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Role of anti-oxidants in oral diseases

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Abstract

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.

Antioxidants are compounds which destroy the free radicals in the body, thereby preventing against harmful oxidation- reduction reactions. The best sources are fruits and vegetables which provide a variety of antioxidants like Vit. A, C, E & carotenoids. Currently available data are compatible with the notion that these vitamins act as chemo preventives against some important cancers, e.g., carotenoids for lung cancer, ascorbic acid for salivary gland cancer, tocopherols for head and neck cancers etc.

Thus, a greater consumption of fruits and vegetables should be encouraged as they are the natural sources of these chemo preventive antioxidants. This paper will briefly review the basics of antioxidants and various scientific studies that bear out the promise of antioxidants for oral care & diseases

Keywords: Antioxidants, Oral cavity, Oral cancer, Periodontal disease, Dental caries.

Introduction

Oxygen is an element indispensable for life. When cells use oxygen to generate energy, free radicals are created as a consequence of ATP (adenosine triphosphate) production by the mitochondria. These by-products are generally reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) At high concentrations, they generate oxidative stress, a deleterious process that can damage all cell structures.[1]

Oxidative stress plays a major part in the development of chronic and degenerative ailments such as cancer, arthritis, aging, autoimmune disorders, cardiovascular and neurodegenerative disease. The human body has several mechanisms to counteract oxidative stress by producing antioxidants, which are either naturally produced in situ, or externally supplied through foods and/or supplements. Endogenous and exogenous antioxidants act as "free radical scavengers" by preventing and repairing damages caused by ROS and

RNS, and therefore can enhance the immune defense and lower the risk of cancer and degenerative diseases.[2]

An antioxidant is a molecule which inhibits oxidation reaction. Antioxidants terminate the chain reaction caused by free radicals of oxidation reaction, preventing cell damage or death of the cells. Insufficient levels of antioxidants or inhibition of antioxidant enzymes causes oxidative stress and damage or kill the cells. It has been suggested that negative effects of nicotine are reversed by antioxidants.

Antioxidants are available from different sources, including vitamins, minerals, enzymes and hormones, as well as food and herbal supplements. These supplements may be in bar, gel, capsule, drops and tablet forms. As an alternative medicine, herbal therapy is a treatment modality to remedy many medical and dental conditions. Antioxidants have also been used in combination with dried, fresh, and blended herbal paste. The majority of herbal supplements include green tea catechins, aloe vera, star anise oil, myrrh gum, calendula extract, ammonium glycyrrhizate (from liquorice root), fennel oil, and neem extracts.[3]

Most recently, dental manufacturers and distributors have incorporated antioxidant supplements into toothpastes, mouth rinses / mouthwashes, lozenges, fluoride gels and dentifrices, oral sprays, breath fresheners, and other dental products for the control of gingival and periodontal diseases. While we are familiar with antioxidants taken systemically, such as foods and vitamin supplements, topical antioxidants may have an effect on oral cells.

The success of topical antioxidants on skin cells suggests perhaps a similar effectiveness of topical compounds on cells in the oral cavity. Research studies are currently under way to examine the effectiveness of combinations of antioxidants applied topically to oral cells. Results from clinical studies, though incomplete, are positive. In addition, published research studies confirmed that antioxidants that work on skin cells also have an effect on oral, gingival, and periodontal cells.[4]

Mechanism of Action

Free radicals are chemically active atoms that have a charge due to an excess or deficient number of electrons. Free radicals containing oxygen, known as reactive oxygen species (ROS), are the most biologically significant free radicals.

In the recent years the term “Reactive Oxygen Species” or “Reactive Oxygen Intermediates” is a collective term which has been adopted to include molecules like Hydroxyl radical (OH), Superoxide anion (O2), Hydrogen peroxide, Hypochlorous acid (HCIO)4 While most reactive oxygen species have extremely short half-life, they can cause substantial tissue damage by initiating free radical chain reaction. Reactive oxygen species can cause tissue damage by a variety of different mechanism which include;[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 eg Antiprotease such as; 1 antitrypsin
- Stimulation of pro inflammatory cytokine release by monocytes and macrophages by depleting intracellular thiol compounds and activating nuclear factor.

Types of anti-oxidants

Vitamin e

Recent studies have indicated that vitamin E may have therapeutic effects in treating and preventing periodontal pathology. Vitamin E is a powerful lipid-soluble

antioxidant that is valuable in decreasing wound-healing time. To determine whether free radicals have an effect on the normal process of the cell cycle and whether vitamin E inhibits cell damage, normal human oral epithelial cells were treated with hydrogen peroxide (H2O2) in culture in the presence or absence of vitamin E. Cultures exposed to H2O2 showed characteristic features common among premalignant epithelial lesions. Therefore, the conclusion is that vitamin E may have the potential to reduce oxidative damage caused by hydroxyl radicals.[6]

Folic acid

Another vitamin supplement that is essential is folic acid. Low serum folate levels have been associated with an increased risk of periodontal disease in older adults as shown in a recent population-based, cross-sectional study.

