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Antioxidants and Oral Cancer: A Review

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Abstract

Oral cavity cancer is sixth most frequent cancers in the world. The oral cavity is constantly under the influence of external food and drinks, as well as substances such as alcohol, tobacco products, nicotine, and dental materials. Antioxidants terminate the chain reaction caused by free radicals of oxidation reaction, preventing cell damage or death of the cells. Antioxidants such as α and β carotene, pro-vitamin A, vitamin C, vitamin E, zinc, selenium and spirulina are believed to have a preventive role against oral cancer. Maintaining a good balance of oxidants and antioxidants is very essential for maintaining oral health.

Keywords: Antioxidants, cancer, free radical, tobacco.

1. Introduction

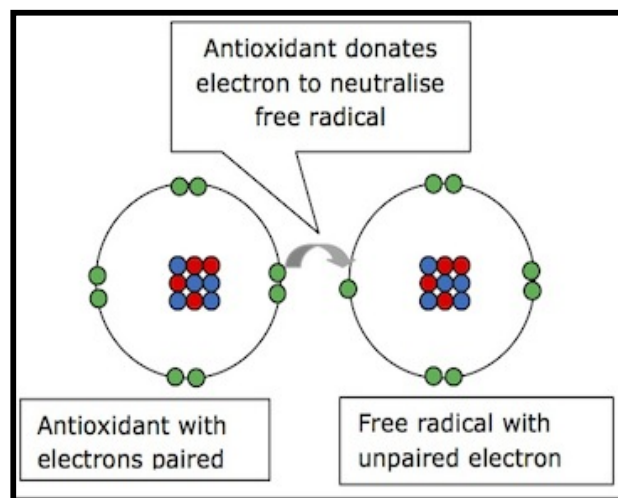
The oral cavity is constantly under the influence of external food and drinks, as well as substances such as alcohol, tobacco products, nicotine, dental materials and much more. Microbial agents and other disease-causing factors, along with systemic conditions make further insult. As oral tissues are delicate, they are especially vulnerable to cell damage caused by free radicals and oxidative stress. Maintaining a good balance of oxidants and antioxidants is very essential for maintaining oral health.

An antioxidant is a molecule which inhibits the oxidation reaction. Antioxidants terminate the chain reaction caused by free radicals of oxidation reaction, preventing cell damage or death of the cells. Antioxidants are sumptuously present in different sources, including vitamins, minerals, enzymes and hormones, as well as food and herbal supplements. These supplements may be in the form of gel, capsule, drops and tablets. Nowadays, dental manufacturers have incorporated 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^[1]Recent studies also suggest that, topical use of antioxidants in the skin is very much effective so it does efficiently in oral cavity too^[2]. This review will give an update on various antioxidants, their role in the regression in leukoplakia and oral cancer.

1.1. Reactive Oxygen Species

Reactive oxygen species like malondialdehyde (MDA), nitroxide (NO), lipid peroxidation, and decreased activities of antioxidants, including glutathione (GSH), ascorbic acid (AA), glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD), and catalase associated with tobacco users and potentially malignant disorders, produce both phenotypic and genotypic alterations which may progress to cancer. For prevention of malignant transformation, the use of antioxidants at early stages becomes mandatory^[3].

Antioxidants neutralize free radicals by donating one of their electrons in the outer shell, ending the electron stealing reaction. The antioxidant nutrient, however, does not become a free radical by donating electrons because they are stable in both the forms. There are few important sources of free radical formation. Normal cellular metabolisms like mitochondrial electron transport chain, endoplasmic reticulum oxidation and many enzymatic activities. Some external factors like radiation, oxidation of engine exhaust, carbon tetrachloride, cigarette smoke and oxygen itself^[4].



Antioxidants and their mechanism of action

Reactive oxygen species can cause tissue damage by a variety of different mechanism which include^[4, 5]:

- DNA damage
- Lipid peroxidation (through activation of cyclogenase and lipo oxygenase 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.

1.2. Free radicals and diseases

Free radicals have been implicated in the causation and progression of several diseases such as

- Cardiovascular disease
- Cancer
- Inflammatory diseases
- Respiratory diseases
- Diabetes
- Cataract formation
- Male infertility
- Aging process
- Other diseases: Parkinson's disease, Alzheimer's disease, multiple sclerosis, liver cirrhosis, muscular dystrophy, toxemia of pregnancy, etc^[6].

2. Naturally Occurring Antioxidants

2.1. Vitamin C

Vitamin C is biochemically known as 'ascorbic acid' which is a water-soluble vitamin. It is essential for collagen, elastic fibers and neurotransmitters synthesis. Health benefits of vitamin C are antioxidant, anti-atherogenic, anti-carcinogenic, immune-modulator. Vitamin C works synergistically with vitamin E to quench free radicals and also regenerates the reduced form of vitamin E. Natural sources of vitamin C are acid fruits, green vegetables & tomatoes. Vitamin C has antioxidant 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 to avoid damage to DNA and cellular proteins^[7].

2.2. Vitamin E

The most biologically active form of vitamin E is α -tocopherol. It is a fat-soluble vitamin & major lipid-soluble antioxidant of the cell membrane. It is a free radical scavenging antioxidant, maintains membrane integrity, immune function and reduces tumor cell growth/differentiation, cell cytotoxicity, inhibits mutagenicity and nitrosamine formation, preservation of DNA and RNA including protein synthesis in cancer cells.

