



Role of Antioxidants in Oral Cancer and Oral Lesions–Literature Review

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[Review Article](#)

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Crossref doi: <https://doi.org/10.36437/ijdrd.2020.2.4.1>

ABSTRACT

The successful control of oral cancer will depend on its prevention. Main Prevention measures are discontinuing tobacco use and the use of various nutritional agents containing antioxidants. The antioxidants can be endogenous or obtained exogenously as a part of a diet or as dietary supplements. Antioxidants are molecules that inhibit oxidation of other molecules, thereby preventing the formation of free radicals.¹

Keywords: Oral Cancer, Antioxidants, Free Radicals.

Introduction

Oral cancer is one of the major global threats to public health. Many oral carcinomas arise within regions that previously had premalignant lesions. A large majority of oral cancers are squamous cell carcinomas. As defined by WHO “oral squamous cell carcinoma” is an extensive epithelial neoplasm with varying degrees of squamous differentiation and a propensity of early and extensive lymph node metastasis occurring predominantly in alcohol and tobacco using adults in the 5th and 6th decades of life. Recent epidemiological studies have suggested that oral cancer development varies in different areas of the world with South Asia showing the highest incidence of oral cancers accounting for 18% of all cancers.²

Types of Free Radicals

Free radicals are continuously produced in our bodies.³ When cells use oxygen to generate energy free radicals are produced by the mitochondria. Once formed these highly reactive radicals can start a chain reaction. This process is called peroxidation. Peroxidation is useful because the body's immune system purposefully create them to destroy germs and parasites. However, peroxidation, when left unchecked, also destroys or damages healthy cells. The by-products formed are generally reactive oxygen species (ROS) and reactive nitrogen species (RNS) that result from the cellular redox process. The free radicals have a special affinity for lipids, proteins, and nucleic acid (DNA).⁴

ROS/RNS can have Following Effects:

- Cause structural damage to the DNA (base-pair addition, deletion, sequence amplification, etc.)
- Cause intracellular damage (phospholipid and protein breakdown) along with cytoskeletal damage.
- Affects cytoplasmic and nuclear signal transduction pathways which further dysregulates the extrinsic and intrinsic pathways of apoptosis.⁵

Formation of Free Radicals

There are a few important sources of free radical formation. Normal cellular metabolisms like mitochondrial electron transport chain, endoplasmic reticulum oxidation, and many enzymatic activities. Some external factors like radiation, oxidation of engine exhaust, carbon tetrachloride, cigarette smoke, and oxygen also cause the production of free radicals.⁶

Mechanism of Action of Antioxidants

Free radicals are atoms or groups of atoms with an odd (unpaired) number of electrons and can be formed when oxygen interacts with certain molecules. The free radicals can also cause harmful chain reactions and that are responsible for cell damage or cell death, which in turn leads to carcinogenesis. Antioxidants neutralize these radicals by donating their electrons thereby ending the electron-taking reaction. The antioxidant nutrient does not become a free radical by donating an electron because they are stable in either form.⁶ Thus antioxidants work by binding to the free radicals and transforming them into non-damaging compounds. They are also capable of deactivating free radicals before they attack the human cells. More importantly, antioxidants return to the surface of the cell to stabilize the cell membrane and prevent damage to other cellular components.⁷

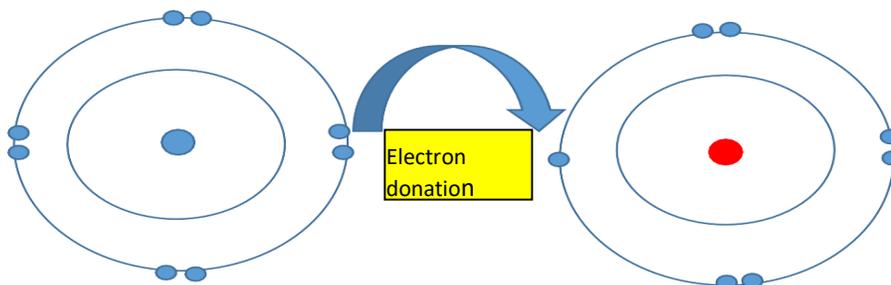


Figure: 1

Role of Antioxidants in Oral Cancer

- ✓ Inhibits oral carcinogenesis
- ✓ Reduces the risk of developing oral cancer.

- ✓ Causes reversal of premalignant lesion like oral leukoplakia.

