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REVIEW ARTICLE

DESTRUCTIVE ROLE OF REACTIVE OXYGEN SPECIES AND PROTECTIVE ROLE OF ANTIOXIDANTS IN PERIODONTITIS: A SHORT REVIEW

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ABSTRACT

Free radicals are the molecules or molecular species containing one or more unpaired electrons with independence existence. Reactive Oxygen Species are constantly formed during normal cellular metabolism (lipid peroxidation) and due to various environmental influences (ionizing radiations). Free radicals are highly reactive, capable of damaging almost all type of bio-molecules, and have been implicated in the causation of many diseases including periodontitis. To mitigate the harmful effects of free radicals, the aerobic cells have developed antioxidant defense mechanism- enzymatic antioxidants (superoxide dismutase, catalase) and non-enzymatic antioxidants (Glutathione, selenium, α-tocopherol, β-carotene).

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INTRODUCTION

Oxygen (O_2) forms a life support system as this is absolutely essential for existence and survival of higher organisms. Energy is life and the production of energy in the body depends upon oxygen. It also combines with the metabolic waste products to facilitate their elimination from the body, which forms the part of oxidation-reduction cycle. However, very high concentrations of O_2 are found to be toxic and detrimental to the tissues (Satyanarayana *et al.,* 1999). Periodontitis has been defined as, "an infectious disease resulting in inflammation within the supporting tissues of the teeth with progressive attachment loss and bone loss" (Flemmig, 1999). This inflammatory process is initiated by periodontal plaque, in which the Gram-negative, anaerobic or facultative bacteria are predominant (Dibart *et al.,* 1998; Dzink *et al.,* 1989). Acute inflammatory cells like neutrophils protects local tissues by controlling the periodontal microbiota within the gingival crevice and junctional epithelium. Neutrophils engulf the bacteria by the process of phagocytosis resulting in entrapment of bacterial cell into membrane delimited structure known as phagosome. Bacteria within the phagosome may be killed by oxidative or non-oxidative mechanisms (Kenney and Ash, 1969). Oxidative mechanism of neutrophils and other phagocytes involve production of reactive oxygen species(ROS) (Roos *et al.,* 2003).

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Various sources of ROS

Exogenous sources

Heat, trauma, ultrasound, ultraviolet light, ozone, smoking, exhaust fumes, radiation, infection, excessive exercise and therapeutic drugs (Chapple and Matthews, 2000).

Endogenous source

a. **Bi-products of metabolic pathways:-**During cell metabolism, electrons leak from their transporters at a constant rate during the process of glycolysis, reducing oxygen to superoxide anion (Chapple and Matthews, 2000).
b. ROS can also be generated by phagocytes and cells of the connective tissue. The process comprises the "respiratory burst" and is stimulated by a variety of mitogens or antigens (Weighardt *et al.,* 2000).

Generation of ROS by phagocytes (Figure 1)

During the course of phagocytosis, inflammatory cells, particularly phagocytes produce Superoxide (O_2^-) by a reaction catalyzed by NADPH oxidase. This O_2^- radical gets converted to H_2O_2 and then converts to Hypochlorous acid (HClO). The superoxide radical along with hypochlorous ions brings about bactericidal action. This represents the beneficial effects of the

free radical generated by the body. A large amount of O_2 is consumed by the phagocytes during their bactericidal function, a phenomenon referred to as Respiratory Burst. About 10% of the O_2 taken up by phagocytes is utilized for the generation of free radicals (Satyanarayana and Chakrapani, 1999).

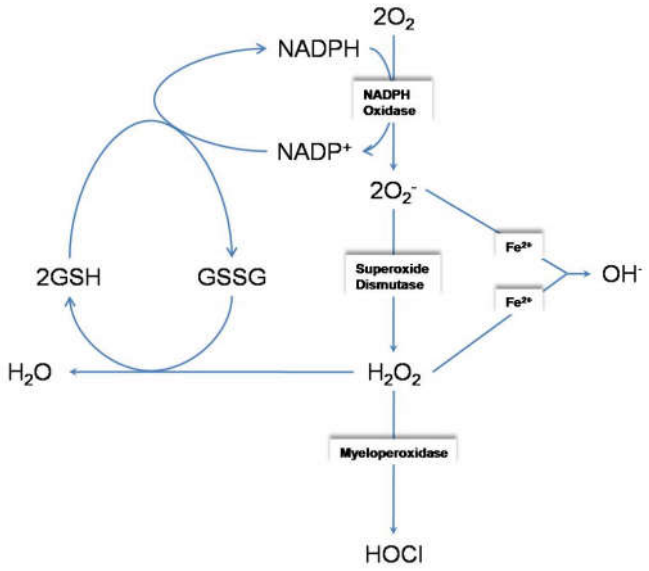

Figure 1.

