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## Antioxidants - A Boon in Dentistry - A Review

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## Abstract

The oral cavity is under invariable attack from foods and drinks, as well as substances such as alcohol, tobacco products and nicotine, dental materials and much more. Bacteria and other disease-causing agents along with systemic conditions present promote insult. As the oral tissues are fragile, they are especially susceptible to cell injury caused by free radicals and oxidative stress. Maintaining a good quality balance of oxidants and antioxidants is very essential for maintaining oral health. There are many types of antioxidant products in the market and they can be produced from several sources including minerals, vitamins or food and herbal supplements. In developed countries, consumption of antioxidants has become widespread. As in every medical field, the usage of antioxidants is becoming more frequent. Antioxidants can help adjunct treating the progress of oral problems such as periodontitis or gingivitis. The properties of antioxidants have been studied to understand their mechanisms, to clarify their activities and the increasing evidences are raising hopes about antioxidants for human health.

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

## Introduction

Oxygen is an ever-present element and a fundamentally important substance for life on earth especially for human life and it can both be valuable and harmful to life. The process of oxidation is a natural phenomenon of energy generation system and its by- product called "Free Radicals" which can damage healthy cells of the body. These by products are commonly reactive oxygen species and reactive nitrogen species. They play a dual role as both toxic and beneficial compounds.

In a normal cell there is stability between formation and removal of free radicals. However this equilibrium can be shifted towards more formation of free radicals or when levels of antioxidants are diminished. This state is called "Oxidative Stress" and can end in serious cell damage if the stress is massive and prolonged. Living cells are frequently exposed to oxidants from a mixture of sources that can be exogenous and endogenous. This free radical formation is safeguarded by a choice of valuable compounds known as "Antioxidants". Antioxidants are capable of stabilizing or deactivating free radicals prior to the attack cells.

They are completely critical for maintaining optimal cellular and systemic health and well- being. Oxidative stress plays a major role in development of chronic and degenerative ailments such as cancer, arthritis, ageing, autoimmune, cardiovascular. neurodegenerative, pulmonary and ocular diseases, AIDS, psychological stress in foetus, diabetes, male infertility. Antioxidants can also be enzymatic or nonenzymatic which work in permutation with each other to protect cells or organs against free radicals. Endogenous and exogenous antioxidants act as "Free radical scavengers" by preventing and repairing damages caused by reactive oxygen and nitrogen species. This can increase the immune defense and lower the danger of cancer and degenerative diseases.

Antioxidants are accessible from diverse sources such as vitamins, minerals, enzymes and hormones as well as food and herbal supplements. Oral cavity is bare to lot of carcinogens and is prone to develop precancerous lesions and conditions which may turn to oral cancer. Dietary substitute play a vital role in prevention of oral cancer, potentially malignant disorders like leukoplakia, lichen planus, oral submucous fibrosis, burning mouth syndrome, dental caries, aids in bone healing and treating peri implantitis. These dietary products includes а betacarotene, provitamin A, vitamin A, C and E, polyphenols, curcumin.

## **Oxidative Stress and Free Radicals**

Free radicals are chemically active atoms that have charge due to an surplus or lacking number of electrons. A free radical is a molecule with one or more unpaired electron in its outer shell. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are well recognizable for playing a dual role as both deleterious and beneficial species. At low or moderate levels of concentration, ROS take part in the biosynthesis of molecules such as thyroxine, prostaglandin and enhances the immune system. Macrophages and neutrophils make ROS in order to destroy the bacteria that may engulf by phagocytosis. At high concentrations, they produce oxidative stress and nitrosative stress, that can harm all cell structures.

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#### **Generation of Free Radicals and Oxidants**

Formation of ROS and RNS can take place by enzymatic and non-enzymatic reactions.Enzymatic reactions consist of those involved in the respiratory chain, the phagocytosis, the prostaglandin synthesis and cytochrome P450 system.

Previously formed, it has various ROS and RNS such as hydrogen peroxide, hydroxyl radical (OH-), peroxynitrite (ONOO-), hypochlorous acid (HOCL) etc.