Antioxidants with electrons paired

Free radicals with electrons unpaired

The development of cancer in humans is a complex process including cellular and molecular changes mediated by various endogenous and exogenous stimuli. It is well known that oxidative DNA damage is responsible for cancer development.^{8,9,10} Cancer initiation and promotion are associated with chromosomal defects and oncogene activation induced by free radicals. Free radicals are highly reactive and are capable of damaging almost all types of biomolecules.^{11,12} A common form of damage is the formation of hydroxylated bases of DNA, which are considered an important event in chemical carcinogenesis.⁸ Oxidative DNA damage produces modifications in the DNA structure including base and sugar lesions, strand breaks, DNA-protein cross-links, and base-free sites. A highly significant correlation is seen between consumption of fats and death rates from leukemia and breast, ovary, rectum cancers among elderly people may be the reflection of greater lipid peroxidation.^{13, 14}

Endogenous antioxidants play an important role in maintaining optimal cellular functions and thus systemic health and wellbeing of an individual. However, under certain conditions endogenous antioxidants may not be sufficient and dietary antioxidants may be required to maintain optimal cellular functions. The most efficient endogenous enzymatic antioxidants are glutathione peroxidase, catalase, and superoxide dismutase. To reduce the risk of oral and pharyngeal cancer 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, beta -carotene, lycopene, Vitamin C, vitamin E (alpha-tocopherol), Zinc and Selenium.¹⁵

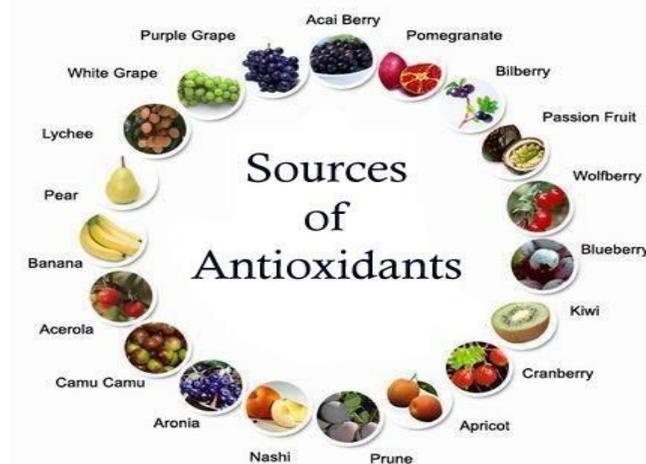


Figure2

Now, these supplements are also available in the form of gel, capsule, drops, and tablets. And also dental manufacturers have incorporated antioxidant formulations into toothpaste, mouth rinses/mouthwashes, lozenges, fluoride gels, dentifrices, oral sprays, and other dental products for the control of gingival and



periodontal diseases.¹⁶ Recent studies also suggest that topical use of antioxidants are very much effective in the skin and oral cavity.¹⁷

Antioxidants show preventive and therapeutic potential in many stages of oral carcinogenesis. They are considered scavengers of free radicals. In oral squamous cell carcinoma, a recent study has suggested that antioxidants can 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 tumor's blood supply or by cellular differentiation.¹⁸ Antioxidants can act as an adjunctive aid in the treatment of dysplastic lesions. They can also decrease the toxicities of specific therapies in cancer.¹⁹

Antioxidants and Premalignant Lesions

Reversal or suppression of premalignant lesions is an important strategy against carcinogenesis for the prevention of cancer. Various studies showed the chemopreventive role of antioxidant nutrients such as beta carotene and Vit E against oral cancer.²⁰ Vitamins such as A, Beta carotene, C, E, B12, and folate are the micro Nutrients which show an important role in cancer prevention and control. The deficiency of these vitamins will interact with tobacco use and increased the risk of oral precancerous lesions. The use of Vit A supplements in the treatment of oral leukoplakia began in the early 1960s. It was noted that the administration of 3-9 lakhs IU of Vit A per day resulted in partial or complete resolution of leukoplakia.²¹ A population-based case-control study from Japan showed that males with leukoplakia had significantly lower levels of serum lycopene and beta carotene than controls.²⁰

Antioxidants are also effective in treating oral submucosal fibrosis. Dietary antioxidants can protect the lipids and other membrane molecules against oxidative damage by intercepting oxidants before they try to destroy the tissues. Antioxidants such as Vitamin C and Vitamin E may be utilized in oral Lichen planus patients to counteract free radical-mediated cell.²²

Classification of Antioxidants

Endogenous antioxidants in cells can be classified as enzymatic and nonenzymatic antioxidants.^{23, 24}

