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Antioxidants in Endodontics

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ABSTRACT

In recent years, free radical chemistry has received a great deal of attention. Our body generates Free radicals as reactive oxygen species (ROS) and reactive nitrogen species (RNS) by various endogenous systems and exposure to various physiochemical conditions or pathological states. Oxidative stress results if free radicals overwhelm the body's ability to regulate them. Free radical thus decreases lipids, proteins, and DNA and leads to number of human diseases. Hence use of external source of antioxidants can help to overcome this oxidative stress. Over the past years, the free radicals and antioxidants have gained tremendous importance in the era of dentistry. These free radicals in the body, can be beneficial or hazardous. Antioxidants are the substances that coincide with and stabilize free radicals thereby guarding and sheltering cells from the harm caused by free radicals. The present article represents a review how free radicals are formed, their interaction in disease pathogenesis, and their potential use in endodontics.

Keywords: Free radicals, antioxidants, endodontics.

INTRODUCTION

An antioxidant is molecule that can hinder oxidation of other molecules. Free radicals are generated by oxidation of molecules. These radicals can cause harmful chain reactions which are responsible for cell damage or cell death, and can be capable of carcinogenesis or low-density lipoprotein (LDL) oxidations in cardiovascular diseases. Antioxidants acts by neutralizing these radicals by donating their electrons, ending the electron accepting reaction. Oxidative stress is an important characteristic feature in many diseases. The major free radicals that damage biological mechanisms are oxygen-free radicals which are called as 'reactive oxygen species' (ROS)(1). Oxygen is an important element of life, and can act both so as to promote and also can deteriorate the health of the body. Gershman's free radical theory of oxygen toxicity in 1954 explains the poisonous effect , which proves that the toxicity of oxygen is due to partially or incompletely reduced forms of oxygen(2). ROS scavengers/ antioxidants are mainly of prime importance for preceding and dominating human diseases by counteracting ROS formation. Antioxidants help by preventing the harmful effects of ROS by reacting with oxygen(3).

FREE RADICALS

Any molecular species which are capable of independent existence which contains an unpaired electron in an atomic orbital are responsible for the formation of free radicals. These unpaired electron results in sharing some certain common properties that are distributed by most radicals. Many of these radicals are unstable and highly reactive. They can either give away an electron to or accept or gain an electron from other molecules, therefore mimicking as oxidants or reductants.(4).

Role of free radical production in the human body

External sources such as exposure to X-rays, ozone, smoking cigarette, pollutions from air, and industrial chemicals or normal essential metabolic processes in

the human body are some sources where free radical and other ROS are obtained.(5)Free radical formation occurs repeatedly in the cells as a result of both enzymatic and nonenzymatic reactions. Enzymatic reactions, which serve as source of free radicals, contain those which involved in the respiratory chain, in phagocytosis, in prostaglandin synthesis, and in the cytochrome P-450 system.(6) nonenzymatic reactions of oxygen with organic compounds can also form free radicals as well as those initiated by ionizing reactions.

Some sources of free radicals generated internally are(7)

Mitochondria
Xanthine oxidase
Peroxisomes
Inflammation
Phagocytosis
Pathways like arachidonate pathways
Exercise
Ischemia or reperfusion injury
Sources generated externally as free radicals are:
Cigarette smoking
Environmental pollutants
Radiation
Certain drugs, pesticides
Industrial solvents
Ozone

Sources of Free Radical found in Dental Therapy (8)

commonly used dental materials in dentistry which may form free radicals are as:-

Bleaching agents
Composite fillings
Dental cements
Ceramic restoration
Metals in restoration
Dental implants
Intracanal medicament

Classification of anti-oxidants(9)

1. **Enzymatic:** Superoxide dismutase, Glutathione Peroxidase, Selenium enzyme, Catalase enzyme, Glutathione reductase enzyme, enzyme Glutathione transferase
2. **Non-enzymatic:** They are further subdivided into two.

Nutrient such as : Alpha tocopherol, β- Carotene Ascorbate, Glutathione, Selenium, Proanthocyanidin, Lycopene or tomato extract, Green tea

NonNutrient such as: Ceruloplasmin extract, Transferrin, uric acid, Peptides Camosine Anserine Vitamin E, catechins, flavonoids, gallic acid derivatives, salicylic acid derivatives, cinnamic acid derivatives chlorogenic acid, resveratrol, folate, curcumin, caffeine, anthocyanins and tannins are some of the examples of polyphenolic natural antioxidants derived or obtained from plant sources.
Non-phenolic secondary metabolites such as melatonin, carotenoids, thiols, jasmonic acid, retinal, ei-cosapentaenoic acid, ascopyrones and allicin that show excellent antioxidant activity (10).

