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# Antioxidants and Periodontal Diseases

*Ahmet Cemil Talmaç and Metin Çalışır*

## Abstract

Excessive reactive oxygen species production plays an important role in the pathogenesis of various chronic inflammatory diseases, including periodontal disease. Reactive oxygen species could damage the cells and the tissues. In the pathogenesis of periodontal diseases, the increased PMN count and activity cause a high rate of ROS release. This leads to increased oxidative stress in periodontal tissues. Periodontal tissues require adequate levels of antioxidants to prevent tissue damage caused by reactive oxygen species. The use of antioxidants in the treatment of periodontal disease and periodontal health has gained importance in recent studies. Antioxidants can be used to treat periodontal disease locally or systemically. Therefore, this chapter focuses on the effects of antioxidant on periodontal tissues.

**Keywords:** antioxidants, oxidative stress, periodontal diseases, reactive oxygen species, tissue damage

## 1. Introduction

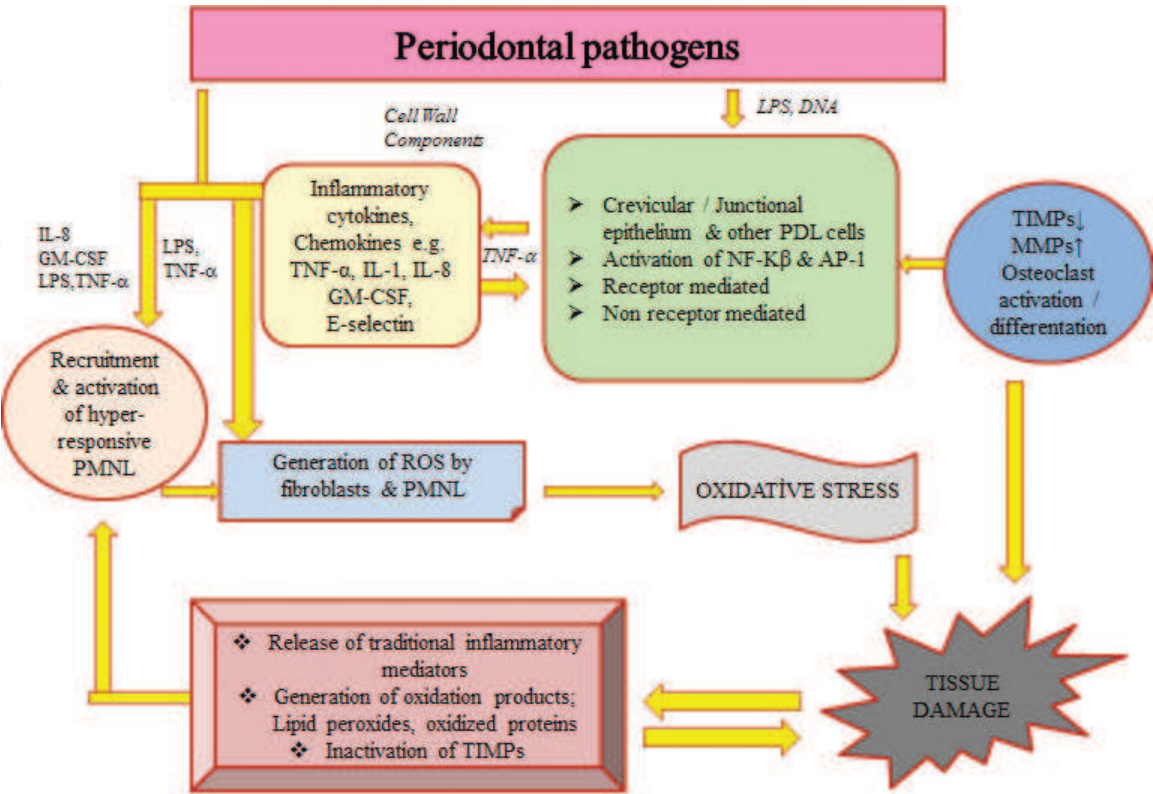
### 1.1 Antioxidants

Reactive oxygen species (ROS) form as a part of the physiological functions of all cells, and the significance of their role as mediators in cell signaling has become more evident [1]. ROS can harm different types of cells and tissues through protein damage, lipid peroxidation, and DNA damage. Excessive ROS production plays a role in the pathogenesis of various chronic inflammatory diseases, including periodontal disease [2] (**Figure 1**). Cells and tissues require antioxidants to prevent the tissue damage caused by overproduction of ROS [3].

