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Review Article

Relationship between Antioxidants and the Development of the Periodontal Disease

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Abstract

The role of oxidative stress linking the free radical damage at the cellular level causes premature aging, including periodontal disease. To overcome this, it is important to explore the role of host specifically with regard to antioxidant status along with conventional periodontal therapy. Periodontal counselling and supplementation may very well reduce inflammation and thereby enhance outcomes of conventional periodontal therapy. The purpose of this review is to summarize available research in the role of antioxidants as an adjunct to periodontal therapy.

Keywords: Antioxidants; Free radical; Inflammation; Periodontal therapy

Key Messages: Antioxidants have shown to have beneficial outcome when used as adjunct to traditional periodontal therapy. Implication of antioxidants has promising results in future.

Introduction

Periodontitis is a chronic inflammatory disease caused primarily by bacteria in dental plaque, affecting the supporting structures of the teeth. Specific periodontal pathogens such as the gram-negative anaerobic bacteria inhabiting within the sub-gingival plaque are associated with the progressive form of the disease. Although bacteria are the major etiological agents, the host immune response to these bacteria is of fundamental importance. Hence, it is evident that periodontitis is a multifactorial disease, affiliates with specific microorganisms, social and behavioral factors, genetic or epigenetic trait, all of which are modulated and controlled by the underlying immune and inflammatory responses of the host [1].

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The recent focus on the progression of periodontitis is on the molecular aspects of host modulation. The discovery of the role of free radicals in chronic disease is as important as the discovery of the role of microorganism in inflammatory disease [2].

Free radicals & Reactive Oxygen Species (ROS) production is an essential component of the host response for immune system, prostaglandin biosynthesis, anti-bacterial biosynthesis and variety of insults like trauma/burns [3]. Besides, the physiological system, ROS generation are induced by several exogenous factors such as pollution, smoke, radiation, pesticides and drug consumption. Major producers of ROS are mitochondrial cytochrome P-450 reactions, peroxisomal fatty acid metabolism and NADPH oxidase activity [4]. An imbalance between the ROS production and anti-oxidant mechanism leads to oxidative stress. Oxidative stress has been associated with both onset of periodontal destruction and systemic inflammation [5,6].

Primary immune response against periodontal pathogens is elevated numbers of neutrophils seen in connective tissue, junctional epithelium (50%) and gingival crevicular fluid (90%) and it can cause loss of epithelial cell-cell attachment in junctional epithelium (>60%) leading to apical shift of junctional epithelium [7].

Neutrophil have several mechanisms for controlling bacterial invasion which includes both intracellular and extracellular oxidative and non-oxidative killing mechanisms [8]. When neutrophils and macrophages get stimulated by a phagocytic stimulus, produces a 'respiratory burst', which is characterized by an increase in oxygen consumption, activation of the Hexose-Monophosphate (HMP) shunt and generation of Free Radicals (FR), Reactive Oxygen Species (ROS) and their metabolic products. At sites of chronic inflammation (periodontium in case of periodontitis), there is considerable over production of FR and reactive species.

Research with scientific evidence confirmed that inflammation in the oral tissues especially that associated with periodontitis can be a factor in chronic illness such as cardio and cerebro vascular diseases [9,10], diabetes mellitus, rheumatoid arthritis, advance pregnancy outcomes and a growing list of other conditions such as cancer, psoriasis, chronic kidney disease and anemia. Several hypotheses proposed to describe the interlinking between periodontal diseases and systemic diseases. One of the explanations is imbalance between systemic oxidants and antioxidants [11-13]. "An antioxidant is any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate" [14].

Hence the concept of inhibition of building up oxidative stress within cells through anti-oxidative therapy is implicated in inflammatory disorders and periodontitis along with gold standard therapy for periodontitis is through removal of subgingival biofilm through scaling and root planing has shown to be advantageous. The present article reviews on the comprehensive appraisal of the newer aspects of anti-oxidative therapy and it's applications in Periodontology (Figure 1).

