ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 04 | April - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ANTIOXIDANTS IN ORAL DISEASES: A REVIEW

Dental Science

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ABSTRACT

Antioxidants are compounds that destroy the free radicals in the body, thereby preventing harmful oxidation-reduction reactions. Free radicals are chemical species possessing an unpaired electron that can be considered fragments of molecules and generally very reactive. They are produced continuously in cells either as accidental by-products of metabolism or deliberately during, phagocytosis. However, excess free radical production originating from endogenous or exogenous sources might play a role in many diseases. Antioxidants are man-made or natural substances that may prevent or delay some types of cell damage. Antioxidants are crucial for maintaining optimum health and well-being. Free radicals have been implicated in numerous oral diseases like leukoplakia, Periodontal diseases, and oral cancer.

KEYWORDS

Antioxidant, Periodontal disease, oral cancer, leucoplakia.

INTRODUCTION:

An antioxidant is "any substance that, when present in low concentrations compared to that of an oxidizable substrate, significantly delays or inhibits the oxidation of that substrate."[1] The physiological role of antioxidants, is to prevent damage to cellular components arising as a consequence of chemical reactions involving free radicals. [1] A free radical is any molecular species capable of independent existence that contains an unpaired electron in an atomic orbital—the presence of unpaired electron results in certain common properties shared by most radicals. Many radicals are highly reactive and can either donate an electron to or extract an electron from other molecules, therefore behaving as oxidants or reductants. The most important free radicals in many disease states are oxygen derivatives, particularly superoxide and the hydroxyl radical. Radical formation in the body occurs by several mechanisms involving both endogenous and environmental factors.[1] Antioxidants are nutrients as well as enzymes that assist in chemical reactions.[2]

HISTORY OF ANTIOXIDANTS:

Duclaux first demonstrated the participation of atmospheric O_2 in the oxidation of free fatty acids. The first reports on antioxidants employed for food lipids were about using natural sources. Olcott and Mattill first reported antioxidant synergism in food. This was significant in achieving oxidative stability in food by using various 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 to prevent radiation-induced oral mucositis.[3]

GENERATION OF FREE RADICALS AND OXIDANTS:

Free radicals are chemically active atoms with a charge due to an excess or a deficient number of electrons. Free radicals containing oxygen, known as reactive oxygen species (ROS), [4] and reactive nitrogen species (RNS) are the most biologically significant free radicals. ROS includes the radicals superoxide and hydroxyl. Free radicals and other reactive oxygen species are derived from normal essential metabolic processes in the human body or external sources such as exposure to X-rays, ozone, cigarette smoking, air pollutants, and industrial chemicals. Because they have one or more unpaired electrons, free radicals are highly unstable. They scavenge the body to grab or donate electrons, thereby damaging cells, proteins, and DNA.[2]

Superoxide (O2 −) is produced by the addition of a single electron to oxygen, and several mechanisms exist by which superoxide can be produced in vivo.[5] Several molecules, including adrenaline, flavine nucleotides, thiol compounds, and glucose, can oxidize in the presence of oxygen to produce superoxide. These reactions are greatly accelerated by the presence of transition metals such as iron or copper. The electron transport chain in the inner mitochondrial membrane performs the reduction of oxygen to water. During this process, free radical intermediates are generated, which are generally tightly bound to the transport chain's components. However, there is a constant leak of a few electrons into the mitochondrial matrix, resulting in superoxide formation.[6] The activity of several other enzymes, such as cytochrome p450 oxidase in the liver and enzymes involved in the synthesis of adrenal hormones, also results in the leakage of a few electrons into the surrounding cytoplasm and hence superoxide formation. There might also be continuous superoxide production by vascular endothelium to neutralize nitric oxide, production of superoxide by other cells to regulate cell growth and differentiation, and superoxide production by phagocytic cells during the respiratory burst.[7]

Any biological system generating superoxide will also produce hydrogen peroxide as a result of a spontaneous dismutation reaction. Several enzymatic reactions, including those catalyzed by glycolate D-amino acid oxidase, might produce hydrogen peroxide directly.[8]Hydrogen peroxide is not a free radical itself but is usually included under the general heading of reactive oxygen species. It is a weak oxidizing agent that might directly damage proteins and enzymes containing reactive thiol groups. However, its most vital property is the ability to cross cell membranes freely, which superoxide generally cannot do. Therefore, hydrogen peroxide acts as a conduit to transmit free radical-induced damage across cell compartments and between cells.