Free radicals can be formed from non-enzymatic reactions of oxygen with organic compounds like well as those initiated by ionizing radiations.

## Mechanism of Action of Free Radicals:

- 1. DNA harm.
- 2. Lipid peroxidation (through activation of cycloxygenase and lipo oxygenase pathway).
- 3. Protein break including gingival hyaluronic acid and proteoglycans.
- 4. Oxidation of essential enzymes.

5. Stimulation of pro inflammatory cytokine release by monocytes and macrophages by depleting intracellular thiol compounds and activating nuclear factor kappa beta. **Role of Oxidative Stress and Free Radicals in Oral Cavity** 

The diseases related with oxidative stress in oral cavity includes periodontitis, oral submucous fibrosis, oral lichen planus, oral cancers, dental caries, burning mouth syndrome, peri-implantitis etc. The association of ROS and antioxidant defense mechanisms in human saliva has been established in various processes of oral cavity like healing periodontal disease, preventing oral carcinogenesis, reducing oral mucosa inflammatory reactions. In potentially malignant disorders and in malignancy the dietary factors and environmental sources are liable for generating oxidants.

Frequently used dental materials may form free radicals which includes bleaching agents, composite fillings, dental cements, ceramic restorations, metals in restorations, dental implants, intracanal medicament and dentin bonding agents.

Antioxidants are able of stabilizing or deactivating free radicals prior to the attack cells.

A biological definination of antioxidant is as "A substance present in low concentrations compared to an oxidizable substrate (eg., proteins, lipids, carbohydrates and nucleic acids) that significantly delays or inhibits oxidation of a substrate. Antioxidants may be considered as the scavengers of free radicals".

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.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.

## Various types of antioxidants

#### 1) Beta- Carotene

It is the primarily active carotenoid. One of the key carotenoids in our diet and in human blood and tissues and its color varies from yellow to orange.

It has an significant nutritional role as the most important precursor of vitamin A.

It is found in vegetables and fruits like beet root, apricots, carrots, pumpkin, sweet potato, tomatoes, watermelon, papaya, mango, peaches, oranges, green beans, broccoli and spinach.

## **Main Actions of Beta Carotene**

- 1. Anti-oxidant and free radical scavenging.
- 2. Immunomodulation, stimulation of raise in the numbers of T-helper and NK cells and cells with IL-2 receptors.
- 3. Inhibition of mutagenesis and cancer cell growth.

#### Pathogenesis

Carotenoids have the ability to trap peroxyl radicals and quench singlet oxygen.  $\beta$ -Carotene is a scavenger of peroxyl radicals, specially at low oxygen tension.

The electron rich conjugated double bond structure is primarily responsible for the excellent ability of betacarotene to physically quench singlet oxygen without degradation and for the chemical reactivity of betacarotene with free radicals and for its instability toward oxidation.The highest protection to quench singlet oxygen is specified by those carotenoids having nine or more double bonds.A diet supplemented with beta-carotene can stop changes in oral mucosa especially in smoker patient who present low serum levels of vitamin C and betacarotene as compared to non smokers. It stimulates the activity of immune cells against tumor cells.

Cancer risk increases when our dietary intake of carotene is low.It increases the number of receptors on WBC for molecules known as major histo compatibility complex II (MHC II) which help in monocyte action and direct killer T cells to cancerous cell.Beta-carotene can guard phagocytic cells from autoxoidative damage, improve T and B lypmphocyte proliferative responses, stimulate effector T cell functions and enhance macrophage, cytotoxic T cell and NK cell tumoricidal capacities.It plays an significant role in the pathogenesis of OSMF (oral submucous fibrosis). The degree of oxidative damage in OSMF can be assessed by estimation of serum beta carotene levels in affected patients, and that the underlying deficiency of antioxidants can be corrected by dietary supplementation of beta carotene. This may be helpful for booming management of this condition and for avoiding the consequences of malignancy.

**Therapeutic dose:** 25,000 to 100,000 IU/day

## **Commercial preparation:**

Lutivit (L-arginine, vit E, beta carotene, lycopene, leutin) Luvion intra (leutin, beta carotene)

## Retinoids

Retinoids are a group comprising natural derivatives and synthetic analogues of Vitamin A .Its metabolically active form is Retinol. Dietary sources of retinol are chiefly animal products which includes milk, butter, egg, liver and fish.