General characteristics of free radicals

- Highly reactive
- Very short half life
- Can generate new radicals by a chain reaction
- Cause damage to biomolecules, cells and tissues

Destructive effects of free radicals

Free radicals being highly reactive, are capable of damaging almost all the types of biomolecules, includes proteins, lipids, carbohydrates and nucleic acids. This is because of their property to generate free radicals from normal compounds which continues as a chain reaction.

Proteins: Biological activity of proteins is lost as a result of damage caused by fragmentation, cross-linking, and aggregation of proteins from ROS.

Lipids: Lipid peroxidation caused by free radicals results in damage to poly-unsaturated fatty acids (PUFAs).

Carbohydrates: Linkage of carbohydrates to proteins makes proteins more susceptible to attack by free radicals. This seems to be of clinical significance in the patients with diabetes mellitus in which glycosylation of protein scan result in various complications such as diabetic microangiopathy, diabetic nephropathy, periodontitis, etc.

Nucleic acids: Damage to the DNA caused by free radicals resulting in fragmentation of bases, strand breakage and fragmentation of deoxyribose, which may in turn be associated with cytotoxicity and mutations.

Further, damage caused by free radicals has been implicated in a variety of diseases, including, cardiovascular diseases (CHD), cancer, inflammatory diseases, respiratory diseases, diabetes, cataract, male infertility, ageing, periodontitis, etc (Satyanarayana and Chakrapani, 1999). ROS, having a very short half-life, are capable of causing extensive tissue damage by initiating free radical chain reactions. Body has various antioxidant mechanisms which can help by removing free radicals, in order to prevent, or repair the damage caused by free radicals. Normally, there exists a dynamic equilibrium between ROS activity and antioxidant defense capacity. In inflammatory challenges faced by the body as in periodontitis, the equilibrium shifts in the favor of ROS, which occurs either by increased production of ROS or reduction in antioxidant defense, and 'oxidative stress' results (Waddington *et al.,* 2010).

Effects of ROS on Periodontal tissues

The reactive oxygen species cause periodontal tissue damage by;

- Degradation of Ground substance.
- Oxidation of proteases which may result in collagenolysis, either directly or indirectly.
- NF-κB activation stimulates excessive production of pro-inflammatory cytokine.
- Lipid peroxidation and superoxide released results in production of PGE2, both of which have been linked with bone resorption.
- Following the stimulation by periodontal pathogens, there results endotoxin mediated cytokine production e.g.- IL-1 & TNF-α, which positively regulate their own production, along with the respiratory burst of phagocytes in response to the same stimulus. These additive effects may lead to periodontal destruction (Chapple and Matthews, 2000).

Chapple and Matthews found that there is an increase in generation of free oxygen radicals with an increase in ratio between elastase and lactoferrin at the peripheral neutrophils, thus causing tissue destruction (Chapple and Matthews, 2000). Whyte *et al* suggested that hyperactive phenotype of peripheral neutrophils may be a reason for localized tissue destruction, by enhanced generation of ROS in response to periodontal pathogens (*Fusobacterium nucleatum, Aggregatobacteractino mycetemcomitans*) (Whyte *et al.,* 1989). Raised levels of Myeloperoxidase in GCF at the site of disease have been reported in the case of gingivitis, chronic periodontitis, (Cao and Smith, 1989) rapidly progressive periodontitis, localized aggressive periodontitis. A review performed by Battino *et al* have also demonstrated the correlation between Myeloperoxidase levels in GCF and clinical parameters, which reduced after treatment (Battino *et al.,* 1999). Other risk factors like smoking may induce oxidative stress in the body resulting in the disturbance between ROS and antioxidants. Increased destruction in periodontal disease in smokers has been attributed to decreased levels of Superoxide Dismutase in smokers as compared to the non-smokers (Agnihotri *et al.,* 2009).

