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ROLE OF ANTIOXIDANTS IN ORAL MEDICINE

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ABSTRACT

The realization that reactive oxygen species and oxidative stress play an important role in the etiology and progression of major human degenerative diseases has triggered enormous and worldwide interest in endogenous and exogenous antioxidants. The 1990's have seen the explosion of interest in antioxidants. The article reviews free radical chemistry, antioxidant systems & their role in human diseases with special reference to oral malignancies & premalignancies.

INTRODUCTION: Even with improved living standard of modern life, many diseases still develop and the factors are likely to be as follows: imbalanced diet, overly consuming high levels of calories, absorbing few fibers, and the lack of vitamins and mineral substances. As a result, the patients of all kinds of chronic diseases are increasing by record numbers.

Free radicals are atoms or molecules that contain one or more unpaired electrons. Many radicals are highly reactive and can function as reducing or oxidizing agents by donating electrons to or removing electrons from other molecules. Small amounts of free radicals are constantly being generated in all living organisms. Although free radicals are potentially harmful to cellular components, a substantial body of evidence supports a role for these highly reactive chemical molecules in fundamental cellular reactions and cell–cycle regulation.

Nature has endowed each cell with adequate protective antioxidant mechanisms against any harmful effects of free radicals for eg., superoxide dismutase (SOD), glutathione peroxidase, glutathione reductase, thioredoxin, thiols and disulfide bonding are buffering systems in every cell. Antioxidants are substances or agents that scavenge reactive oxygen metabolites, block their generation or enhance endogenous antioxidants capabilities [1]. Moureu & Dufraise (1921) introduced the term "antioxygen" to describe these compounds that act catalytically by retarding oxidation [2].

In recent years there is an upsurge in the areas related to newer developments in prevention of diseases specially the role of free radicals and antioxidants. So it will be pertinent to examine the possible role of 'free radicals' in disease and how 'antioxidants' play an important role in their prevention, especially the current status of the subject matter and future prospects.

Free Radicals: Oxygen is a highly reactive atom that is capable of becoming part of potentially damaging molecules commonly called "free radicals." *A free radical can be defined as chemical species possessing unpaired electron* [3]. Free radicals are capable of attacking the healthy cells of the body, causing them to

lose their structure and function. Reactive oxygen species (ROS) is a term which encompasses all highly reactive, oxygen-containing molecules, including free radicals. Types of ROS **(Table 1)** include the hydroxyl radical (OH^-), the superoxide anion radical (SO_2^-), hydrogen peroxide (H_2O_2), singlet oxygen (O^-), nitric oxide radical (NO^-), hypochlorite radical ($HOCl^-$), and various lipid peroxides. All are capable of reacting with membrane lipids, nucleic acids, proteins and enzymes, and other small molecules, resulting in cellular damage [4].

TABLE 1: VARIOUS ROS & CORRESPONDING NEUTRALIZING ANTIOXIDANTS

FREE RADICAL (Reactive Oxygen Species)	CORRESPONDING NEUTRALIZING ANTIOXIDANT
Hydroxyl radical	Vitamin C, Glutathione, Flavonoids, Lipoic Acid
Superoxide radical	Vitamin C, Glutathione, Flavonoids, SOD
Hydrogen peroxidase	vitamin C, Glutathione, Beta Carotene, Vitamin E, CoQ10, Flavonoids, Lipoic Acid
Lipid peroxides	B- carotene, Vitamin E, ubiquinone, flavonoids, Glutathione peroxidas

ROS are generated by a number of pathways. Most of the oxidants produced by cells occur as [5];

1. A consequence of normal aerobic metabolism: approximately 90% of the oxygen utilized by the cell is consumed by the mitochondrial electron transport system.
2. Oxidative burst from phagocytes (white blood cells) as part of the mechanism by which bacteria and viruses are killed, and by which foreign proteins (antigens) are denatured.
3. Xenobiotic metabolism, i.e., detoxification of toxic substances.

Consequently, things like vigorous exercise, which accelerates cellular metabolism; chronic inflammation, infections, and other illnesses; exposure to allergens and the presence of "leaky gut" syndrome; and exposure to drugs or toxins such as cigarette smoke, pollution, pesticides, and insecticides may all contribute to an increase in the body's oxidant load.[5]

Concept of "Oxidative Stress": Increases in the intracellular levels of ROS, frequently referred to as *oxidative stress*. Free radical damage within cells has been linked to a wide range of diseases including arthritis, arteriosclerosis, Alzheimer's diseases and diabetes. Generation of the reactive oxygen species and the activity of the antioxidant defenses appear approximately balanced in vivo, although there seems to be an ongoing oxidative damage. Oxidative stress is said to result if there is a serious imbalance between the two (ROS & antioxidant defenses) [6].