#### Functions

- 1. To maintain integrity and activity of epithelial tissue and glands.
- 2. It is primarily concerned with process of differentiation of epithelial cell.

#### Pathogenesis

The mechanism of action of the retinoids is probably correlated to different nuclear RARs (retinoic acid receptors). The availability of RARs and retinoids is involved in the regulation of cell growth. After binding to the receptors, transcription factors (heterodimers or homodimers) are produced that bind to specific DNA sequences, leading to an up-regulation or down-regulation that finally affects gene transcription. It is supposed that retinoids act by regulating gene expression through RAR nuclear receptors.In prophylactic doses, the toxicities includes skin srash, dryness and bleeding of the nasal mucosa, conjunctivitis, oral mucositis, chelitis, hyper triglycerinemia, teratogenic effects.

#### Dose

0.5 to 1 mg/Kg/d of 13-cisretinoic acid

## **Commercial preparation**

Acitretin 50

A-Ret-HC (tretinoin)

#### Lycopene

Lycopene is rich source in Red fruits and vegetables including tomatoes processed tomato products such as juice, ketchup, sauce and soup, watermelons, pink-grapefruits, apricots and pink-guavas.Average daily dietary lycopene ingestion is to be 25-30 mg/day.

## Pathogenesis

It is a highly unsaturated straight chain hydrocarbon with total of 13 double bonds, 11 of which are conjugated. This unique nature of lycopene molecule makes it a very potent antioxidant.Biologically lycopene tends to act as singlet oxygen and peroxyl radical scavenger. The highly conjugated double bonds of lycopene play the most important role in energy transfer reactions. Lycopene has quenching ability towards singlet oxygen, based on the excited energy state and is greatly related to the length of the conjugated double bond system.

Lycopene causes up regulation of antioxidant response element leading to synthesis of cytoprotective enzymes, the enhancement of intercellular gap junctions communication, the modulation of hormonal,

inflammatory and immune system. Lycopene can promote apoptosis in human cancer tissue with anti invasion and anti metastatic activity.Lycopene has been reported to increase p53 protein levels in cancer cells.Lycopene has shown significant improvement in leukoplakia, tomato consumption has the most protective effect on oral leukoplakia.Several studies explained marked improvement in mouth opening and noticeable reduction of burning sensation on OSMF patients with the lycopene treatment than patients treated with placebo.

This curative effect is due to inhibition of abnormal fibroblasts, up regulation of lymphocyte resistance to stress and suppression of inflammatory response.

It is also found to be effective in reducing signs and symptoms of oral lichen planus.Lycored is a drug containing vitamin A, alpha-tocopherol, zinc and selenium with antioxidant properties and adds synergistically to the positive effects of lycopene.High intakes of lycopene rich foods or supplements may result in a deep orange discoloration of skin known as lycopenodermia.It is available in the day to day market in the form of syrups and capsules.

DOSE: 8 mg/day for treatment of oral leukoplakia

## **Commercial preparation**

Lycored, L-bex forte (lycopene 4000 IU, lutein, beta carotene 10 mg)

## Ascorbic acid

Vitamin C is mainly found in citrus fruits. The current recommended daily allowance for ascorbic acid ranges between 100-120 mg/per day for adults.

It has been suggested that a daily intake of at least 140 mg/day is required for smokers because they usually present a reduction of L-Ascorbic acid (L-AA) concentration in serum leukocytes.

#### **Pathogenesis**

Vitamin C is a potent reducing agent and scavenger of free radicals in biological systems. Ascorbate readily undergoes two consecutive, yet reversible, one-electron oxidations to generate dehydroascorbate (DHA) and an intermediate, the ascorbate free radical (AFR).AFR is relatively unreactive free radical.The current recommended dietary daily allowances for vitamin C are 90 mg for men and 75 mg for women.Vitamin C is essential for collagen. Its deficiency results in disease of skin, gums and other tissues with high collagen content, carnitine and neurotransmitter biosynthesis. Health benefits of vitamin C are antioxidant, anti-atherogenic, anticarcinogenic, immunomodulator.