Evidence of ROS presence and role in Periodontal Tissue Damage (Chapple and Matthews, 2007)

Halliwell proposed four criteria, similar to that proposed by Robert Koch in 1884, to establish causal relationship between an organism and disease.

- ROS or the oxidative damage caused must be present at the site of injury.

- The time course of ROS formation or the oxidative damage caused should occur before or at the same time as tissue injury.
- Direct application of ROS over a relevant time course to tissues at concentrations found in vivo should reproduce damage similar to that observed in the diseased tissue.
- Removing or inhibiting ROS formation should decrease tissue damage to an extent related to their antioxidant action in vivo.

Antioxidants

A biological antioxidant may be defined as a substance that significantly delays or inhibits oxidation of a substrate. They are present in low concentration as compared to an oxidizable substrate. They are also commonly known as scavengers of free radicals.

Classification of antioxidants

Antioxidants can be classified according to;

A. Antioxidants according to lipid peroxidation

- **Preventive Antioxidants** that will block the initial production of free radicals e.g. catalase, glutathione peroxidase.
- **Chain breaking Antioxidants** that inhibit the propagative phase of lipid peroxidation e.g. superoxide dismutase, vitamin E, uric acid.

B. Antioxidants according to their location

- **Plasma Antioxidants** e.g. β-carotene, ascorbic acid, bilirubin, uric acid, ceruloplasmin, transferrin.
- **Cell membrane Antioxidants** e.g. α-tocopherol.
- **Intracellular Antioxidants** e.g. superoxide dismutase, catalase, glutathione peroxidase.

C. Antioxidants according to their nature and action

- **Enzymatic Antioxidants** e.g. superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase.

- **Non-Enzymatic Antioxidants**

  a. **Nutrient antioxidants** e.g. carotenoids (β-carotene), α-tocopherol, ascorbic acid, selenium.
  b. **Metabolic antioxidants** e.g. glutathione, ceruloplasmin, albumin, bilirubin, transferrin, ferritin, uric acid.

Mechanism of action of antioxidant enzymes (Figure 2)

The antioxidant enzymes are truly scavengers of free radicals. The major reactions are as follows:

- **Superoxide Dismutase (SOD):** It forms the first line of defense to protect the cells from injurious effects of superoxide by carrying out the conversion of Superoxide (O_2^-) to Hydrogen Peroxide (H_2O_2) and oxygen (O_2).
- **Catalase (CAT):** It metabolizes Hydrogen Peroxide (H_2O_2) produced by Superoxide dismutase.
- **Glutathione Peroxidase (GPX):** It detoxifies Hydrogen Peroxide (H_2O_2) to Water (H_2O), along with the conversion of reduced glutathione (G-SH) to oxidized glutathione (GS-SG). The enzyme glutathione reductase (GSR) catalyses the regeneration of reduced glutathione by utilizing NADPH, the major source of which is Hexose Monophosphate Shunt.[1]GSH also protect against the cytotoxic actions of nicotine in periodontal fibro blasts (Chang, 2003).

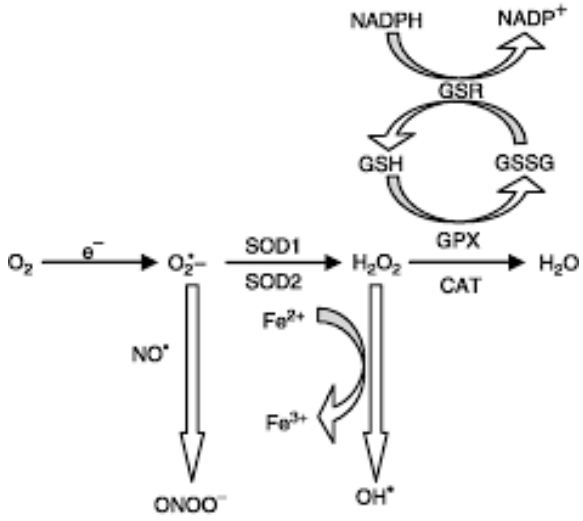

Figure 2.