.In the presence of hydrogen peroxide, myeloperoxidase will generate hypochlorous acid and singlet oxygen, a reaction that plays an important role in the killing of bacteria by phagocytes. The hydroxyl radical (OH.), or a closely related species, is probably the final mediator of most free radical-induced tissue damage. All of the reactive oxygen species described above exert most of their pathological effects by giving rise to hydroxyl radical formation.

Although free radical production occurs due to the endogenous reactions described above and plays a vital role in normal cellular function, it is essential to remember that exogenous environmental factors can also promote radical formation. Ultraviolet light will lead to the formation of singlet oxygen and other reactive oxygen species in the skin. Atmospheric pollutants such as ozone and nitrogen dioxide

lead to radical formation and antioxidant depletion in the bronchoalveolar lining fluid, which may exacerbate respiratory disease.Cigarette smoke contains millimolar amounts of free radicals, along with other toxins. Various xenobiotics also cause tissue damage due to free radical generation, including paraquat, paracetamol, bleomycin, and anthracyclines.[1]

MECHANISM OF ACTION OF FREE RADICALS:

1. DNA harm.
2. Lipid peroxidation
3. Protein break, including gingival hyaluronic acid and proteoglycans.
4. Oxidation of essential enzymes
5. Stimulation of pro-inflammatory cytokine [9]

CLASSIFICATION OF ANTIOXIDANTS:

First Classification:[3](Table-1)

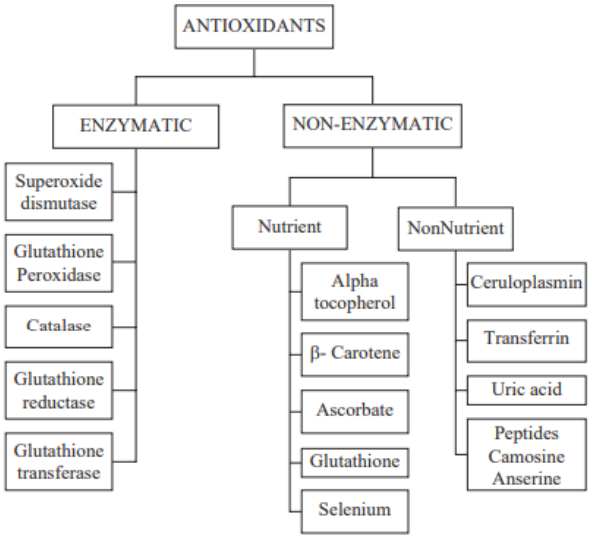

Figure-1: Classification Of Antioxidants

Second Classification

Natural Antioxidants –

Enzymes- superoxide, hydroxyl, and glutathione peroxidase
Low molecular weight antioxidants-
Lipid-soluble antioxidants: tocopherol, carotenoids, bilirubin, & polyphenyls
Water-soluble antioxidants: ascorbic acid, uric acid, & polyphenyls.

Synthetic antioxidants are synthetic chemicals, which include butylated hydroxyl anisole, butylated hydroxyl toluene, and tertiary butylated hydroxyl quinine.[10]

Table-2: Mode Of Action Of Antioxidants:[4,11,12,]

S.No	Antioxidants	Sources	RDA	Actions
1	Beta carotene	Vegetables, such as spinach, carrots, sweet potatoes and in fruits like orange, apricot, papaya, vegetable.	25,000 to 100,000 IU/day	Increases the no. of circulating lymphocytes, enhances the proliferation and induction of cytotoxic T cells, increases the number of helper T cells, increases TNF and enables natural killer cells to be more effective.
2	Retinol	carrot, spinach, green leaves, mangoes, tomatoes	0.5 to 1 mg/Kg/d	Disturbs normal epithetical growth, Tumor surveillance & directly influences gene expression.
3	Vitamin C	citrus fruits, strawberry, honey dew, papaya and mangoes.	60 mg/ day, for smokers - 100 mg/ day	Hydroxylation reactions, synthesis of nor—epinephrine, serotonin carnitine, scavenges reactive oxygen and nitrogen species.
4	Vitamin E	plant oils, wheat and green leafy vegetables	8 to 10 mg/day	Protects cellular membrane from lipid peroxidation, enhances the mitogenic response, inhibit certain prostoglandins and improves T cell mediated response, decreases the incidence of symptomatic oral radio-induced mucositis in patients with cancer.
5	Phenolic compounds		150-200 mg/ day	antioxidant activity, capillary protective effect, inhibitory effect elicited in various stages of tumor, and scavenge reactive oxygen species
6	Selenium	fish, shellfish, red meat, grains, eggs and chicken, Vegetables		fight cell damage by oxygen-derived compounds and thus may help protect against cancer.
7	Superoxide dismutase	Cabbage, Brussels sprouts, wheat grass, barley grass and broccoli		Catalyzed the dismutation of the highly reactive superoxide anion to O2 and to the less reactive species H2O2
8	Catalase (CAT)			degradation of hydrogen peroxide.
9	Glutathione peroxidase			protecting cells from damage due to free radicals like hydrogen and lipid peroxides, educe lipid hydroperoxides to their corresponding alcohols and to reduce free H_2O_2 to water
10	Glutathione reductase			prevention of oxidative damage within the cell by helping to maintain appropriate levels of intracellular glutathione
11	Glutathione-S-transferase			detoxification of endogenous compounds such as peroxidised lipids as well as metabolism of xenobiotics.
12	Lycopene	tomatoes, apricots, papaya and other yellow fruits	8 mg/day for treatment of leukoplakia	prevent carcinogenesis and atherogenesis by protecting critical cellular biomolecules, including lipids, lipoproteins, proteins, and DNA
13	Green tea extract (Epigallocatechin- 3-gallate)			Scavenging effect, reduce the risk of dental caries and plaque formation, effective in oral leukoplakia.
14	Spirulina fusiforms (blue green micro algae)			Potent quencher of highly reactive singlet oxygen, effective in Squamous cell carcinoma