#### **Commercial preparation**

Limcee tablet 500 mg -1 gm

Chew-Cee 500 mg.

#### **Tocopherol** (Vitamin E)

Vitamin E is a fat soluble vitamin with high antioxidant potency. The dietary sources of vitamin E are vegetable oils, wheat, germ oil, whole grains, nuts, cereals, fruits, soyabean, eggs, poultry, meat. The recommended daily limit rates are 10 mg/day for adult men and 8 mg/day for adult women.

#### Main actions includes

- 1. Free radical scavenging
- 2. Maintenance of membrane integrity, immune function.
- Inhibition of cancer cell growth/ differentiation,mutagenicity and nitrosamine formation and protein synthesis in cancer cells.

Therapeutic Dose:- 400-800 IU a day.

## **Commercial preparation:**

Evion 200 mg, Viteolin 200 mg.

#### **Polyphenols/ Flavonoids**

Methoxylated flavonoids, present in citrus fruits, inhibit DNA adduct formation promoted by known carcinogens, such as tobacco nitrosamines. Proanthocyanidins present highly concentrated in red wine, pigmented fruits, nuts and chocolate.

#### **Functions :**

It reduces cell proliferation in human oral cancer cells infected by human papillomavirus.Inhibit proliferation in non-infected cells.It show cytotoxic activity and induce apoptosis and cell differentiation.

#### Pathogenesis

The anticancer activity of several polyphenols is due to their ability to inhibit enzymes in carcinogenesis and tumour development.

Prevention of oxidative stress, modulation of carcinogen metabolism and prevention of DNA damage have been suggested as possible cancer preventive mechanisms for tea and tea polyphenols.

High consumers of coffee, barley coffee, tea and wine show lower lactobacilli and streptococci mutans levels in plaque and saliva and lower dental plaque scores than low/nonconsumers.

**Dose :** 150-200 mg per day

#### Curcumin

The polyphenol curcumin is the active ingredient in the herbal remedy and dietary spice turmeric.

#### Pathogenesis

In vitro studies have shown that curcumin inhibits lipooxygenase and cyclo-oxygenase activities, xanthine oxygenase activities, nitric oxide production and reactive oxygen species (ROS) generation.

Curcumin also inhibits the production of proinflammatory monocyte/macrophage derived cytokines [interleukin-8] (IL-8), monocyte inflammatory protein-1 (MIP-1), monocyte chemotactic protein-1 (MCP-1), a) or peripheral blood monocytes and alveolar macrophages. Curcumin inhibits cancer development and progression, targeting multiple steps in the pathway to malignancy. Curcumin has activity as both a blocking agent, inhibiting the initiation step of cancer by preventing carcinogen activation and as a suppressing agent, inhibiting malignant cell proliferation during promotion and progression of carcinogenesis. Curcumin has been shown to interfere with many processes involved in angiogenesis. It inhibits fibroblast growth factor induced neovascularization.

interleukin-1b (IL-1b), and tumor necrosis factor-a (TNF-

The angiogenic ligands vascular endothelial growth factor and angiopoetin 1 and 2 which act in a coordinated fashion in angiogenesis are inhibited by curcumin.

It can exert both radioprotective effects in normal cells and radiosensitizing effects in cancer cells.

It has been suggested that curcumin's ability to reduce oxidative stress and inhibit transcription of genes related to oxidative stress and inflammatory responses may afford protection against the harmful effects of radiation where as the radiosensitizing activity might be due to the upregulation of genes responsible for cell death.

Minor adverse effects related to the use of curcumin include gastrointestinal adverse effects and haematological adverse effects

#### **Commercial preparations**

Turmeric curcumin 450, Turmix tablets 300 mg (curcumin extract).