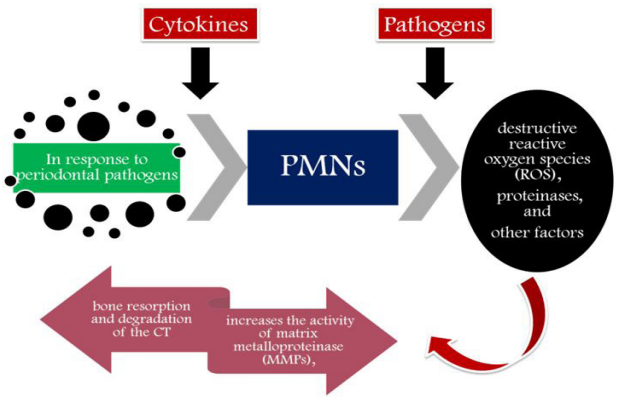


Figure 1: Role of polymorphopneutrophils.

Reactive Oxygen Species (ROS)

Every day, numerous free radicals and ROS are produced in each cell by various exogenous and endogenous sources and these ROS are counteracted or balanced by anti-oxidants present within each cell, there by prevents oxidative stress build up. Reactive oxygen species and their sources are enumerated in table 1.

Recent literature postulate that, non-radicals which have the capability of radical transformation in the extra- and intracellular environment (singlet oxygen, hydrogen peroxide and hypochlorous acid) are grouped under reactive oxygen species category [15,16]. Tissue damage by ROS [5,15,17] (Table 2).

Free radicals Sources		Sources		
Oxygen derived free radical	Non- Oxygen derived free radical	Exogenous	Endogenous (byproducts)	
			Metabolism	Function
Superoxide ($O2^-$)	Singlet oxygen ($^1O_2$)	Heat, Trauma	Cell metabolism and oxidative phosphorylation (electrons transport chain)	By Osteoclasts at ruffled border during bone resorption. Oxidative pathway of phagocytosis is by neutrophils and other phagocytes.
Hydroxyl (OH^-)	Ozone (O_3)	Ultrasound, Ultraviolet Light, Ozone, Smoking		
Hydroperoxyl (HOO)	Hypochlorous acid (HOCl)	Exhaust Fumes, Radiation, Infection, Excessive Exercise, Therapeutic Drugs		
Alkoxyl (RO)	Hydrogen peroxide (H_2O_2)			
Aryloxyl (ArO)				
Arylperoxyl (ArOO)				
Peroxyl ROO				
Acyloxyl (RCOO)				
Acylperoxyl (RCOOO)				

Table 1: Reactive oxygen species and their sources.

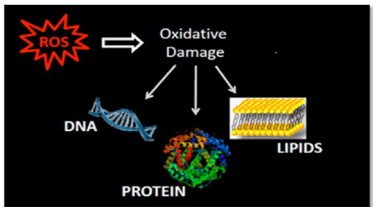
ROS (Mainly Hydroxyl and peroxynitrate anion)	Target molecule	Example	Effects
	Protein	Gingival hyaluronic acid and Proteoglycans	• Folding/unfolding, Fragmentation • Protease degradation of the modified protein • Formation of protein radicals and protein bond ROS • polymerization of proteins • Formation of stable end products (acetaldehydes)
	Lipid	Cell membrane (activation of cyclooxygenases and lipo-oxygenases pathways)	• Peroxidation and formation of products these are bioactive molecules, Conjugated dienes • Lipid Proxides, Aldehydes • Volatile-hydrocarbons, Prostagladin-E2(PG-E2) production eg: Malondialdehyde, Acrolein, Isoprostanes and Neuroprostanes
	DNA		• Strand breaks, Base pair mutations, Deletions, Insertions, conversion of guanine to 8- hydroxyguanine, • Nicking and Sequence amplifications.
		Activating nuclear factor kB (NFkB)	Stimulation of pro-inflammatory cytokine release by monocytes and macrophages
	Enzymes	Antiproteases such as α-1antitrypsin	Oxidation
Superoxide and hydrogen peroxide	Cells	Osteoclast activation	Bone resorption

Table 2: Tissue damage by ROS.

Halliwell established 4 criteria for causal relationship between ROS and disease [18];

1. ROS or the oxidative damage caused must be present at the site of injury.
2. The time course of ROS formation or the oxidative damage caused should occur before or at the same time as tissue injury.
3. 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.
4. Removing or inhibiting ROS formation should decrease tissue damage to an extent related to their antioxidant action *in vivo*.

Growing evidence exist in causal relationship between oxidative stress and periodontitis [19] (Table 3).