Types of Antioxidants Vitamin C

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, and tomatoes. Vitamin C shows a protecting effect for cancer of the stomach and upper aerodigestive tract.²⁵ Vitamin C has antioxidantizing properties and reacts with superoxide produced as a result of the cell's normal metabolic processes, this inactivation of superoxide inhibits the formation of nitrosamines during protein digestion and helps to avoid damage to DNA and cellular proteins.²⁶

Vitamin E

Tocopherol is the commonest and most active form of vitamin E. It is found in plant oil, margarine, and green leaves. Tocopherol is an effective antioxidant at high levels of oxygen, protecting cellular membranes from lipidic peroxidation. The main actions of Tocopherol are free radical scavenging, maintenance of membrane integrity, inhibition of cancer cell growth/differentiation, inhibits mutagenicity and nitrosamine formation, inhibition of DNA and RNA, and protein synthesis in cancer cells. Studies by Balwant Rai et al (2008) have proved that antioxidants such as Vitamin C and Vitamin E may be utilized in oral Lichen planus, leukoplakia, and oral cancer patients to counteract free radical-mediated cell disturbances.²⁷



Beta-carotene

A precursor of vitamin A has antioxidant and free radical scavenging property. It also helps in immunomodulation, promotes an increase in the numbers of T-helper and NK cells as well as cells with IL-2 receptors and inhibits mutagenesis and cancer cell growth.²⁸ Beta carotene is used for scavenging free radicals in areas of low oxygen concentration. Results from a recent study have demonstrated that one-third of patients (15 out of 46) that used 360 mg betacarotene per week during 12 months presented a complete resolution of oral leukoplakia.²⁹

Lycopene

Lycopene can prevent carcinogenesis by protecting cellular biomolecules, including lipids, lipoproteins, proteins, and DNA. Lycopene, when given in the dosage of 4.8 mg/day orally for three months, leads to the reversal of dysplastic changes in leukoplakia and when given in the dosage of 16 mg/day leads to a substantial increase in the mouth opening in oral submucous fibrosis. The major dietary source of lycopene in tomato. Lycopene also has the capacity to modify intercellular exchange junctions, and this is considered to be an anticancer mechanism.^{30,31}

Selenium: Selenium is important in cell signaling and immune reactions, which may furnish to its cancer chemopreventive potential.³² Selenium and vitamin E may act synergistically to slow down carcinogenesis. The amount of selenium that is in our food is estimated by the selenium content of the soil in which fruits and vegetables are grown. Seafood, liver, and meat are also good sources of selenium.³³

Isoflavones: They have antiestrogenic effects, and thus could act as chemopreventive agents in hormone-dependent cancers. Genistein is a prominent isoflavone in soy foodstuffs known to promote apoptosis *in vivo*.³⁴

Curcumin: It can prevent DNA damage and is involved in apoptosis.³⁵ A number of animal studies have shown that curcumin is effective in inhibiting carcinogenesis in the skin, colon, stomach mammary gland, and oral cavity.³⁶ This is used as a spice.

Omega -3 and Omega -6 Fatty Acids

Omega -3 fatty acids help to reduce inflammation and prevent chronic ailments such as heart disease, stroke, memory loss, depression, arthritis, cataract, and cancer. But omega -6 fatty acids tend to promote inflammation and improve diabetic neuropathy, eczema, psoriasis, osteoporosis, and aid in cancer treatment.³⁷

Vitamin D

Vitamin D alters the expression of several oncogenes, reduces lipid peroxidation and angiogenesis, and induces differentiation.³⁸ Epidemiologic studies support an inverse association among vitamin D intake and colorectal cancer risk.³⁹

Folic Acid

Together with vitamin B12, methionine, and choline, folic acid is involved in methyl group metabolism. Much of the basic cancer research has focused on DNA methylation.⁴⁰ A converse association involving dietary folate intake and adenomatous polyps or colorectal cancer has been stated.⁴¹



Green Tea Catechins/Polyphenols

Green tea causes reversible G1 arrest of the cell cycle by Inhibition of Rb phosphorylation in oral leukoplakia.⁴² Green tea polyphenols were able to induce apoptosis in oral squamous carcinoma cells, while normal human epidermal keratinocytes survived.⁴³ Topical application of green tea extract has been shown to reduce the thickness of oral leukoplakia.^{44,45}

Superoxide Dismutase (SOD)

Superoxide dismutase is an endogenously produced intracellular enzyme present in every cell in our body. Cellular superoxide dismutase is represented by a group of metalloenzymes with various prosthetic groups. The prevalent enzyme is cupro-zinc (CuZn) SOD, which is a stable dimeric protein. SOD is considered fundamental in the process of eliminating free radicals by reducing (adding an electron to) superoxide to form H₂O₂.