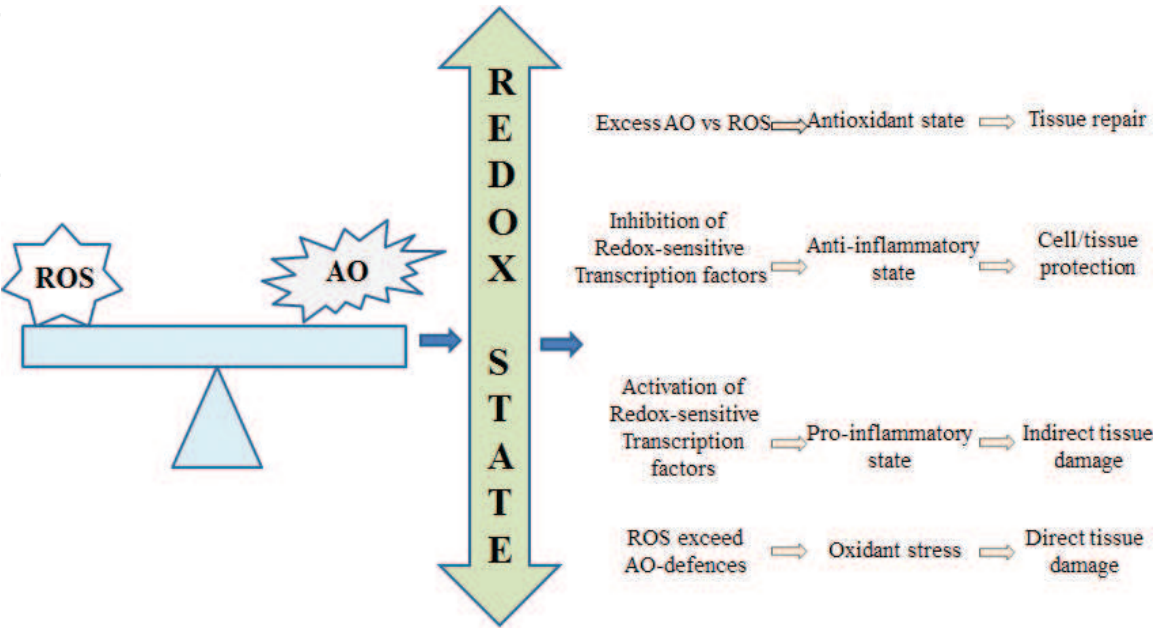
Antioxidants (AOs) are compounds that prevent the initiation or progression of oxidation reactions by trapping oxygen in the environment [4]. They play an important role in preserving the structural integrity of cells and tissues, by maintaining their normal functions and ensuring the maintenance of balance between oxidant and antioxidant mechanisms [2] (**Figure 2**). Antioxidants show their effects against oxidative stress in four different ways:

- by acting on the free radical producing steps, such as chain-forming lipid peroxidation;  $\alpha$ -tocopherol
- reducing the concentration of ROS directly; glutathione

- by neutralizing the primary radicals that initiate free radical production; super-oxide dismutase
- forming a chelate with transition metals; lactoferrin, transferrin, ferritin, ceruloplasmin, and albumin [5].



**Figure 1.** It is shown that ROS has a key role in tissue injury occurred during reacting against periodontal pathogens and occurrence of chronic inflammation [2]. MMP, matrix metalloproteinase; TIMP, matrix metalloproteinase tissue inhibitor; NF-κB, nuclear factor-kappa B; AP-1, activator protein-1; PDL, periodontal ligament; TNF, tumor necrotizing factor; IL, interleukin; GM-CSF, granulocyte-macrophage colony stimulating factor; LPS, lipopolysaccharide; and ROS, reactive oxygen species.