Targeted Periodontal tissue	Reaction of ROS	Effect
Ground substance	Depolymerization and Degradation (non-sulfated glycosaminoglycans are more susceptible than sulfated)	All these events leads to periodontal tissue destruction (Figure 2) and alveolar bone resorption
Collagen	Collagenolysis	
Monocytes and macrophages	Stimulation of excessive pro-inflammatory cytokine	
Lipid peroxidation	PG-E2 production leads to bone resorption	

Table 3: Reactive oxygen species on periodontal tissues.

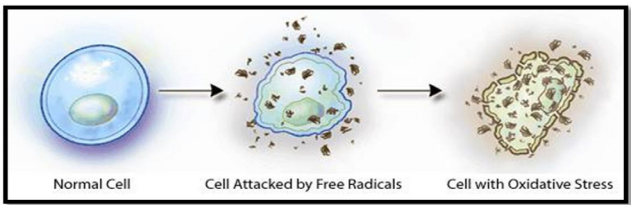


Figure 2: Periodontal tissue destruction by ROS [20].

Evidence suggesting causal relationship between ROS and periodontitis

It is more than a decade the physiological and pathological roles of ROS in the development of periodontitis have been studied

Chapple and Matthews postulated that periodontal tissue destruction results in increased production of ROS and increased ratio between elastase and lactoferrin by peripheral neutrophils [5].

Agnihotri have been reported that increased levels of ROS in smokers was responsible for excessive periodontal tissue destruction [21].

Patil et al., have reported that the severity of tissue destruction due to excessive ROS is more when periodontal disease is associated with type 2 DM, indicating that oxidative stress is common factor involved in tissue destruction [22].

Di Meo et al., suggested that low levels of ROS are beneficial, but excessive generation or antioxidant deficiency results in periodontal tissue destruction [23].

Liu et al., He et al., have shown the potential link between ROS and autophagy in periodontitis [16,24].

Antioxidants (AO)

The concept of inhibition of building up oxidative stress within cells through anti-oxidative therapy is implicated in inflammatory disorders and periodontitis. Antioxidants are agents which scavenge free radicals or otherwise reactive oxygen species, thereby preventing damage caused by them. Antioxidant therapy as adjunct to conventional treatments such as scaling and root planing has shown to be advantageous. Antioxidant can be classified in the following way (Table 4).

Sl.no	Based on	Examples
1	**Mode of action**	
	Preventive	Suppress the formation of free radicals: Catalase, Glutathione peroxidase, and Serum transferase
		Metal ion sequestrators- Albumin, Lactoferrin, Transferrin, Ceruloplasmin, Uric acid, Polyphenolic flavenoids
		Quenching of active oxygen: Superoxide dismutase, Carotenoids
	Scavenging (Chain breaking)	Ascorbate, Carotenoids, Uric acid, Vitamin E, Bilirubin, Reduced glutathione & other
2	**Location**	
	Intracellular	Superoxide dismutase enzymes-1& 2, Catalase, Glutathione peroxidase, DNA repair enzymes & Reduced glutathione.
	Extracellular	Superoxide dismutase enzyme-3, Slenium glutathione peroxidase, Reduced Glutathuione,
	Membrane associated	α-tocopherol
3	**Solubility**	
	Water soluble	Haptoglobin, Ceruloplasmin, Albumin, Ascorbic Acid, Uric acid, Albumin, Polyphenolic flavenoids, Reduced glutathione & other thiols, Cysteine & Transferrins
	Lipid soluble	α-tocopherol, Carotenoids, bilirubin, Ubiquinol and Vitamin A
4	**Repair De novo enzymes**	DNA repair enzymes, Protease, Lipase and Transferase
5	**Structures they protect**	
	DNA protective antioxidants	Superoxide dismutase enzymes 1 and 2, Glutathione peroxidase, DNA repair enzymes [e.g., Poly(ADP-ribose) polymerase], Reduced glutathione, Cysteine
	Protein-protective antioxidants	Sequestration of transition metals by preventative antioxidants Antioxidant enzymes
	Lipid-protective antioxidants	a-Tocopherol (vitamin E), Ascorbate (vitamin C), Carotenoids (including retinol – vitamin A), Reduced ubiquinone, Reduced glutathione, Glutathione peroxidase, Bilirubin
6	**By their origin**	
	Exogenous antioxidants	Carotenoids, Ascorbic acid, Tocopherols (a, b, c, d), Polyphenols (e.g. Flavenoids, Catechins such as Epigallocatechin-gallate), Folic acid, Cysteine
	Endogenous antioxidants	Catalase, Superoxide dismutase, Glutathione peroxidase, Glutathione-S-transferase, Reduced glutathione, Ceruloplasmin, Transferrin, Ferritin, Glycosylases, Peroxisomes, Proteases
	Synthetic	N-acetylcysteine, Penicillinamine, Tetracyclines

Table 4: Anti-oxidant classification.