Protective role of antioxidants in periodontal disease

A dynamic equilibrium exists between Reactive Oxygen Species (ROS) and antioxidants in normal circumstances. Whenever this equilibrium shifts in the direction of increased production of ROS, whether because of their increased production or decreased antioxidant levels, oxidative stress results. This oxidative stress compromises the ability of periodontal tissues to maintain normal homeostasis and control the bacterial damage. Thus, low levels of antioxidants are considered a significant risk factor for periodontal tissue damage. Numerous substances are available that can serve as antioxidants. These include the following:

Tocopherols (Vitamin E)

It serves as an important antioxidant present in all the cell membranes. It is a fat soluble vitamin and among the tocopherols, α-tocopherol is the most active. It can directly act on oxyradicals (e.g. O_2^-, OH^-, singlet oxygen), thus serving as an important chain breaking antioxidant. It protects against lipid peroxidation. A study demonstrated a significant decrease in GCF levels in patients with periodontitis who were under vit-E mouth rinses for 21 days compared to controlled groups (Goodson and Boules, 1973).

Ascorbic acid (Vitamin C)

It serves as an important antioxidant present in biological fluids. It is a water soluble vitamin, scavenges free radicals and inhibits lipids peroxidation. It participates in many metabolic reactions in the body and also promotes regeneration of α-tocopherol. A statically significant relationship between

dietary intake of vit. C and periodontal disease in current and former smokers has been demonstrated by Mieko Nishida *et al*. It is the only endogenous antioxidant in plasma that can completely protect against peroxidative damage induced by the oxidants released from activated neutrophils. The protection is provided by scavenging superoxide and peroxyl radicals and decrease the pro-inflammatory gene expression via effects on nuclear factor κB transcription factor (Nishida *et al.,* 2000). Another study by Amaliya *et al* suggested that vit. C deficiency may contribute to severity of periodontal breakdown (Wood *et al.,* 2004).

Carotenoids

Another group of antioxidants which are the natural compounds with lipophilic properties. It serves as an antioxidant under low partial pressure of O_2. Among the carotenoids, β-carotene is the most important, which functions in association with vit. C and vit. E, lycopene, lutein, and zeaxanthin are also the pigmented carotenoids which imparts colors to many fruits and vegetables and serve as an antioxidants. Wood *et al* (2004) in their study concluded that high monthly tomato consumption appears to affect the relationship between periodontitis and congestive heart failure in a positive direction (Wood *et al.,* 2004).

Selenium

It is basically an essential trace element which functions along with vit. E as an antioxidant. It is also required for the function of another antioxidant enzyme, namely glutathione peroxide.

α-lipoic acid

They play a key role in the recycling of other important antioxidants like ascorbic acid, glutathione, α-tocopherol.

Flavonoids

These are polyphenolic compounds, found in fruits, vegetables and certain beverages. Their consumption in the diet is high as compared to other dietary antioxidants. They have anti-inflammatory, anti-allergic, anti-platelet and anti-tumor properties (Joe *et al.,* 2001). Flavonoids also possess the property of inhibiting lipopolysaccharides, thus may prove to be beneficial in preventing periodontal disease by reducing bone resorption.

Lazaroids

The 21-aminosteroids (lazaroids) are inhibitors of lipid membrane peroxidation and appear to function as oxygen free radical scavengers. They are derived from gulcocorticoids but lacking the properties of both glucocorticoids and mineralocorticoid (Chapple and Matthews, 2000).

Co-enzyme Q 10

It exist in both oxidized form (ubiquinone / co Q) and a reduced form (ubiquinone / co Q H2). Both possesses antioxidant properties and is also regarded as a pro-oxidant molecule in response to various patho-physiological events. Studies are lacking to substantiate its clinical therapeutic benefits in periodontitis (Pooja, 2016).

Polyphenols

Battino *et al.* in 1999, stated that they are absorbed following dietary intake of, in particular, vegetables, fruits, tomatoes, red wine and tea. E.g. water soluble catechin, epigallo-catechingallate, and poly phenol (Battino *et al.,* 1999).

Their function:

- Radical scavenging;
- Terminating lipid peroxidation;
- Iron chelation;
- Sparing vitamin E;
- Restoration of vitamin.

Conclusion

Free radicals have been implicated in the causation and progression of several diseases e.g. CHD, cancer, periodontitis etc. The respiratory burst of phagocytes accompanied by the generation of ROS brings about bactericidal effects and is beneficial to the body. Dietary consumption of variety of nutrient antioxidants (Vit C, E, β-carotene, lycopenes, selenium, β-lipoic acid) is desirable since each antioxidant targets certain types of damaging free radicals.

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