sensation was reduced by 84% and lowered oxidative stress than in the placebo group 67% in a placebo-controlled trial(6). Curcuminoids are components of *Curcuma longa* (turmeric) known to have anti-inflammatory and antioxidant 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(7).

Oral Leukoplakia (OL), is the most common potentially malignant disorder with multifactorial etiology. Lycopene is beneficial in treating leukoplakia. Lycopene increases the expression of the gene encoding connexion-43, a gap junction protein, effect being independent of provitamin- A or antioxidant properties (8). Retinoids have a potent therapeutic activity for leukoplakia. Kaugars et al. implemented retinoic supplementation in various dosages for OL treatment. Topical use of 13-Retinoic acid (0.1% isotretinoin gel) is found to have a complete clinical response to treatment and none of the patients reported adverse effects.3-9 lakhs IU of Vitamin A per day resulted in partial or complete resolution of leukoplakia (9).

Oral submucous fibrosis

Areca nut is one of the most addictive substance in the world and contains alkaloid arecoline, polyphenols and trace elements like copper. Moreover, in the presence of slaked lime Ca (OH) 2 enhances the alkaline environment in the oral cavity, favoring ROS generation. These increases the collagen production, decreases collagen degradation, and abnormal cross

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linking of the collagen by copper dependent enzyme lysyl oxidase. It was first demonstrated by Nair *et al*., that aqueous extracts of areca nut were capable of generating superoxide anion and hydrogen peroxide at pH > 9.5 (10). This causes oxidative damage to the DNA of buccal mucosa cells of betel quid chewers. Lycopene in the dosage of 16mg per day along with other treatment regimens like intralesional injection has been found to be significantly reducing the clinical signs and symptoms (11). Other synthetic antioxidants like curcuminoids has been found to have effective antioxidant, DNA-protectant, and antimutagen action (12).

Oral cancer

The most potent etiology of oral cancer is tobacco use. Chronic exposure to tobacco leads to oxidative stress. Free radicals are also produced in excessive amounts in alcoholics. Chronic ethanol ingestion can induce single nucleotide polymorphism of CYP2E1 leading to increased generation of ROS (13). The initiation and progression from dysplasia to neoplasia in a single cell occurs through multiple events through three stages initiation, promotion, and progression. The generation of ROS is involved in all three above mentioned stages (13). The synergistic activity of tobacco and alcohol increases the risk and transforms the dysplastic states to oral cancer (14). Antioxidants have the potential to prevent, inhibit, and reverse the multiple steps involved in oral carcinogenesis. Antioxidant micronutrients inhibit angiogenesis in tumours by inhibiting transforming growth factor (TGF)-alpha (15). Antioxidants are regarded as one of the chemo preventive agents and used in the management of oral cancer. Retinoid, beta-carotene, curcumin, lycopene, zinc, selenium, vitamin E (tocopherol), vitamin C (ascorbic acid), vitamin A (carotene), and spirulina are believed to have a preventive role against oral cancer. Retinoid and curcumin have found to possess anti-proliferative & anti-mutagenic activity respectively(15).

Recurrent aphthous stomatitis (RAS) is an ulcerative disorder of the oral mucosa, characterized by painful single or multiple round shallow ulcers with well-demarcated erythematous margin and yellowish-greyish pseudomembranous central area**.** In RAS the inflammatory and immune response triggers the production of free radicals. 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(16). Other herbal topical applications like curcumin and ocmium sanctum are found to be effective against RAS since they possess anti-ulcerogenic properties(17).

Oral candidiasis

Antioxidant properties of the 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*(18). Recent studies have demonstrated that antioxidants like propolis, Pelargonium graveolens (olive oil), Equisetum giganteum (horsetail plant extract), Punicagranatum (pomegranate), and Melaleuca alternifolia (tea tree oil) are ideal for the treatment of denture stomatitis due to their *in vitro* inhibitory actions on the colonization and development of *Candida* biofilm. Reduction in fungal load and improvement in clinical signs were also proved(19).

The summary of list of antioxidants found to be effective against oral mucosal diseases are enumerated in Table No.3 (20),(21),(22),(23).

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Table 3. ANTIOXIDANTS FOR ORAL MUCOSAL DISEASES

Oral disease	Antioxidant	Dosage
Oral lichen planus& lichenoid reaction	Lycopene	6–60 mg/day
	Curcumin	6000mg/day
	Raspberry leaf extract Epigallocatechin gallate- green tea Glycyrrhizaglabra- Licorice	Under clinical trials
	Selenium	40–80 µg/day
	Multivitamins vitamins A, C, E and B complex	As recommended by RDA (recommended dietary allowances)
Oral leukoplakia	Beta-carotene	20 to 90mg/day systemic dose – 300,000 IU
	Retinoids (Vitamin A/ Retinol)	0.5 to 1 mg/Kg/day
	Tretinoin or isotretinoin	0.05%- 0.1% gel – topical
	Lycopene	8 mg/day
	Vitamin-E	8-10mg/day
	Curcumin	4000-8000 mg/day
Oral submucous fibrosis	Lycopene	16mg/day
	Curcumin	500-800mg/day
	Multivitamins vitamins A, C, E and B complex	As recommended by RDA
	Minerals Zinc Copper Selenium	In combination with vitamins 25-30mg/ day 1 mg/day 40–75 µg/day
	Alpha lipoic acid Alpha tocopheryl acetate	50 mg 10 IU
Oral cancer	Vitamin- A Retinoids	1 mg/Kg/day
	Beta carotene	25,000 to 100,000 IU/day
	selenium	40–75 µg/day
	Vitamin E	400-800 IU /day
	Vitamin-C	140-500 mg/day
	Curcumin	300 mg /day
	Lycopene	12 mg/day
	Gingerol Epigallocatechingallate (EGCG) Spirulina fusiformis	Under clinical trials
Recurrent aphthous stomatitis	Quercetin	500-1000mg/day
	Curcumin	150 mg /day
	ocmium sanctum (tulsi)	Gel (Under clinical trials)

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Oral candidiasis	Propolis Pelargonium graveolens (olive oil) Equisetum giganteum (horsetail plant extract) Punicagranatum (pomegranate) Melaleuca alternifolia	Under clinical trials

Conclusion

The antioxidant system and oxidative stress balance in humans depend upon numerous factors like diet, immune function, altered inflammatory response, obesity, smoking, alcohol, chemicals, and radiation. These factors also govern the pathophysiologic role in oral diseases. Hence understanding the basic concepts of free radical formation and its role in oral disease progression is necessary. For the past several years, antioxidants are widely used in the treatment of oral mucosal diseases. The antioxidants can prevent, protect, and repair the damage produced by the free radicals in the oral cavity. The knowledge of these therapeutic agents as the systemic and topical treatment in oral diseases is very useful. So far many studies have done to identify the anti-inflammatory, anti-ulcerogenic, anti-tumurogenic, immunomodulatory, antimicrobial activities in various naturally-derived antioxidants and their potentiality in treating oral diseases. Since there are some debates on dose factors, biocompatibility, drug interactions and combination therapy, it is necessary to increase the evidences through more clinical trials and research.

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