Antioxidant enriched diet and periodontal diseases [25]

Recent evidence has demonstrated a significant role for oxidative stress in promoting bone resorption via activation of certain transcription factors (Fox Os, which decreases want signalling), Modulated by insulin resistance and increasing age [26]. Antioxidant micronutrients combat such pro-inflammatory cascades through modulation of oxidative stress by directly scavenging Reactive Oxygen Species (ROS) and also by down-regulation of some redox-sensitive pro-inflammatory gene transcription factors such as nuclea factor-kappa B and activator protein-1 while up regulating anti-inflammatory gene transcription factors such as nuclear factor [5]. Following are some of the examples of antioxidant diets.

Green Tea

Green tea is a non-fermented product of tea (*Camellina sinensis*) leaves that is consumed as a beverage worldwide. Green tea extract is documented to have antibacterial, antioxidant, anti-inflammatory and anticarcinogenic properties. It is a rich source of flavonoids, mainly catechins. The four major catechins include

- Epigallocatechin-3-gallate (59%)
- Epigallocatechin (19%)
- Epicatechin-3-gallate (13.6%)
- Epicatechin

Local drug delivery of green tea extract has also shown promising results in treating periodontal diseases [27]. Dentifrice and mouthwashes can be contemplated as vehicles for self-application of chemotherapeutics. Recently, the addition of green tea catechins to dentifrice has shown reduction of periodontal inflammation in the rat model, by decreasing gingival oxidative stress and expression of pro-inflammatory cytokines [28].

Hrishi et al., conducted a study to evaluate the effect of adjunctive use of green tea dentifrice in periodontitis patients and concluded that green tea dentrifice may serve as a beneficial adjunct to non-surgical periodontal therapy as it showed greater reduction of gingival inflammation and improved periodontal parameters on comparison with fluoride-triclosan dentrifice [29].

Grape Seed Extracts (GSE)

Grape seed extract is a naturally occurring polyphenolic compound obtained from seeds of *Vitis vinifera*. It possesses a wide range of biological activities such as immunomodulator agent, antioxidant, anticarcinogenic, and anti-inflammatory effects [30,31]. The immunomodulator effect is particularly due to its proanthocyanidin content. GSE may beneficial for the treatment of inflammation associated with bone destruction as it may strongly inhibit osteoclast differentiation, reduce osteoclast activity, and stimulate bone formation through its positive action on osteoblast differentiation [32]. The anti-inflammatory effect is modulated by calibrating the delicate balance between pro-inflammatory and anti-inflammatory cytokines through regulating their release and gene expression delicate balance between pro-inflammatory and anti-inflammatory cytokines through regulating their release and gene expression [33].

Ozden FO et al., investigated the effects of GSE application on periodontium before and after ligature induced experimental periodontitis [34], using histological and immunohistochemical analyses. Histopathological findings showed improvements in the inhibition of periodontal inflammation and destruction following GSE intake.

The bark contains magnolol and honokiol, two polyphenolic compounds that have been demonstrated as peroxisome proliferator-activated receptor gamma (PPAR gamma) agonists and gamma-aminobutyric acid modulators. Magnolol extracted from Magnolia officinalis is widely used in oriental medicine. Preclinical studies have evaluated their various potential applications including antioxidant, anti-inflammatory, antitumor and antimicrobial properties [35].

Magnolol has been reported to have a potent anti-inflammatory activity via inhibition of proinflammatory cytokine, ROS formation, iNOS, COX-2 expression, and nuclear factor-kappaB (NF-kappaB) activation, a key transcription factor regulating inflammation, in LPS-induced inflammatory disease [36,37]. Furthermore, magnolol exerts a marked antimicrobial activity against periodontopathic bacteria and activates osteoblast function [38]. Magnolol may be used as a potential candidate for treating periodontitis.

Lu SH et al., concluded in their study that magnolol significantly ameliorates the alveolar bone loss in ligature-induced experimental periodontitis by suppressing periodontopathic microorganism accumulation [39], NF-κB-mediated inflammatory mediator synthesis, RANKL formation, and osteoclastogenesis. These activities support that magnolol is a potential agent to treat periodontal disease.