## Aloe Vera

It has very strong antioxidant nutrients. Glutathione peroxide activity, superoxide dismutase enzymes, and a phenolic antioxidant were found to be present in Aloe vera gel, which may be responsible for antioxidant effects. It also contains A, C, and E vitamins. In oral cavity it is used for treatment of apthous ulcers, gingivitis, lichen planus,

alveolar osteitis, as a denture adhesive. Applications directly at sites of periodontal surgery, as an adjunct to scaling and root planning in periodontitis, chemical burns caused by accidents with aspirin, angular chelitis, burning mouth syndrome, patients with sore gums and teeth with dentures maladaptive, around dental implants to control inflammation caused by bacterial contamination.

## **Commercial preparation**

Aloe-E, Nidwash forte (glycolic acid, salicylic acid, aloe vera extract).

#### **Honey Bee**

Propolis is a sticky, resinous substance collected by honey bees from the sap, leaves, and buds of plants, and then mixed with secreted beeswax.

In dentistry, propolis has been used for the treatment of aphthous ulcers, candidiasis, acute necrotizing ulcerative gingivitis (ANUG), gingivitis, periodontitis and pulpitis.

#### Pathogenesis

Propolis can prevent tissue damage from oxidative stress by decreasing the overproduction of superoxide anion and by restoring respiratory control ratio in mitochondrial tissue. Current research involving propolis in dentistry spans many fields and highlights its antimicrobial and antiinflammatory activities, particularly in cariology, oral surgery, pathology, periodontics, endodontics and pedodontic.

It may boost the effects of anticarcinogenic drugs, thus enabling a decrease in the administered dose and in turn leading to reduction in side effects.

Propolis has been reported to promote epithelial formation as well as vascular and fibroblastic neoformation of the connective tissue. Thus it can be hypothesized that the topical application of propolis on surgical wounds may promote faster epithelium and connective tissue healing. It can be used in the treatment of dental caries, plaque, chronic periodontitis, oral candidiasis, pulp therapy in primary and permanent teeth, dental hypersensitivity, halitosis, lichen planus, recurrent apthous stomatitis, denture stomatitis, radiation mucositis, new storage media following avulsion of tooth.

Dispensable forms for treatment in dentistry: Propolis mouthwash (0.5% aqueous alcohol solution), tooth paste, propolis ointment, propolis intracanal medicament, propolis extract, tablet form, propolis mouth spray.

#### **Commercial preparations**

Bioglan propolis 1000

Triple bee complex .

#### **Endogeneous Enzymatic Antioxidants**

The body depends on several endogeneous defence mechanisms supplementary to dietary antioxidants, to help protect against free radical induced cell damage. The antioxidant enzymes - glutathione peroxidase, catalase, and superoxide dismutase (SOD) - metabolize oxidative toxic intermediates and require micronutrient cofactors such as selenium, iron, copper, zinc and manganese for optimum catalytic activity. It has been suggested that an inadequate dietary intake of these trace minerals may compromise the effectiveness of these antioxidant defense mechanisms. All these play very important role in saliva by keeping free radicals in check thus preventing various oral pathologies particularly periodontitis. The indications of enzymatic antioxidants is they destroying the free radicals that damage cells, promoting the growth of healthy cells, protecting cells against premature, abnormal ageing, it help fight age- related macular degeneration, provide excellent support for the body's immune system. It is contraindicated in pregnant womens. High doses can cause amenorrhoea, polyps ,abortion and inhibition of ovarian steroidogenesis

#### Conclusion

In conclusion, the properties of mainly of the antioxidant have been studied to know their mechanisms and to clarify

their activities. Future researches should continue with the aim of investigating the antioxidants biocompability, pharmacokinetics, pharmodynamics and considerating their pathways on human health. Some antioxidants have more anti-inflammatory activity whereas some have more anti-tumor properties. Nutritional counselling and supplementation may very well reduce inflammation and thereby enhance outcomes of conventional periodontal therapy. The root of cancer control lies in early diagnosis and treatment. The knowledge of antioxidants is helpful in reducing the incidence of oral cancers at early stages though non invasive techniques. The natural products like fruits and vegetables helps in preventing oral cancers at beginning stage. Nutrients will be widely utilized and will play an important role in preventing cancers once their effectiveness is conclusively demonstrated by prospective clinical studies, and when their mechanisms of actions are more obviously understood

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