ROLE OF ANTIOXIDANTS IN ORAL CAVITY:

SALIVARY ANTIOXIDANTS: Saliva is rich in antioxidant compounds. The primary antioxidants include uric acid, albumin,

ascorbic acid, glutathione and antioxidant enzymes. Antioxidants neutralize free radicals—reactive oxygen species and reactive nitrogen species —and counteract oxidative stress.[13]

ANTIOXIDANTS AND PERIODONTAL DISEASES:

Periodontal diseases are inflammatory disease process resulting from interaction between bacterial attack and host inflammatory response. Free radicals and reactive oxygen species 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. 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 necessitates an elevated need for zinc, copper and selenium, nutrients which are involved in antioxidant defenses. Systemic glutathione (GSH) is decreased with inflammation. The functions of GSH include defense and immune regulation. 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 produce energy, they release ROS within the cell. 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.

ANTIOXIDANTS AND DENTAL CARIES:

Dental caries is one of the most common oral health problem that affects all people regardless of their sex, socioeconomic status, race, and age. It is also profoundly affected by other factors like oral hygiene and saliva.[14] Recently, it has been stated that the imbalances in levels of free radicals, ROS, and antioxidants in saliva may play an important role in the onset and development of dental caries. 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, that inhibits the growth and metabolism of many micro-organisms thereby inhibiting caries or atleast slowing down the progress of caries.[15]

ANTIOXIDANTS AND 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. 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 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. To reduce the risk of oral and pharyngeal cancer, especially oral cell carcinoma, diet must be optimized, primarily to reduce calorie intake, monosaturated fat and red or processed meat.

The important dietary micronutrients that are antioxidant in action include vitamin A, C, E (α tocopherol), β carotene, lycopene, Zinc and selenium. These antioxidant nutrients act to inhibit the development of cancer cells and to destroy them through apoptosis, 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. The retinoids in the body originate from retinyl esters, carotenoids, and retinal in diets. The effects of retinoids are mediated by retinoid acid receptors (RARs) and retinoid X receptors (RXRs). Recently, retinoids have been implicated in the induction of cell death in many tumor-derived culture cell systems in both retinoid receptor-dependent and independent manners. In addition to the chemotherapeutic and chemopreventive agents, a number of dietary components and micronutrients are emerging with considerable potential for the induction of apoptosis.

Lycopene is a prominent carotenoid in serum which is the red antioxidant pigment. This is a fat-soluble red pigment found in some fruit and vegetables. Lycopene and other carotenoids rich foods also are inversely related to oral cancer. Lycopene has been hypothesized to prevent carcinogenesis and atherogenesis by protecting critical cellular biomolecules. Lycopene has the uncommon feature of getting bound to chemical species that react to oxygen, thus being the most efficient biological antioxidizing agent.[16]

REVERSAL OF ORAL LEUKOPLAKIA WITH ANTIOXIDANTS:

The reversal or regression of premalignant lesions such as leukoplakia is an important stategery for cancer prevention. The agents used by general population to reduce the incidence of lesion are antioxidants such as β carotene and vitamin E. 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.[17,18] Lycopene (8 mg/ day) are useful in improvement of oral leukoplakia.[19]

CONCLUSION:

The knowledge of antioxidants is useful in reducing the incidence of oral cancers at initial stages though non-invasive techniques. Hence, natural products like fruits and vegetables helps in preventing oral cancers at an early stage. Nutrients will be widely utilized and will play an important role in preventing cancers.

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