Practice Paper

Antioxidants in Oral Mucosal Lesions

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ABSTRACT

Recent trends in the field of medicine aims at halting the diseases at their very onset and preventing its progression to morbid state. This leads to the identification of the important role of the free radicals in the development of the disease. At the same time the utility of antioxidants in curbing the actions of free radicals. This article aims at reviewing the commonly used antioxidants, their sources and their mechanism of action that are of importance in the management of the premalignant lesions and conditions.

Keywords: Antioxidants, Free Radicals, Premalignant lesions and conditions, Oral cancer

INTRODUCTION

Antioxidants are agents that block the process of oxidation by neutralization of free radicals. Free radicals are known to play a crucial role in human diseases like diabetes mellitus, immune dysfunction, rheumatoid arthritis, atherosclerosis as well as various oral diseases like leukoplakia, oral submucous fibrosis and oral cancer.[1]

Several biological processes lead to the production of endogenous free radicals. They are highly unstable and react with biological molecules that tends to irreversible alter the chemical structure of the cellular components. Most commonly affected are the lipid structures, low-density lipoproteins, proteins and nucleic acids. Free radicals are thus responsible for the oxidative damage to the body, favoring mutagenesis and carcinogenesis. The human body counteracts oxidative stress by activating antioxidant defense systems.[1,2] Normally there is equilibrium between free radicals and antioxidant defense capacity. Any imbalance in this equilibrium due to either by reduction in antioxidants or an increase in free radicals production can result in oxidative stress.[1] Oxidative stress play major role in pathogenesis of many diseases of oral cavity. Antioxidants can be natural or synthetic, water or lipid soluble, exogenous or endogenous in nature. Primary or natural antioxidants are the chain breaking antioxidants which react with lipid radicals and convert them into more stable products. Secondary or synthetic antioxidants are phenolic compounds that perform the function of capturing free radicals and stop chain reactions. Antioxidants are thus critical for homeostasis.[1,3,4]

Antioxidants play a pivotal role in the management of potentially malignant disorder. Antioxidants like Beta carotene, Lycopene, Ascorbic acid, vitamin E, Curcumin, Retinoids play an important role in the pharmacological management of common oral mucosal lesions like Leukoplakia, Oral Submucous Fibrosis, Lichen Planus. Antioxidants thus are considered as essential components of balanced diet as they contribute to the prevention and reduction of risk factors and management for several diseases.[1-3]

CLASSIFICATION

Antioxidants can be categorized by their origin in to:

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- Exogenous Antioxidants: Carotenoids (β-Carotene, lycopene), Vitamin C, Vitamin E, Vitamin A, polyphenols (flavonoids, Curcumin), minerals (selenium, zinc).
- Endogenous antioxidants: Catalase, superoxide dismutase, glutathione peroxidase, glutathione transferase, ceruloplasmin, transferrin.

VARIOUS ANTIOXIDENTS

Lycopene: Lycopene is a bright red phytochemical that is found in tomatoes and other red fruits and vegetables like red carrots, red bell peppers, watermelons, and papaya. Lycopene has been hypothesized to prevent carcinogenesis and atherogenesis by protecting critical cellular biomolecules, including lipids, lipoproteins, proteins, and DNA.[2]

In leukoplakia it has shown to protect cells against damage and progression of dysplasia by inhibiting tumor cell proliferation.[5] In a study performed on patients with oral leukoplakia a supplement of Lycopene in the dosage of 8 mg and 4 mg was given. The patients who were given supplementation showed significant difference in the response as compared to the placebo group. [6]

Studies have shown that Lycopene inhibits hepatic fibrogenesis in liver endothelial cell of rats, and it may also exert a similar inhibition on the abnormal fibroblasts in OSMF. It up-regulates the lymphocyte's resistance to stress and suppresses the inflammatory response.[1]

Beta-Carotene: It is a precursor of Vitamin A with free radical scavenging activity. Beta-carotene is a carotenoid commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato, mango, papaya, and orange. It plays a role in immunomodulation, increase in the numbers of T-helper and NK cells as well as cells with IL-2 receptors.

Sankaranarayanan *et al*.[7] in their study on 46 patients demonstrated that one third of patients that used 360 mg beta-carotene per week during 12 months presented a complete resolution of Leukoplakia.