2.3. Flavonoids

These are phenolic compounds with anticarcinogenic properties. Flavonoids are abundantly available in fruits, vegetables and tea leaves. A number of animal studies have confirmed that catechins, the main flavonoids found in tea leaves, prevent induction of cancers of the lungs, colon, esophagus, pancreas, and liver^[8].

2.4. Beta-carotene

A precursor of vitamin A has antioxidant and free radical scavenging property. It also helps in immune-modulation, promotes & increases the number of T-helper cells.

2.5. Retinoids

The best known retinoid is vitamin A or retinol, found in foods of animal origin, such as liver, milk and dairy products, egg yolk and fish liver oils, they are required for the maintenance of normal cell growth and differentiation^[9].

2.6. Curcumin

This is a plant phenol widely used as a spice (curry) and food-coloring agent. A number of animal studies have shown that curcumin is effective in inhibiting carcinogenesis in the skin, colon, stomach mammary gland and oral cavity^[9].

2.7. Folic acid

It is majorly found in fresh fruits and vegetables. Together with vitamin B12, methionine and choline, it is involved in methyl group metabolism. Together with vitamin B12, methionine and choline, it is involved in methyl group metabolism. Now a day, Much of the basic research in cancer has focused on DNA methylation.

2.8. Selenium

This is a trace element and a critical cofactor for the major antioxidant enzyme glutathione peroxidase, which catalyses the oxidation of hydroperoxide. Selenium is also implicated in cell signaling and immune reactions, which may furnish to its cancer chemopreventive potential^[10].

2.9. Salivary Antioxidants

Saliva is rich in antioxidant compounds. The primary antioxidants include uric acid, albumin, ascorbic acid, glutathione and antioxidant enzymes. Antioxidants are critical to the body's defense system because of their ability to neutralize free radicals-reactive oxygen species and reactive nitrogen species-and counteract oxidative stress^[11].

3. Oral Premalignant Lesions and Conditions

Various oral premalignant lesions such as leukoplakia, erythroplakia and stomatitis are associated with reverse smoking are common in Indian subcontinent. These lesions are potentially malignant i.e they have potential to transform into frank malignancy^[12].

The regression of premalignant lesions such as leukoplakia is

an important strategy for cancer prevention. Any agent chosen for treating oral premalignancy has an ultimate goal of prevention of cancer. Our main objective is to develop agents for use by the general population to reduce the incidence of oral cancer, then preferred antioxidants are α -carotene, vitamin E, vitamin A, selenium, folic acid, curcumin. Intervention trials on betel, quid-tobacco chewers show that administration of Vitamin A cause complete remission of leukoplakia. The most commonly used synthetic retinol, 13 cis- retinoic acid, is toxic even when given at very low dose. There is an increasing emphasis on the use of relatively non-toxic antioxidants such as beta-carotene and Vit.E [13]

4. Antioxidants and Oral Cancer

Oral cavity cancer is sixth most frequent cancers in the world as to 25% of all malignancies are found in the oral cavity. Tobacco is the predominant cause of this cancer. About 48.2% of cancers in men and 20.5% in women are related to tobacco, a major proportion of which is in the oral cavity, pharynx, larynx, oesophagus (74.7%), while lung cancers account only for 15%.

The role of antioxidants in cancer chemoprevention is by inhibiting oral carcinogenesis by reversal of premalignant lesions like oral leukoplakia. Oxidative damage is recognized as playing a major role in the pathogenesis of cancer. This could arise from incorrect nutritional habits and lifestyle practices. This process can cause DNA damage, which is a one of the basic mechanism in cancer induction. Sufficient antioxidative status is crucial in free radical defence. The important dietary micronutrients that are antioxidant in action include vitamin A, β carotene, lycopene, Vitamin C, vitamin E (alpha- tocopherol), Zinc and selenium^[9]. In oral squamous cell carcinoma, a recent study has suggested that the antioxidant nutrients act to inhibit the development of cancer cells and destroy them through apoptosis (programmed cell death), by their stimulation of cytotoxic cytokines, by their action on gene expression, by preventing the development of tumor's necessary blood supply or by cellular differentiation^[9].

5. Controversial areas in antioxidants therapy

Current literature reports that the lack of predictability of antioxidant therapy and it has not been validated by the scientific method. Widespread use of antioxidants has failed to conquer the pandemic of cancer, diabetes, and cardiovascular disease or to stop or reverse the aging process. Antioxidant therapy in human reproductive medicine is controversial. High doses of Vitamin A may have toxic and teratogenic effects. Large doses of ascorbic acid may be associated with the inhibition of ovarian steroidogenesis and increased probability of abortion^[14].

6. Conclusion

The knowledge of antioxidants is useful in reducing the incidence of oral cancers at initial stages. Recent clinical studies have shown that the beneficial effects of these antioxidants in oral leukoplakia and oral cancer. Future researches should continue with the aim of investigating the antioxidants biocompatibility, pharmacokinetics, pharmacodynamics and understanding their pathways on human health.

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