The role of folic acid in combination with oral hygiene measures was investigated in a 1-year follow-up study on epileptic children treated with phenytoin (an anticonvulsant). This study led to the conclusion that the combined effects of systemic folic acid and phenytoin slow down the onset and decrease the incidence and severity of phenytoin-induced gingival overgrowth.[7]

Beta-carotene

Beta-carotene is a fat-soluble member of the carotenoids which are considered provitamins because they can be converted to active vitamin A. Beta-carotene is converted to retinol, which is essential for vision. It is a strong antioxidant and is the best quencher of singlet oxygen. Beta-carotene is present in many fruits, grains, oil and vegetables (carrots, green plants, squash, spinach)[8]

Selenium

Selenium is a trace element. It forms the active site of several antioxidant enzymes including glutathione peroxidase. Similar to selenium, the minerals manganese and zinc are trace elements that form an essential part of various antioxidant enzymes. Se is a trace mineral found in soil, water, vegetables (garlic, onion, grains, nuts, soybean), sea food, meat, liver, yeast. At low dose, health benefits of Se are antioxidant, anti-carcinogenic and immunomodulators.[9,10]

Lycopene

Lycopene has been hypothesized to prevent carcinogenesis and atherogenesis by protecting critical cellular biomolecules, including lipids, lipoproteins, proteins, and DNA. Lycopene, when given in the dosage of 4.8 mg/day orally for 3 months leads to the reversal of dysplastic changes in leukoplakia12 and when given in the dosage of 16 mg/day leads to substantials increase in the mouth opening in oral submucous fibrosis. The major dietary source of lycopene is tomatoes, with the lycopene in cooked tomatoes, tomato juice and tomato sauce included, being more bioavailable than that in raw tomatoes.[11]

Flavonoids

They are polyphenolic compounds which are present in most plants. The main natural sources of flavonoids include green tea, grapes (red wine), apple, cocoa (chocolate), ginkgo biloba, soybean, curcuma, berries, onion, broccoli. They have been reported to prevent or delay a number of chronic and degenerative ailments such as cancer, cardiovascular diseases, arthritis, aging, cataract, memory loss, stroke, Alzheimer's disease, inflammation, infection. Green tea is a rich source of flavonoids, especially flavanols (catechins) and quercetin. Catechin levels are 4-6 times greater in green tea than in black tea. Many health benefits of green tea reside in its antioxidant, anticarcinogenic, anti-hyper cholesterol emic, antibacterial (dental caries), anti-inflammatory activities.[12,13]

Omega-3 and omega-6 fatty acids

They are essential long-chain polyunsaturated fatty acids. Dietary sources of omega-6 fatty acids (linoleic acid) include vegetable oils, nuts, cereals, eggs, poultry. It is important to maintain an appropriate balance of omega-3s and omega- 6s in the diet, as these two substances work together to promote health.[14]

Salivary anti-oxidants

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.[15]

Anti-oxidants and oral diseases

Periodontal diseases

Periodontal diseases are inflammatory disease process resulting from interaction between bacterial attack and host inflammatory response.

Free radicals and reactive oxygen species (ROS) are responsible for the inflammatory response. Periodontal pathogens can induce ROS overproduction and thus may cause collagen and periodontal tissue breakdown. When ROS are scavenged by antioxidants, collagen breakdown can be minimised. Although poor nutrition does not cause periodontal disease directly, many researchers believe that the disease progresses faster and may be more severe in people with nutrient-poor diets because of compromised host response. Chronic subclinical inflammation is the driver of most, if not all, chronic diseases.

It is a fact that the same basic inflammatory state underlies heart disease, cancer, Parkinson's disease, Alzheimer's disease, osteoporosis, osteoarthritis, chronic pain, and periodontitis. Low levels of vitamins A and C, β carotene, and β cryptoxanthin also increased the risk of gum disease significantly. Low levels of most antioxidants are a risk factor for periodontal disease and infection. Free radicals are released as a result of bacteria clearance and killing.

Periodontal tissue depends on natural antioxidants to overcome this oxidative stress and maintain homeostasis. When antioxidants are depleted, the ability of gum tissue to overcome oxidative stress, maintain normal tissue and control the bacterial damage appears to be compromised".

Increased production of reactive oxidative species (ROS) necessitates an elevated need for zinc, copper and selenium, nutrients which are involved in antioxidant defense. Systemic glutathione (GSH) is decreased with inflammation. The functions of GSH include antioxidant defense and immune regulation. The vitamins pyridoxal phosphate (B6) and riboflavin (B2) are important in maintaining GSH status.

Selenium has important oxidation-reduction functions, and selenium-dependent GSH enzymes are involved in changing lipid and phospholipids hydroperoxides to harmless products, neutralizing the inflammatory process at the cellular level. Therefore, vitamins B2, B6, copper, zinc and selenium are needed to maintain systemic glutathione and selenium-dependent GSH enzymes for antioxidant defense, immune regulation, and neutralization of the inflammation process at the cellular level. Micronutrients—beta-carotene and vitamins A, C and E— can be depleted during inflammation.