**Figure 2.** The biological effects of small and large shifts on the balance of activity between reactive oxygen species (ROS) and antioxidant (AO) species [2].

Antioxidants, such as vitamins, minerals, enzymes, and hormones, are molecules that could be obtained from exogenous and endogenous sources, in addition to nutrients and herbal supplements. Antioxidants such as vitamin E, vitamin C, ceruloplasmin, glutathione peroxidase, and superoxide dismutase protect cells and tissues from tissue damage caused by free radicals [6].

#### *1.1.1 Endogenous antioxidants*

Endogenous antioxidants are classified as enzymatic and nonenzymatic antioxidants.

##### *1.1.1.1 Enzymatic antioxidants*

###### *1.1.1.1.1 Glutathione peroxidase (GSH-Px)*

GSH-Px is a tetrameric enzyme found in the cytosol and contains four selenium (Se) atoms. It shows its effect by reducing hydroperoxides and hydrogen peroxide ( $H_2O_2$ ). Essentially, GSH-Px acts on lipid hydroperoxides released by phospholipase A2 (PLA2), which is a membrane phospholipid. It also has important effects on phagocytic cells. The decrease in GSH-Px activity leads to hydrogen peroxide accumulation and cell damage. GSH-Px prevents lipid peroxidation and enables the metabolism of lipid hydroperoxides that are the products of lipid peroxidation [7, 8]. The gingival and serum GSH-Px levels were shown to be higher in periodontitis patients compared to healthy people and gingivitis patients [9].

###### *1.1.1.1.2 Glutathione reductase (GSH-Red)*

Glutathione reductase, a flavoprotein, catalyzes the reduction of oxidized glutathione (GSSG) to glutathione with the help of NADPH. For the successful maintenance of many antioxidant enzyme activities, it is important that glutathione stays at the reduced state [10]. Increased GSH-Red salivary concentrations have been shown to be a strong/independent prognostic indicator of the amount and extent of oxidative stress-related periodontal injury in both chronic periodontitis (CP) and aggressive periodontitis (AgP) [11].

###### *1.1.1.1.3 Glutathione transferase (GSH-Tr)*

Glutathione transferases, a multienzyme family, are responsible for the detoxification process. They produce an antioxidant defense mechanism by showing selenium-independent GSH-Px activity against lipid hydroperoxides, especially arachidonic acid and linoleic acid hydroperoxides. They have been shown to have increased activity in periodontal diseases [12].

###### *1.1.1.1.4 Catalase*

Catalase, which catalyzes the conversion of  $H_2O_2$  to molecular oxygen and water, is a protein that is found in both peroxisomes and cytosol and contains heme [7]. The lowered level of catalase is associated with hyper lipid peroxidation in periodontal disease [13].

###### *1.1.1.1.5 Superoxide dismutase (SOD)*

Superoxide dismutases are found in the cytosol and mitochondria of all aerobic cells. These enzymes eliminate the effects of superoxide radicals and protect the

cells against the harmful effects of these radicals. This enzyme plays a role in the intracellular destruction of phagocytosed bacteria and is important for granulocyte function [14]. Gingival SOD activity was found to be higher in patients with chronic periodontitis [15].

#### *1.1.1.1.6 Mitochondrial cytochrome oxidase*

Mitochondrial cytochrome oxidase is the last enzyme in the respiratory chain and detoxifies superoxide ( $O_2^-$ ) [16]. Maeda et al. [17] have suggested that mitochondrial cytochrome oxidase is a useful marker enzyme for demonstrating sensory receptors in the periodontal ligament.