Curcumin: Curcumin is the principal curcuminoid of the popular Indian spice, turmeric, which is a member of the ginger family (Zingiberaceae). Turmeric's other two curcuminoids are desmethoxycurcumin and bis-desmethoxycurcumin. The curcuminoids are natural phenols that are responsible for the yellow color of turmeric. It suppresses cyclooxygenase, lipooxygenase and other inflammatory mediators and destroys free radicals.[8]

In a study conducted on 27 patients suffering from oral lichen planus were treated with topical curcumin ointment which was applied thrice daily for 2 weeks. Significant improvement in erythema, pain and ulceration was noted.[8] Effect of topical application of turmeric and tulsi in treatment of 41 patients of oral submucous fibrosis was noted in a study. Significant improvement in burning sensation and mouth opening was seen after monthly visits for 3 months.[9]

Vitamin C: Vitamin C also known as L-ascorbic acid (L-AA) is a water-soluble vitamin. Sources of vitamin C are Citrus fruits such as kiwi, strawberries, papaya, mango, amla and tomatoes. Vitamin C has antioxidizing properties and reacts with superoxide produced as a result of the cells normal metabolic processes; this inactivation of superoxide inhibits the formation of nitrosamines during protein digestion and helps avoid damage to DNA and cellular proteins. It also blocks formation of mutagens. It has the ability to regenerate alpha tocopherol from the tocopherol radical that forms at membrane surfaces thereby reduces the vitamin E degradation.[6] It can be used in the treatment of oral mucosal lesions in dose of 1000 mg/d.[10]

Studies have shown approximately 50% lower oral premalignant lesions risk with high dietary vitamin C.[11]

Vitamin E: Vitamin E also known as α-Tocopherol is a fat-soluble vitamin with high antioxidant potency. It is fat-soluble so it protects cell membranes against damage by free radicals. Its antioxidant function mainly is to protect membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation.[12] The dietary sources of vitamin E are vegetable oils, wheat germ oil, whole grains, nuts, cereals, fruits and eggs. The therapeutic use of vitamin E for oral lesions are due to the actions which includes free radical scavenging, maintenance of

membrane integrity and immune function, inhibition of cancer cell growth/differentiation, cytotoxicity and inhibition of mutagenicity and nitrosamine formation in cells.[13,14] The recommended daily limit are 10 mg/day for adult men and 8 mg/day for adult women.[10]

In a study the toxicity and efficacy of α-Tocopherol was evaluated in 43 patients with leukoplakia and observed 90% clinical improvement in those patients who had reduced risk factors.[15]

Studies have shown that antioxidants such as Vitamin E can be utilized in oral Lichen planus patients to counteract free radical mediated cell disturbances.[16]

Retinoids: These include all the natural and synthetic compounds with an activity similar to that of Vitamin A. This can be obtained from carotene and animal products such as meat, milk, and eggs.[17] Vitamin A is required in the normal pathway of epithelial cell differentiation. Retinoids modulate growth and differentiation of normal and malignant cells by their effects on gene expression. The retinoids induce apoptosis and suppression of carcinogenesis.

In a study, 85% Clinical remission was found in oral leukoplakia patients when isotretinoin was administered topically at 0.05% and 0.18% of concentrations for 3 consecutive months.[18,19]

Selenium: Selenium is a trace element. It forms the active site of several antioxidant enzymes including glutathione peroxidase. It is a trace mineral found in water, vegetables such as garlic, onion, grains, nuts, soybean, sea food and yeast. At low dose, selenium acts as an antioxidant, anti-carcinogenic and immunomodulators. The recommended daily limit is 55 mcg/day.[20]

A study performed to evaluate the impact of selenium as intervention agent in 150 subjects with precancerous lesions has shown regression of lesions present on the palate.[21]

Flavonoids: These are polyphenolic compounds which are present in most plants. The main natural sources of flavonoids include green tea, grapes, apple, soybean, berries and broccoli. Green tea is a rich source of flavonoids, especially flavonols (catechins).

Green tea contains four major polyphenols, these are Epicatechin (EC), Epigallocatechin (EGC), Epicatechin-3-gallate (ECG) and Epigallocatechin-3-gallate (EGCG). Green tea is known to have anti-inflammatory and chemo preventive properties.[22] It is known to reduce the incidence of oral lichen planus by regulating the factors which are involved in the etiopathogenesis of the disease by inhibiting T-cell activation, migration, proliferation, antigen presentation and control other inflammatory mediators.[23]

Studies have shown promising results in patients with high risk oral premalignant lesions who randomly received green tea extract thrice a day for a duration of 12 weeks.[24]

Ocimum Sanctum: It is one of the holiest and sacred herbs grown widely in India and is known to have anti-fungal, anti-microbial and anti-inflammatory actions. It also acts as a cytotoxic agent against oral cancer cells. This cytotoxic effect is mainly because of the apoptosis caused by phytochemical compounds.

Shivpuje *et al*.[25] in their study found that aqueous extract of Ocimum sanctum exhibited significant cytotoxic effect against oral cancer cell line.

CONCLUSION

In the last decade, preventive medicine has undergone a great advance. Research has demonstrated that nutrition plays a crucial role in the prevention of chronic diseases, as most of them can be related to diet. Antioxidants can protect against the damages induced by free radicals acting at various levels. Substantial evidences from various studies indicate that the antioxidant nutrients may be of major importance in disease prevention. Thus antioxidants have been widely used as dietary supplements and can be a valuable adjunct in management of potentially malignant oral mucosal lesions and conditions and efforts should be made to ensure an optimum intake of foods containing these important molecules.

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