Mechanism of Action of Antioxidants (11)

Antioxidants act by ending the electron stealing action of free radicals by donating one of their electrons. The antioxidant itself does not become a free radical by donating an electron as they are unchangeble in any form. Antioxidants action takes place by scavenging or chain breaking, some of the examples are as Vitamin E such as (alpha tocopherol), Vitamin C as(ascorbic acid), or Vitamin A as (beta carotene) and preventative antioxidants that function primarely by sequestering action by transition of metal ions and preventing fenton reactions and are therefore predominantly proteins by nature for e.g., albumin, transferrin, or lactoferrin.
Commonly used antioxidants are:

Lycopene:-

Lycopene extract is one of the most potent and effective antioxidants primarily found in tomatoes (12). Lycopene present in the form of the red pigment of tomato, which chemically is a tetra-terpene assembled from eight isoprene units composed and enveloped entirely of carbon and hydrogen, also containing 11 conjugated and two non-conjugated carbon–carbon double bonds (13). Mageshwaran et al., explained the neutralizing effect and result of proanthocyanidin (grape seed extract) and lycopene extract (tomato extract) on reactive oxygen species (ROS) especially created by the mixture when used as an intra canal medicament. Lycopene has shown more antioxidant potential when compared with proanthocyanidin (14).

Proanthocyanidin (Grape Seed Extract):-

Oligomeric proanthocyanidin complexes which is grape seed extract (OPCs) are primarily known for their antioxidant activity. However, they are also reported as compounds having anti-bacterial, anti-viral, anti-carcinogenic, anti-inflammatory, anti-allergic, and vasodilatory actions (15). Manimaran et al., studied the application of proanthocyanidin agent (PA) which act by improving the bond strength of root dentin when it is treated with sodium hypochlorite (NaOCl). The results concluded by demonstrating that 5.25% NaOCl can cause

significant reduction ($p<0.05$) in the bond strength, but this can be reversed or vice versa if 5% PA is significantly more than the 10% sodium ascorbate (16). Study done by Abraham et al has demonstrated the beneficial effect of grape seed extract (oligomeric proanthocyanidin complexes {OPCs}) action on the bond strength of composite resin to bleached enamel by using 5th and 7th generations of dentin bonding agents. Results showed that use of grape seed extract as an antioxidant agent after bleaching significantly improves the bond strength of composite resin to the bleached enamel. 5th generation bonding agents have shown higher shear bond strength of composite resin to enamel (17). Another study investigated that the long-term resin-dentin bond strength of dentin biomodified by proanthocyanidin-rich (PA) agents. Higher μTBS were seen for 6.5% grape seed extract (GSE) immediately (SB- 62.9MPa; OS- 51.9MPa) when it was compared with 6.5% cocoa seed extract and , ethanol-water(CSE-ET) (SB- 56.95MPa; OS- 60.28MPa), 6.5% cocoa seed extract acetone-water(CSE-AC) (SB- 49.97MPa; OS- 54.44MPa), and distilled water (CO) (SB- 52.0MPa; OS- 44.0MPa). GSE and CSE-ET agents also showed improved and enhanced immediate adhesion action and stabilization to demineralized dentin after long-term storage, depending on adhesive system (18).

Alpha-Tocopherol:-

Vitamin E is fat soluble antioxidant generally considered the most important and effective lipid soluble antioxidant which helps in maintaining and helping cell membrane integrity from lipid and also in decreasing wound-healing time (19) Invitro study done by Sasaki RT, Flório FM, Basting RT reveals that the shear bond strength of human enamel and dentin submitted to a bleaching treatment with 10% carbamide peroxide and also treating with antioxidant agents containing 10% α-tocopherol and 10% sodium ascorbate formulated as in solution and gel. Results which were observed showed that the antioxidant treatment with 10% α-tocopherol solution was the only agent that was effective to revert the oxidizing effects of the bleaching treatment on enamel (20). Some studies also compared the composite bond strength to carbamide peroxide bleached enamel followed by the application and use of 10% and 25% sodium ascorbate with alpha-tocopherol solutions. Result showed that soon after the 10 min application of 10% and 25% sodium ascorbate along with 25% alpha tocopherol solutions significantly enhanced and improved the shear bond strength of composite resin when applied to enamel (21). Alpha tocopherol also allowed free-radical polymerization of the adhesive resin to proceed the action without incomplete premature termination by restoring the altered or reduced redox potential of the oxidized bonding substrate shows results with improve resin bonding (20,22).

