

Antioxidants in Oral Health and Diseases: Future Prospects

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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 chemopreventives 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 chemopreventive 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.

Key words: Antioxidants, chemopreventive, free radicals, carotenoids.

I. 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 structures¹. 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 diseases².

II. Mechanism of action of free radicals

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.³ 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 (H₂O₂), Hypochlorous acid (HClO)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;

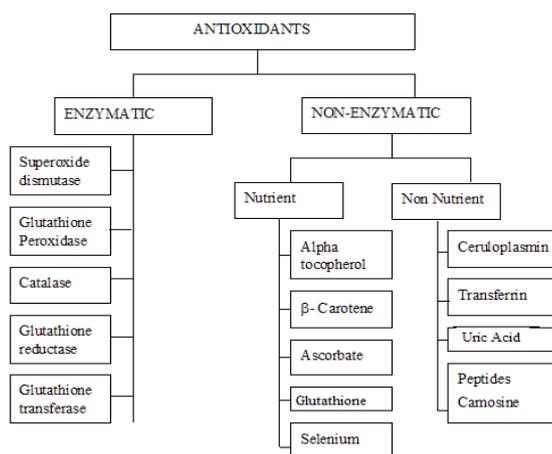
- DNA damage
- Lipid peroxidation (through activation of cyclogenase and lipo oxygenase pathway)
- Protein damage including gingival hyaluronic acid and proteoglycans
- Oxidation of important enzymes eg Antiprotease such as ; 1 antitrypsin
- Stimulation of pro inflammatory cytokine release by monocytes and macrophages by depleting intracellular thiol compounds and activating nuclear factor



Diseases caused by free radicals

Classifications

<u>ENDOGENOUS ANTIOXIDANTS</u>	<u>DIETARY ANTIOXIDANTS</u>	<u>METAL BINDING PROTEINS</u>
BILIRUBIN	Vitamin C	Albumin (Copper)
THIOLS eg. Glutathione, lipoic acid, N acetyl cysteine	Vitamin E	Ceruloplasmin (Copper)
NADPH, NADH	β -Carotene	Metallothionin (copper)
UBIQUINONE (COENZYME Q 10)	Other carotenoids & oxy carotenoids like lycopene & lutein	Ferritin (iron)
URIC ACID	Polyphenols eg. Flavonoids, flavones, flavonols & proanthocyanidins	Myoglobin (iron)
ENZYMES- 1. Cu/Zn & Mn dependent superoxide dismutase(SOD) 2. iron dependent catalase 3. selenium dependent glutathione peroxidase		Transferrin(iron)
HORMONES – Melatonin ⁵		



Iain L, C. Chapple et al⁶

Types of antioxidants

Antioxidants from our diet play an important role in helping endogenous antioxidants for the neutralization of oxidative stress.

Vitamin C Vitamin C also known as ascorbic acid, is a water-soluble vitamin. It is essential for collagen, carnitine and neurotransmitters biosynthesis. Health benefits of vitamin C are antioxidant, anti-atherogenic, anti-carcinogenic, immunomodulator.⁷ 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, tomatoes³.

Vitamin E -Vitamin E is a fat-soluble vitamin with high antioxidant potency. Because it is fat-soluble, α -tocopherol safeguards cell membranes from damage by free radicals. Its antioxidant function mainly resides in the protection against lipid peroxidation. The dietary sources of vitamin E are vegetable oils, wheat germ oil, whole grains, nuts, cereals, fruits, eggs, poultry meat⁸. Vitamin E has been proposed for the prevention against

colon, prostate and breast cancers, some cardiovascular diseases, ischemia, cataract, arthritis and certain neurological disorders.⁹

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)⁵

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.³ Se is a trace mineral found in soil, water, vegetables (garlic, onion, grains, nuts, soybean), sea food, meat, liver, yeast.¹⁰ At low dose, health benefits of Se are antioxidant, anti-carcinogenic and immunomodulators.¹¹

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 substantial increase in the mouth opening in oral submucous fibrosis.¹³ 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.

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 flavonols (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, antihypercholesterolemic, antibacterial (dental caries), anti-inflammatory activities¹⁴

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 health¹

Recent antioxidant

Decades of research have proven that precise combinations of the antioxidants phloretin, tetra-curcuminoid and ferulic acid, including formulations applied topically, can neutralize cell-damaging free radicals, particularly those caused by UV rays, nicotine, alcohol, and hydrogen peroxide.¹⁵ Recent research has further confirmed that certain antioxidants, including phloretin, silymarin, and hesperetin, significantly inhibit the inflammatory response associated with *Actinobacillus actinomycetemcomitans*, one of the pathogens that cause periodontal disease.¹⁶ Lutein; dark green vegetables such as kale, broccoli, kiwi, sprout and spinach. Lignan; oatmeal, barley, rye. Herbs; turmeric (curcumin), [grape seed or pine bark](#) extracts They can also provide powerful antioxidant protection for the body¹⁷.

Antioxidant-enzymes

Superoxide dismutase, catalase, and glutathione peroxidase serve as primary line of defense in destroying free radicals

Mechanism of action of antioxidants³

Antioxidants neutralize free radicals by donating one of their electrons, which ends the electron stealing reaction. The antioxidant nutrient, however, does not become a free radical by donating an electron because they are stable in either form. Important antioxidants include the following:

1. Chain breaking or scavenging ones, such as Vitamin E (alpha tocopherol), Vitamin C (ascorbic acid), or Vitamin A (beta carotene)
2. Preventative antioxidants that function largely by sequestering transition metal ions and preventing Fenton reactions and are therefore largely proteins by nature (e.g., albumin, transferrin, or lactoferrin)

Therapeutic use of antioxidants for oral Lesions⁴

The possible uses of antioxidants for oral mucosal lesions include the following:

1. Prevention of lesions in high-risk individuals with mucosa that clinically appears normal with no history of either premalignant or malignant lesion

2. The treatment of premalignant oral lesions
3. In patients who have had either premalignant or malignant oral lesions that have been successfully treated, in order to prevent recurrence of the treated initial lesion or to prevent the development of a second or a separate primary.

Protective Roles of Micronutrients in Carcinogenesis¹⁸

Nutrient	Functions
Beta- Carotene	Precursor of vitamin A; anti-oxidant and free radical scavenging; immunomodulation, stimulation of increase in numbers of T-helper and NK cells as well as cells with IL-2 receptors; inhibition of mutagenesis; inhibition of cancer cell growth.
Vitamin A (Retinoids)	Inhibit keratinization and terminal differentiation of epidermal cells; enhancement of cellular immunity; arrest/reverse leukoplakia progression; induction of cytotoxic and cytostatic effects on cancer cells; influence DNA, RNA, gene expression; interfere with carcinogenic stimulation/ binding.
Vitamin E (A-Tocopherol)	Free radical scavenging; maintenance of membrane integrity, immune function; inhibition of cancer cell growth/differentiation; cytotoxicity; inhibits mutagenicity and nitrosamine formation; inhibition of DNA, RNA, protein synthesis in cancer cells
Vitamin C (Ascorbic Acid)	Anti-oxidant; reduce vitamin E degradation; enhance chemotaxis, phagocytosis, collagen synthesis; inhibit nitrosamine formation; enhance detoxification via cytochrome P450; block formation of fecal mutagens; reduce oncogene expression ¹⁹

Controversial areas in antioxidants 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.¹⁹ Large doses of ascorbic acid may be associated with the inhibition of ovarian steroidogenesis and increased probability of abortion.²⁰

III. 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 biomembranes 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. .

Free yourself from free radicals Eat more fruits and vegetables

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