#### *1.1.1.2 Nonenzymatic antioxidants*

##### *1.1.1.2.1 Melatonin*

It is found in foods such as sour cherries, almonds, hazelnuts, chamomile tea, and St. John's wort [18]. Because it has lipophilic properties, melatonin can be found in almost all cells. It exerts its antioxidant effect by quenching hydroxyl and superoxide radicals. Melatonin shows strong antioxidant properties in the inflammatory process and oxidative injuries. Melatonin was found to be lower in gingival crevicular fluid and saliva of individuals with periodontitis compared to healthy individuals. It has also been reported to enhance bone formation [19, 20]. Melatonin is released with saliva to the oral cavity and protects the mucosa and gingival tissues from radical damage [21].

##### *1.1.1.2.2 Ceruloplasmin*

Ceruloplasmin oxidizes  $Fe^{2+}$  to  $Fe^{3+}$  to prevent the Fenton reaction and hydroxyl radical formation [22]. In CP and AgP patients, the serum ceruloplasmin level increases, especially in AgP patients, it may be a potential marker for diagnosis of periodontitis [23].

##### *1.1.1.2.3 Transferrin*

Transferrin prevents the Fenton reaction by binding free iron ions [22]. There was an inverse relationship between transferrin serum levels and chronic periodontitis [24].

##### *1.1.1.2.4 Lactoferrin*

Lactoferrin binds to iron ions in low pH environments [25]. Lourenço et al. [26] indicated that lactoferrin (Lf) is a possible marker for periodontal diseases in immunocompetent and immunocompromised subjects.

##### *1.1.1.2.5 Glutathione (GSH and GSSG)*

Glutathione, which eliminates the effects of harmful compounds in the body, is found in all cells. GSH is reduced glutathione and serves as a substrate for antioxidant enzymes by acting as a radical scavenger during radical cell damage. Glutathione is a very important molecule, especially for the activities of peroxidase and reductase enzymes. GSSG is produced by the oxidation of GSH. During oxidative stress, GSH levels are decreased, and the GSSG levels are increased.  $H_2O_2$  and organic hydroperoxides, which are produced during oxidative stress, are removed by the action of glutathione peroxidase and glutathione reductase [25].



GSH plays a critical role in keeping enzymes and other cellular components from being reduced. Most of the GSH is synthesized in the liver, and approximately 40% of GSH is excreted through bile. It is suggested that the GSH in the bile protects the body against dietary xenobiotics, prevents lipid peroxidation in the lumen of the intestine, and defends the intestinal epithelium against oxygen radicals [27]. Glutathione is the most important redox regulator that controls inflammatory processes, thus damaging the periodontium [28].

#### *1.1.1.2.6 Cysteine*

Cysteine is a superoxide and hydroxyl radical scavenger [29]. The measurement of salivary cysteine may be useful for identifying periodontitis patients with hopeless teeth [30].

#### *1.1.1.2.7 Uric acid*

Uric acid, which is synthesized as the final product of purine metabolism, functions as an endogenous free radical scavenger and antioxidant. It is found in body fluids at a concentration of approximately 0.5 mmol/L [31]. In a recent study, uric acid levels in periodontitis patients have been found to be higher than in gingivitis patients. Moreover, uric acid has many roles in periodontitis than in gingivitis as an antioxidant agent [32].

#### *1.1.1.2.8 Glucose*

Glucose is a hydroxyl radical scavenger [33]. The relationship between the periodontal disease and the blood glucose level among type II diabetic patients has been demonstrated [34].

#### *1.1.1.2.9 Albumin*

It defends against free radicals and is therefore regarded as an important part of the extracellular antioxidant defense system [22]. An inverse relationship between the serum albumin concentration and the chronic periodontal disease has been evaluated [35].

#### *1.1.1.2.10 Bilirubin*

Bilirubin is an important scavenger of peroxy radicals [36]. Serum concentrations of bilirubin were found to be inversely associated with periodontitis and the association being stronger in severe disease [37].