Oxidative Stress and Human Disease: Oxidative damage to DNA, proteins, and other macromolecules has been implicated in the pathogenesis of a wide variety of diseases, most notably heart diseases and cancer. A growing body of animal and epidemiological studies as well as clinical intervention trials suggests that antioxidants may play a pivotal role in preventing or slowing the progression of both heart diseases and some forms of cancer [4].

Conditions associated with Oxidative damages include atherosclerosis, cancer, pulmonary dysfunction, cataracts, arthritis and inflammatory diseases, diabetes, shock, trauma, and ischemia, Renal disease and hemodialysis, Multiple sclerosis, Pancreatitis, Inflammatory bowel disease and colitis, Parkinson's disease, Neonatal lipoprotein oxidation, Drug reactions, Skin lesions & Aging [4].

Oxidative stress in Oral cavity: Several conditions can contribute to oxidative stress in the oral cavity. These include external conditions, such as tobacco smoking and air pollution integrated toxins or internal conditions; including chronic inflammation. In oral tissues, reactive oxygen species are generated as a result of both endogenous and exogenous oxidizing agents. Oxidative species, such as Superoxide, hydrogen peroxide and hydroxyl radical are common byproducts of normal aerobic metabolism. These reactive oxygen species are also generated by the immune system in inflammation or damage tissue such as in chronic periodontitis. In addition to reactive oxygen generated by the host tissue, the oral cavity is also susceptible to reactive oxygen created by inhalation of oxidizing agents in tobacco smoke and air pollution [7].

The realization that *reactive oxygen species* (free radicals) and *oxidative stress* play important role in the etiology and progression of major human degenerative diseases has triggered enormous and worldwide

interest in endogenous and exogenous antioxidants. And the subsequent section deals with ANTIOXIDANTS and their role in systemic & premalignant oral mucosal lesions & conditions and oral cancer.

Antioxidants: Antioxidants are capable of stabilizing, or deactivating, free radicals before they attack cells. Antioxidants are absolutely critical for maintaining optimal cellular and systemic health and well-being.

A biological antioxidant may be defined 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"[8].

Antioxidant Protection: To protect the cells and organ systems of the body against reactive oxygen species, humans have evolved a highly sophisticated and complex antioxidant protection system **(Table 2).** It involves a variety of components, both endogenous and exogenous in origin, that function interactively and synergistically to neutralize free radicals [9].

- Nutrient-derived antioxidants like ascorbic acid (vitamin C), tocopherols and tocotrienols (vitamin E), carotenoids, and other low molecular weight compounds such as glutathione and lipoic acid.
- Antioxidant enzymes, e.g., superoxide dismutase, glutathione peroxidase, and glutathione reductase, which catalyze free radical quenching reactions.
- Metal binding proteins, such as ferritin, lactoferrin, albumin, and ceruloplasmin that sequester free iron and copper ions that are capable of catalyzing oxidative reactions.
- Numerous other antioxidant phytonutrients present in a wide variety of plant foods.

TABLE 2: ANTIOXIDANT PROTECTION SYSTEMS

ENDOGENOUS ANTIOXIDANTS	DIETARY ANTIOXIDATS	METAL BINDING PROTEINS
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		

Significance of Antioxidants in relation to Disease: There are a number of epidemiological studies that have shown inverse correlation between the levels of established antioxidants/phytonutrients present in tissue/blood samples and occurrence of cardiovascular disease, cancer or mortality due to these diseases. However, some recent meta analysis [10] show that supplementation with mainly single antioxidants may not be that effective a view that contrasts with those of preclinical and epidemiological studies on consumption of antioxidant-rich foods. Based on the majority of epidemiological and case control studies recommendations were made for the daily dietary intake of some established antioxidants like vitamin E and C as well as others.

Antioxidant-based drugs/formulations for prevention and treatment of complex diseases like athero-sclerosis, stroke, diabetes, Alzheimer's disease (AD), Parkinson's disease, cancer, etc. appeared over the past three decades. Free radical theory has greatly stimulated interest in the role of dietary antioxidants in preventing many human diseases, including cancer, atherosclerosis, stroke, rheumatoid arthritis, neurodegenerative disorders and diabetes [11].