Catalase and the selenium-dependent glutathione peroxidase are responsible for reducing H₂O₂ to H₂O.

Glutathione Peroxidase

In the next step, the H₂O₂ thus generated is removed by glutathione peroxidase (POD). It is a selenium containing enzyme.



Glutathione Reductase

The oxidised glutathione, in turn, is reduced by the glutathione reductase (GR), in presence of NADPH. This NADPH is produced with the help of G-6 PD in HMP shunt pathway. Therefore in G6-PD deficiency, the RBC's are liable to lysis.

Catalase

When H₂O₂ is generated in large quantities, the enzyme catalase is also used for its removal.

Catalase



Glutathione the Master Antioxidant

Glutathione is the most powerful cancer-curbing, age-slowng nutrients ever discovered. Glutathione is the most powerful antioxidant occurring naturally in all of the 70-100 trillion cells that make up the human body. That is why Glutathione is called the Master Antioxidant (MA). The effectiveness of all other antioxidants like Vitamin A, Vitamin C, Vitamin E, and Selenium all depend upon the availability of Glutathione.

Detoxification

Glutathione is also known as the toxic waste neutralizer of the body. In the liver, it will neutralize toxic pollutants and even carcinogens and eliminate them from the body. Most prescription drugs have negative side effects upon the liver, which Glutathione has been shown to alleviate. It is also beneficial in drug overdoses, chemotherapy, and radiation exposure.⁴⁷

Oral Oxidants and Antioxidants

Oral oxidants lead to the transformation of a normal cell into a neoplastic cell. Saliva in the oral cavity contains a number of nutrients and microorganisms and it is constantly exposed to a variety of oxidants. To counter the toxic effects of these oxidants, saliva has antioxidants like uric acid, ascorbate, reduced



glutathione, and alpha-tocopherol, which are delivered to saliva through the crevicular fluid of gingiva.⁴⁸ Uric acid is the major component of the salivary antioxidant system constituting 70% of the total antioxidant capacity.⁴⁹ Additional sources of antioxidants in the oral cavity are catalase-positive commensal and fresh blood from injured capillaries.⁴⁸

Periodontology

Antioxidants change the progress of periodontitis and gingivitis by compromising the antioxidant capacity of crevicular fluid and plasma. One of the conditioning factors for gingivitis is an ascorbic acid deficiency.⁵⁰ Plant oils and green, leafy vegetables can break free radical chain reactions thus may contribute to reducing periodontal inflammation. Flavanoids possess anti-inflammatory properties that reduce the expressions of monocytes within the gingival connective tissues.⁵¹

Conservative Dentistry

The imbalances in levels of free radicals, reactive oxygen species, and antioxidants in saliva play an important role in the onset and development of dental caries. Salivary peroxidase brings control over oral bacteria which can cause dental caries. Salivary peroxidase catalyzes the peroxidation of thiocyanate ion (SCN⁻) to generate oxidation products (more stable OSCN); this inhibits the growth and metabolism of many micro-organisms thereby inhibiting caries or slowing down the progress of caries.⁵² It was reported that green teas have a scavenging effect on dental caries prevention. Cranberries were capable of having antibacterial activity against *Streptococcus mutans* and stopping dental caries. In the restorative treatment of caries, to increase bond strength of composites, grape seed or pine bark extract solutions can be used, especially to raise decreased bond strength values for restorative treatments after bleaching.⁵⁴

Orthodontics

In bracket bonding, to increase bond strength ascorbic acid solutions were used. The effect of antioxidants on bone formation was statistically significant.^{54,55}

Oral Surgery

Sheresta et al. stated that grape seed extract has a positive effect on treating peri-implantitis.⁵⁶ For bone healing and bone formation, it was reported that caffeic acid phenethyl ester which can be found in propolis has significantly improved bone healing in rat models.⁵⁷

Oral Medicine and Oral Pathology

Antioxidants show preventive and therapeutic potential in many stages of oral carcinogenesis. Antioxidants have an ability to reduce cell growth and proliferation of oral carcinomas and effective in treating various oral lesions.⁵⁷

Advantages of Antioxidants

Dietary antioxidants protect us from the harmful effects of free radicals. Different antioxidants show different levels of effectiveness due to their different molecular structures.⁵⁸