### *1.1.2 Exogenous antioxidants*

#### *1.1.2.1 Vitamin A*

Carotenoids are recognized as substances that give color to vegetables and fruits, and their antioxidant effects as vitamin A precursors are well-known. Most important carotenoids are  $\alpha$ -carotene,  $\beta$ -carotene, lycopene, crocetin, canthaxanthin, and fucoxanthin.  $\beta$ -carotene is a combination of two molecules of vitamin A (also known as retinol). When dietary  $\beta$ -carotene is absorbed by the small intestinal mucosa, it is converted into retinol [5, 38]. Retinol and other retinoids have potential hormone-like effects on cell growth and differentiation [39]. It has been reported that in the case of retinol deficiency, predisposition to some types of cancer including oral cavity cancer is increased [40].

Vitamin A is an important vitamin involved in vision. Vitamin A is soluble in fat, helps maintaining healthy tissues and skin, strengthens the immune system, and is necessary for a healthy bone structure. It also acts as an antioxidant, protects cells against cancer and other diseases, slows down the aging process, and helps to store fat. In vitamin A deficiency, dermatological, mucosal, and ocular changes may occur [41].

#### *1.1.2.2 Vitamin C*

Vitamin C is a water-soluble antioxidant, which is found in citrus fruits, potatoes, tomatoes, and green leafy vegetables [5]. Since it is water soluble, it is not stored in the body, and its excess amounts are excreted through sweat and urine. Therefore, it must be taken daily [42]. Vitamin C is necessary for biosynthesis, structural integrity, and stability of many components in the connective tissue [43]. The function of vitamin C is particularly important in wound healing and tissue regeneration due to its role in collagen synthesis. Vitamin C acts as a coenzyme for many enzymes involved in the synthesis of collagen, carnitine, and neurotransmitters [2].

Vitamin C (also known as ascorbic acid) has many functions such as strengthening the immune system and development of bone and teeth. It enables protection against cancer and heart diseases. Unlike many other antioxidant vitamins, it is a water-soluble vitamin. It functions with glutathione in vitamin E regeneration. A negative correlation was found between plasma vitamin C and clinical attachment loss levels [44].

#### *1.1.2.3 Vitamin E*

Vitamin E is a name given to identify a group of eight natural compounds consisting of various tocopherols and tocotrienols, such as  $\alpha$ ,  $\beta$ , and  $\delta$ . The form of vitamin E with the highest biological activity is  $\alpha$ -tocopherol [45]. Vitamin E (also known as tocopherol) is the most important oil-soluble antioxidant found in nature [46]. It contains alpha, beta, gamma, and delta tocopherols. It is stored in the liver and has many functions in the immune system. It is found in cell membranes and as a component of lipoproteins [47]. Vitamin E is a major chain-breaking antioxidant and is the first line of defense against lipid peroxidation by protecting cell membranes during the early stages of free radical attack [48]. Its function as an antioxidant is mainly to inhibit peroxidation of membrane phospholipids and prevent damage to cell membranes. Lipid peroxidation is common in membranes, erythrocytes, lipoproteins, brain, and other tissues where polyunsaturated fatty acids (PUFAs) are abundant [47].

In an experimental study in rats, vitamin E has been shown to be important in preventing alveolar bone destruction. The effect of vitamin E in reducing periodontal inflammation can be explained by the fact that it is a prostaglandin inhibitor [6, 49].

#### *1.1.2.4 Polyphenols*

Polyphenols are composed of 4000 compounds in 13 classes (flavonoids, phenolic acids, anthocyanins, catechins, flavones, flavonols, flavanones, isoflavones, lignans, proanthocyanidins, procyanidins, resveratrol, and tannins). They are abundant in green tea, grape, and soy. They have anti-inflammatory, antiallergic, antiviral, antiaging, anticarcinogenic, and antioxidant properties [50].

#### *1.1.2.5 Flavonoids*

Flavonoids are free radical scavengers and are sub-grouped into flavanones, flavanols (e.g., Luteolin), flavanols (e.g., quercetin and kaempferol), flavan-3-ols (e.g., catechin), anthocyanins, and isoflavones according to their chemical

structure. Flavonoids are polyphenolic compounds found in vegetables (onion, parsley, etc.), fruits (berry, blackberry, apple, etc.), and beverages (green tea, cocoa, etc.). Due to their antioxidant, anti-inflammatory, antiallergic, antiviral, antibacterial, antiplatelet, and antitumor properties, they are widely used in medicine. Foods containing high amounts of flavonoids help protect blood vessels from rupture or leakage, protect cells from oxygen damage, and prevent inflammation in various tissues and organs [51, 52].