Antioxidants & Oral mucosal lesions: The evidence in support of a chemopreventive role for the so-called antioxidant nutrients, β- carotene and vitamin E, against oral cavity cancer. Studies suggest the role of antioxidants in treatment of oral mucosal lesions particularly include oral Leukoplakia, oral lichen

planus, oral submucous fibrosis & oral cancer. This evidence is from laboratory studies, animal model systems, epidemiologic surveys, intervention trials involving reversal of premalignant changes, and prevention of malignancies in particularly high-risk subjects. Because agents proposed for disease prevention are meant to be used widely without close medical supervision almost any toxicity is unacceptable.

β-Carotene and vitamin E fulfill this criterion for a suitable chemopreventive agent. In several epidemiologic studies, low intakes of vitamin E, carotenoids, or both have been associated with a higher cancer risk. Smoking, a major risk factor, results in lower β -carotene concentrations in plasma and oral mucosal cells. In several laboratory and animal model systems, β-carotene and other antioxidant nutrients are inhibitors of oral cavity carcinogenesis. β-Carotene and vitamin E can produce clinical regression of oral leukoplakia, a premalignant lesion of oral cavity [12].

Concept of Functional Foods: The very concept of food is changing from a past emphasis on health maintenance to the promising use of foods to promote better health to prevent chronic illnesses*. 'Functional foods'* are those that provide more than simple nutrition; they supply additional physiological benefit to the consumer. Indian food constituents such as spices as well as medicinal plants with increased levels of essential vitamins and nutrients (e.g. vitamin E, lycopene, vitamin C, bioflavonoids, thioredoxin etc.) provide a rich source of compounds like antioxidants that can be used in functional foods [11].

Pro-Oxidant Effect of Antioxidants: It has been known for some time that antioxidants, at high levels and under some conditions in vitro and in foods act as *pro-oxidant* (i.e., which promote generation of oxygen free radicals). For example, ascorbate, in the presence of high concentration of ferric iron, is a potent potentiator of lipid peroxidation. Recent studies suggest that ascorbate sometimes increase DNA damage in humans. Recent mechanistic studies on the early stage of LDL oxidation show that the role of vitamin E is not simply that of a classical antioxidant. Unless additional compounds are present, vitamin E can have antioxidant, neutral or prooxidant activity. β-carotene also can behave as a prooxidant in the lungs of smokers. The paradoxical role (pro-oxidant effect) of antioxidants is also directly related to the recently described 'redox signaling' of the antioxidants. The functional role of many antioxidants depends on redox cycling. Whether antioxidants from our diet and especially high levels from nutritional supplements, have pro-oxidant effects in humans remains a matter of scientific debate and controversy [13].

The Importance of Balance: Although much of the research to date focuses on the potential benefit of single antioxidant nutrients, it has become clear that the best protection against oxidative stress comes from a wide assortment of interrelated antioxidants and antioxidant cofactors [9]. In other words, the human body utilizes an integrated antioxidant system composed of several players that work together as a team. The reducing potential of each individual member of the antioxidant defense team is enhanced when a full complement of players is available.

For example, some evidence suggests a poor concentration of any single one of the antioxidants vitamin C, vitamin E, or beta carotene, appears to increase the risk of cardiovascular disease. Additionally, the combination of several suboptimal concentrations may have an additive or even synergistic affect on increasing risk. Conversely, it has been suggested that, under certain conditions, an excess of any one type of antioxidant in the absence of balance with the others may actually be counter-protective [14].

Recent Advances:

- **Nitric Oxide: A New Regulator of Oxidative Stress:** Nitric oxide (NO), discovered to be produced by mammalian cells only in the past decade, is a regulatory molecule that has come under increasing interest and scrutiny due to its role as an important mediator of homeostatic processes and immunity [8]. NO is believed to participate in the regulation of the oxidation/ reduction potential of various cells and may be involved in "either the protection against or the induction of oxidative stress within various tissues, depending upon its concentration."

Emerging evidence suggests that some diseases are related to either an inadequate or excessive production of NO [15].

CONCLUSION: 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 can protect against the damage induced by free radicals acting at various levels. The focus should not be on treating various diseases with antioxidants, but on the intake of a balanced diet with emphasis on antioxidant-rich fruits, vegetables, nuts, whole grains as has been recommended for the general population. It is therefore suggested that serious attention be given to all these factors when designing future studies that are aimed at evaluating the potential role of antioxidants in the prevention of various diseases.

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