Melatonin

Melatonin (N-acetyl-5-methoxy tryptamine) is a substance secreted by multiple organs including the pineal gland, retina, bone marrow, the gastro-intestinal track and the immune system. Because it is lipophilic, it can reach all body cells and cellular components rapidly [40]. In addition to its scavenger effects, melatonin indirectly stimulates various antioxidant enzymes [41,42]. A quality that makes melatonin superior to other antioxidants is that it does not become pro-oxidative by losing an electron during interactions with free radicals; i.e., it is not a potential pro-oxidant [43].

Local and systemic administration of melatonin in rats with lipopolysaccharide-induced periodontitis reduced the level of enzymes (such as serum aspartate aminotransferase, alanine transaminase and blood urea nitrogen) significantly compared with rats in the control group [42,44]. Similarly, locally administered melatonin significantly reduced bone resorption compared with rats receiving no treatment. These studies suggested that topical administration of melatonin can be used as an adjunct to conventional treatment protocols such as scaling, root planing, and surgical debridement to improve the outcomes of periodontal therapy.

Propolis Extract

Propolis, sometimes called bee glue, is a natural resinous substance collected by honey bees (*Apis mellifera L.*) from plant buds and bark exudates. Bio-flavonols are the key contributors to propolis' properties. Propolis is found to have strong inhibitory effects on at least 21 species of bacteria, 9 species of fungi, 3 species of protozoa, and a wide range of viruses.

A number of studies have presented evidence that propolis has strong hepatoprotective, antitumor, antioxidative, antimicrobial and anti-inflammatory properties. Coutinho A in the year 2012 in their clinical study demonstrated the benefits provided by propolis extract and indicated that it should be considered for use as an adjuvant to scaling and root planing [45-48].

Salivary Antioxidant Status

Saliva is rich in antioxidants, mainly uric acid accounting for more than 70% of the total antioxidant activity of resting and stimulated saliva from both healthy and periodontally compromised subjects. Other antioxidants present in lesser concentration than uric acid are albumin, ascorbate and glutathione [49]. Albumin concentration is comparatively low, about 10*m*M, apparently in the same range of that of ascorbic acid [49,50]. Accounting for the 5-10% of antioxidant activity in saliva are the traces of other antioxidants such as transferrin, lactoferrin and caeruloplasmin. They are capable of binding metal ions are found in both saliva and GCF [51].

Antioxidant status in gingival crevicular fluid

An excess of reactive oxygen species and depletion of antioxidant levels in gingival crevicular fluid are responsible for the chronic local activation of periodontal inflammation and tissue destruction [5,52]. Gingival crevicular fluid probably contains a locally derived antioxidant from local three sources such as plaque bacteria, neutrophils and crevicular epithelium [53].

Significantly more intense levels of superoxide dismutases in gingival crevicular fluid comprise the most important antioxidant enzyme defense system against reactive oxygen species.

The reduced and oxidised glutathione concentrations in the gingival crevicular fluid are significantly lower in patients with chronic periodontitis, supporting that the glutathione levels in gingival crevicular fluid can play an important role in the pathogenesis of periodontitis [54].

Total antioxidant capacity

It is the measure of the antioxidant capacity of all antioxidants in a biological sample rather than the antioxidant capacity of a single compound. Total Antioxidant Capacity (TAC) of saliva has been measured by only 3 methods using 3 different biochemical techniques [55];

- Spectrophotometric assay
- Enhanced chemiluminescence assay
- Cyclic voltammetry assay

Salivary TAC decreases or does not changes in periodontal disease.

Mechanism of Action [5,15]

Superoxide Dismutase (SOD)

It is an anti-oxidative enzyme, which has been localized within human periodontal ligament and represent an vital defense mechanism for gingival fibroblasts against superoxide ions by catalyzing and accelerating the reaction (approximately 10,000 times) from superoxide ion to oxygen and less reactive H_2O_2 (Figure 3).

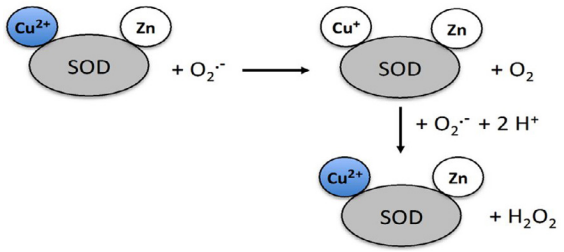


Figure 3: Mechanism of action of superoxide dismutase.