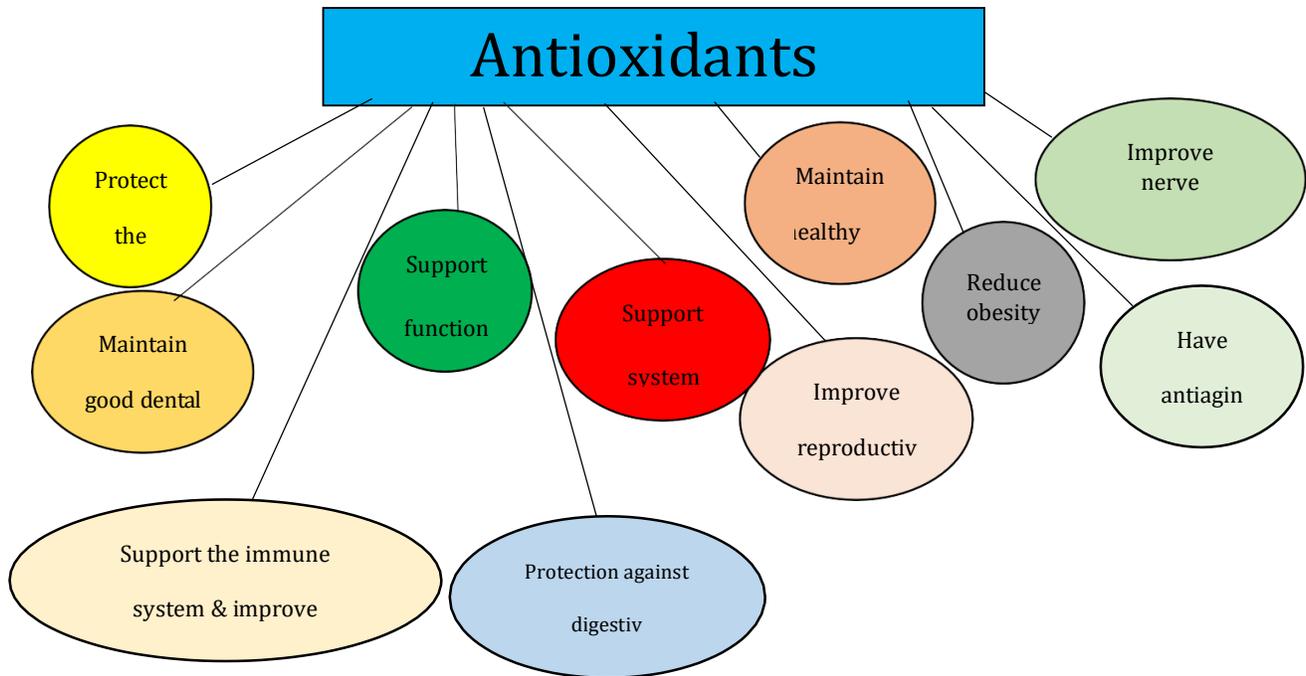


Figure: 3

Limitations of Antioxidants

Current literature reports the lack of predictability of antioxidant therapy and it has not been validated by the scientific method. High doses of vitamin A and vitamin E can cause health risks such as toxic and teratogenic effects. Large doses of vitamin C may be associated with inhibition of ovarian steroidogenesis and an increased probability of abortion. Drug interactions are other problems with using antioxidants.³¹

Conclusion

The knowledge of antioxidants is useful in reducing the incidence of oral cancers at initial stages. Recent clinical studies have shown the beneficial effects of these antioxidants in oral leukoplakia, and other oral precancerous lesions. Hence, natural products like fruits and vegetable supplements in disease prevention remain unsolved. Further research is needed before this supplementation could be officially recommended as adjuvant therapy. In the meantime, it is reminded that avoiding oxidant sources (cigarettes, alcohol, bad food, stress, etc) must be considered as important as taking a diet rich in antioxidants. Indeed, our health also depends on our lifestyle choice.

Note: Free yourself from free radicals, Eat more fruits and vegetables.



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How to cite this Article: Nirupa Thomas, Lekshmi Venugopal, Tibin K. Baby, Lisa Elizabeth, Anju Mathew; *Role of Antioxidants in Oral Cancer and Oral Lesions- Literature Review*; *Int. J. Drug Res. Dental Sci.*, 2020; 2(4): 61-72, doi: <https://doi.org/10.36437/ijdrd.2020.2.4.J>

Source of Support: Nil, **Conflict of Interest:** Nil.

Received: 20-8-2020 **Revised:** 29-10-2020 **Accepted:** 2-11-2020