#### *1.1.2.6 Coenzyme Q10*

Coenzyme Q10, also known as ubiquinone, is a naturally occurring substance and is found in all living cells. It is abundant in veal, fish, and chicken [53]. It constitutes an important part of the energy production system of the body. Coenzyme Q10 strengthens the immune system by increasing immune resistance. It also protects the body against free radicals. It is especially important for the correct functioning of the heart muscle. It is a nutritional supplement that is soluble in fat and has an effect similar to vitamin E. In addition to its antioxidant effect, it is involved in the proper functioning of the circulatory system [54].

Coenzyme Q10 levels have been shown to be relatively low in gingival tissues of individuals with periodontitis. Local or systemic administration of Coenzyme Q10 during treatment helps reduce inflammation in periodontal tissues [55].

#### *1.1.2.7 Selenium*

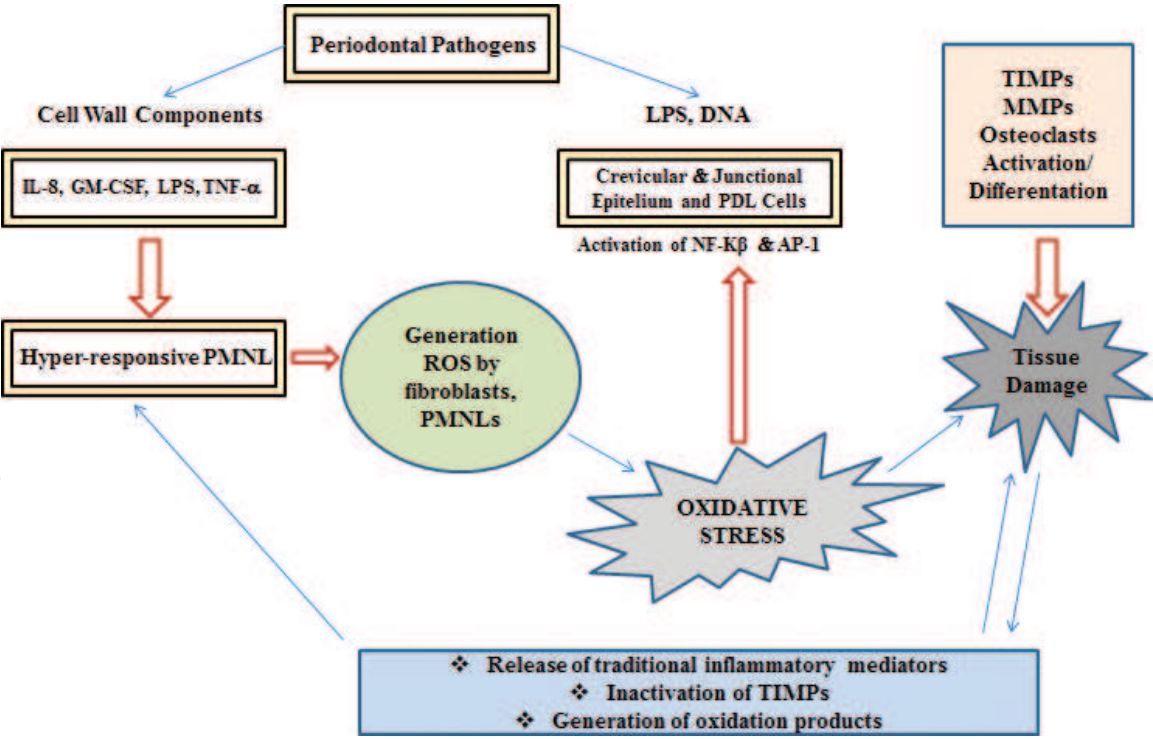
Selenium is found in the structure of selenoproteins and glutathione peroxidase, which is an important antioxidant enzyme. Selenoproteins help to regulate thyroid function and have a role in the immune system. Although selenium is a basic mineral required for a healthy body, the body only needs trace amounts of this mineral [56].