In humans SOD exists in 3 forms (Figures 4 and 5)

- Cytosolic Cu/Zn-SOD,
- Mitochondrial Mn-SOD (major role)
- Extracellular SOD (EC-SOD)

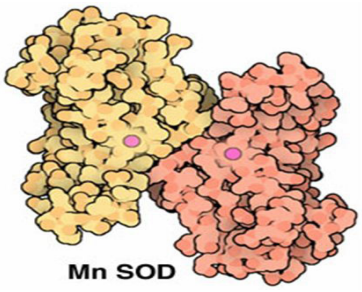


Figure 4: Mitrochondrial SOD.

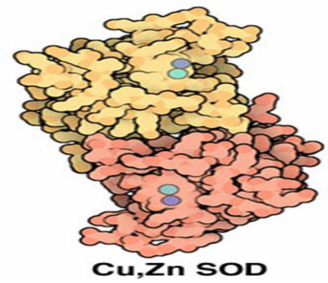


Figure 5: Cytosolic Cu/Zn-SOD.

Catalase (CAT)

It is heme bound iron anti-oxidative enzyme, majorly located in peroxisomes. It protects the cells from hydrogen peroxide by converting it into water (Figure 6).

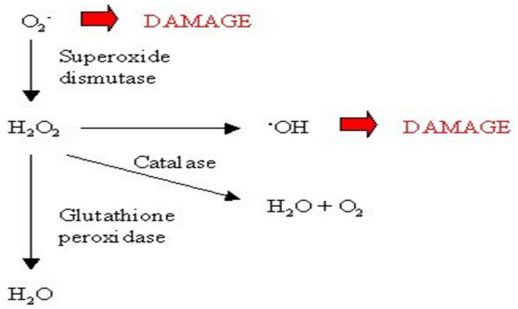


Figure 6: Role of catalase.

Reduced Glutathione (GSH)

GSH is an essential antioxidant enzyme, which AIDs as A- Anti-oxidant, I-Immunobooster, D- Detoxifier. It regulates IL-2 dependent T lymphocyte proliferation (Figure 7).

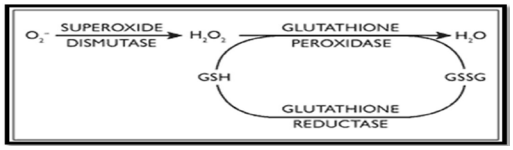


Figure 7: Role of glutathione.

Glutathione Peroxidase

It is a selenium containing peroxidase which reduces variety of hydroperoxides, H_2O_2 and lipids, there by protects the cell particularly against low levels of oxidative stress. It has 5 types of isoezymes, these are GPX1, GPX2, GPX3, GPX4, and GPX5.

Uric acid

Moore et al., in 1994 proposed that uric acid is responsible for 70% antioxidants capacity of saliva and it is one of the major antioxidant present in saliva. Diab-Ladki in 2003 [56] found decreased concentrations of uric acid, ascorbic acid and albumin in saliva of periodontitis patients.

Ascorbic acid (vitamin C)

It is a water soluble vitamin, function as antioxidant by scavenging water-soluble peroxyl radicals, scavenging superoxide and perhydroxyl radicals, prevention of damage mediated by hydroxyl radicals on uric acid, scavenger of hypochlorous acid, decreases heme breakdown and subsequent Fe^{2+} release thereby preventing Fenton reactions, scavenger of singlet oxygen and hydroxyl radicals, re-forms a-tocopherol from its radical and also protects against ROS-release from cigarette smoke.

Conclusion

Following conclusion can be drawn with respect to the role of reactive oxygen species and antioxidants in periodontitis

1. Oxidative stress and reactive oxygen species appear to play a significant role in the patho-physiology of periodontal diseases.
2. Adjunctive use of antioxidants with traditional therapies should be considered to improve the periodontal treatment outcome.
3. This review presents with evidence within the biomedical literature, provides exciting new opportunities for future development of host modulation therapies in periodontology.

Future Research Directions

The results of the review may have relevance for the development of treatment protocols. The impact of the combination of periodontal therapy with antioxidants in terms of antioxidant/oxidative stress parameters requires further investigation with longer follow.

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