As mitochondria (the power house of the cell) produce energy, they release ROS within the cell. In a study in Sagan et al suggested that dietary vitamin C enters the mitochondria and protects against oxidative injury. These vitamins support immune functions and are

involved in the maintenance of structural and functional integrity of epithelial tissues and physiological or metabolic parameters relevant to periodontal health.[16,17]

Dental caries

Dental caries is one of the most common oral health problem and its prevention is one of the most important strategies in many countries. It affects all people regardless of their sex, socioeconomic strata, race, and age. It is also profoundly affected by other factors like oral hygiene and saliva.

Recently, it has been claimed that the imbalances in levels of free radicals, reactive oxygen species, and antioxidants in saliva may play an important role in the onset and development of dental caries.

Hence, evaluation of those factors in saliva that may increase the risk of individuals to dental caries, can pave way to make recommendations that will cater specifically to needs of an individual. Most important would be the function of salivary peroxidase system, which constitutes one of the major salivary antioxidant systems.

Salivary peroxidase brings about the control of oral bacteria that form dental plaque, to imbalances in the ecology, and which lead to dental caries. Salivary peroxidase catalyzes the peroxidation of thiocyanate ion to generate oxidation products this inhibits the growth and metabolism of many micro-organisms thereby inhibiting caries or at least slowing down the progress of caries.[18,19]

Oral cancer

Oral cavity cancer is one of the ten 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%.[20]

The role of antioxidants in cancer chemoprevention is by inhibiting oral carcinogenesis by reversing of premalignant lesions like oral leukoplakia. Oxidative damage is recognized as playing a role in the processed meat. The important dietary micronutrients that are antioxidant in action include vitamin A, β carotene, lycopene, Vitamin C, vitamin E (alpha- tocopherol), Zinc and selenium. Considerable evidence exists suggesting a role for nutrients, particularly the so-called antioxidants vitamin A, β carotene, vitamin C, vitamin E, lipoic acid, zinc, selenium and spirulina in the prevention of this disease.[21]

A recent study has suggested that these antioxidant nutrients act to inhibit the development of cancer cells and to destroy them through apoptosis (programmed cell death), by their stimulation of cytotoxic cytokines, by their action on gene expression, by preventing the development of tumour's necessary blood supply or by cellular differentiation. [22]

In addition to the chemotherapeutic and chemo preventive agents, a number of dietary components and micronutrients are emerging with considerable potential for the induction of apoptosis. These agents include green tea constituents (EGCG and others), and a number of other phytochemicals, such as carotenoids (lycopene) and retinoids. [23]

βcarotene is a vitamin A precursor commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato, mango, papaya and oranges. Main actions of beta carotene include pathogenesis of cancer which could arise from incorrect nutritional habits and lifestyle practices. This process can cause DNA damage, which is a basic mechanism in

cancer induction. Sufficient antioxidative status is crucial in free radical defence.[24]

Leukoplakia

The reversal or regression of premalignant lesions such as leukoplakia is an important slate-grey for cancer prevention. Any agent selected for trial in premalignant lesion, the ultimate goal of which is application for cancer prevention, should have minimal or preferably no toxicity because many subjects whose lesions are unlikely to progress to cancer will be exposed to the intervention. If the object is to develop agents for use by general population to reduce the incidence of oral cancer, then agents preferred are antioxidants such as β carotene and vitamin E. 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. A study showing Lycopene effect on oral cancer has proved that high doses of Lycopene (8 mg/ day) are useful in improvement of oral health.[25]

Contraversies in anti-oxidant therapy

Current literature reports that a half century of data demonstrates the lack of predictability of antioxidant therapy and it has not been validated by the scientific method. Widespread use of antioxidants has failed to quell the current 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 embryo toxic and teratogenic effects. Large doses of ascorbic acid may be associated with the inhibition of ovarian steroidogenesis and increased probability of abortion.[21]

Conclusion

The antioxidant micronutrients are important not only for limiting oxidative and tissue damage, but also in preventing increased cytokine production, which is a result of prolonged activation of immune response.

Dietary and other enzymatic antioxidants protect the lipids of lipoprotein and other bio membranes against oxidative damage by intercepting oxidants before they can attack the tissues. It is important to have an adequate antioxidant intake from both diet and supplementation if needed, and can be a valuable adjunct in the treatment of chronic inflammatory dental disorders. Antioxidants are being widely used in routine general clinical practice.

They are also used in the prevention of cellular damage, the most common pathway for cancer, aging and a variety of disease. Dietary antioxidants like Vitamin C, Vitamin E, Carotenoids may also be of significance in the prevention of degenerative disease and maintenance of good health. There is now convincing evidence that foods containing antioxidants may be of major importance in disease prevention.

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