ASCORBATE:-

L-ascorbic acid (AA) is water soluble vitamin which is white to light-yellow,(23) commonly known as vitamin C. Sodium ascorbate (SA) is a salt of Ascorbic Acid. Both Ascorbic Acid and Sodium Ascorbate have shown antioxidant properties. An amount of 10 wt % AA solution possesses an acidity of approximately to pH 2 (23, 24), whereas SA is a neutral biocompatible antioxidant (25). An AA solution gradually oxidizes and becomes less reductive (24).

It is known that AA helps in enhancing the dentin bonding strength of adhesive resins when used and applied on dentin surfaces as an experimental conditioner for C&B Metabond (23). SA is known to enhance the bonding strength of adhesive resins on dentin surfaces treated with sodium hypochlorite (NaOCl) in endodontic procedures and operative dentistry (26-27). Morris et al. reports stated that there was no statistical variation between AA and SA in terms of their effect on bonding strength (28).

Effective bonding strength is thought to occur while the dentin collagen changes from an oxidized substrate to a decreased substrate, which regains its redox potential. Regarding dentin bonding strength in general, it is known that an optimally moist dentin surface area improves and enhances the bond strength of an adhesive system; thus, wet bonding techniques are employed and used in the clinical setting (29,30). Dentin surface moisture can also be influenced by dentin body moisture, which comparitively varies significantly in reference to various tooth conditions. While it is known that AA and SA help in promoting the bonding strength, it is also not known whether dentin body moisture changes are either caused by AA and SA.

Recently, dentin bonding studies and research has variably expanded to the field and era of endodontics because long-term endodontic treatment prognosis is believed to rely on the prevention of apical along with coronal leakage (31,32). To enhance the effect of hydraulic seal, the option as resin-based adhesive bonding obturation system (33,34) have been developed for use in clinical endodontics.

Vongphan N et al studied the effect of microtensile bond strengths of all together complete total etching adhesive systems to pulp chamber wall dentine after treated with various irrigants. They concluded to state that SA significantly help to improved the bond strengths of NaOCl treated root dentine(35)

Park et al., determined appropriate application and duration of sodium ascorbate (SA) antioxidant gel

results in minimicing microleakage of bonded composite restoration for intracoronally-bleached teeth. Application of SA gel also showed that for three day after nonvital bleaching was significantly effective in minimicing microleakage of composite restoration for intracoronally-bleached teeth (36)

Antioxidants role in restorative dentistry:-

It was revealed that green tea's epigallocatechin-3-gallate molecule have good scavenging effect on dental caries prevention. Cranberries, especially their Type A oligomers, were reported having effective antibacterial action against facultative anaerobic, cocci i.e Streptococcus Mutans and also helps by prevention of dental caries (37). Also as In the restorative management of caries, to increase bond strength of composites, use of grape seed extract or pine bark extract solutions can be performed, especially to increase the lowered bond strength values for restorative treatments after bleaching procedures (38,39).

Antioxidant questionnaires':-

Although many studies has mentioned the importance of antioxidants and its role in treating oral-dental problems, there are some questionnaires need to be studied more. primarily, the amount of effective antioxidants has not been clearly investigated and it varies among populations or species which are studied. (40).

Drug interactions can also be one of the problems while using antioxidants. Simply if any drug helps in enhancing free radical activity, the usage of antioxidants will neutralise this effect. In literature, some studies ans research related to antioxidants have a standardization issues. The studies also lack in determining the accurate protocols for quality control and quality parameters in standardizing antioxidants with respect to potency and safety (41). Moreover, many of the studies done are *in vitro* or animal studies and there are very few clinical studies for its use.

For the selection of antioxidant treatments or their support, a practitioner should be answerable to some questions. Are there enough convincing n appropriate studies in literature to promote your case? Do we clearly understand the adverse effects of the antioxidant which has been choose? Has oxidative damage been implicated in the illness' pathophysiology? In tissue level, do we exactly know the place where the oxidative damage actually takes place? Will our chosen antioxidant get to that area?

CONCLUSION:

Most of the antioxidant have been studied and understand by their mechanisms to clarify their activities. We see numerous studies promoting and advocating the use of antioxidants based supplements for their clinical usage in endodontics routine practice. Antioxidants prevent free radical induced tissue damage by preventing the formation of radicals, through scavenging them, or by promoting their decomposition. The research for effective, nontoxic natural compounds with antioxidative action has been intensified in recent years. Ascorbate, alpha-tocopherol, proanthocyanidin are some of the few which are used till date and showed good antioxidant property. Further research and studies has to be done to know the optimum level and criteria of anti-oxidants and their safest application and use in routine endodontic practice.

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