### **1.2 Periodontal diseases**

Periodontal diseases are inflammatory diseases characterized by inflammation and loss of periodontal tissues. Periodontopathogenic bacteria and their products are important in its etiology. The course of the disease is determined by the interaction between the periodontopathogenic bacteria and the host immune response. Reactive oxygen species play a role in these interactions in favor of tissue destruction [57]. Oxidative stress plays an important role in the pathogenesis of many diseases such as rheumatoid arthritis and atherosclerosis, and it has also been reported to affect the pathogenesis of periodontal diseases [58]. In the case of periodontal disease, the increased PMN count and activity cause a high rate of ROS release. This causes increased oxidative stress in periodontal tissues [6]. ROS produced on the surfaces of osteoclasts may play an important role in alveolar bone resorption [59]. Periodontal tissues require adequate levels of antioxidants to prevent tissue damage caused by reactive oxygen species. Therefore, some studies have focused on the effects of antioxidant use in addition to SRP (scaling and root planning) on periodontal tissue destruction [60]. Natural antioxidants protect the tissues against tissue damage caused by free radicals and play a critical role in maintaining the tissue health [61]. Due to the likely benefits of antioxidants against periodontitis, the intake of such nutrients is recommended [60]. **Figure 3** shows the possible oxidative stress-mediated inflammatory pathways related to periodontal tissue breakdown [62].

In a study, a positive correlation was found between the improvement in sulcus bleeding scores and the intake of grapefruit that leads to an increase in plasma





**Figure 3.** Possible oxidative stress-mediated inflammatory pathways related to periodontal tissue breakdown. LPS, lipopolysaccharide; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL8, interleukin-8; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; PDL, periodontal ligament; NF- $\kappa$ B, nuclear factor-kappa B; ROS, reactive oxygen species; PMNL, polymorphonuclear leukocyte; TIMP, tissue inhibitor of metalloproteinases; and MMP, matrix metalloproteinase.

vitamin C levels [63]. In an 8-month follow-up study on individuals with periodontitis, encapsulated fruit and vegetable powder concentrate was reported to reduce the periodontal pocket depth compared to placebo [64].

### 1.3 Antioxidant micronutrients

Main antioxidant sources in a diet are cereals, fruits, vegetables, chocolates, oils, and beverages such as tea, coffee, wine, and fruit juices [65].

#### 1.3.1 Vitamin C

Leggott et al. [66] showed that ascorbic acid deficiency is not associated with the mucosal pathoses or changes in plaque accumulation or probing depths. In another study, the same researchers showed that vitamin C was not associated with plaque accumulation, pocket depth, and attachment loss [67]. But, in both studies, ascorbic acid status was found directly related to the measures of gingival inflammation [66, 67]. Nishida et al. [68] found a weak but statistically significant inverse relationship between the vitamin C-rich diet and the periodontal disease. Chapple et al. [2] found a strong inverse relationship between the serum vitamin C levels and the prevalence of periodontitis. Jacob et al. [69] found that normal and high doses of vitamin C intake reduced gingival inflammation and sulcus bleeding. Rai et al. [70] found a strong relationship between the low concentrations of vitamin C in serum and saliva and the risk of periodontal disease. In other studies, vitamin C levels in the gingival fluid were found to be 3-folds higher than that of plasma [71], and vitamin C was found to inhibit neutrophil collagenase activation [72]. In an experimental periodontitis study on rats, vitamin C intake decreased interleukin-1 $\alpha$  and interleukin-1 $\beta$  gene expression by more than twofolds compared to the control

group [73]. In the same study, an increase in plasma vitamin C levels by 175% was found to result in a significant decrease in gingival 8-hydroxydeoxyguanosine levels and a significant increase in reduced oxidized glutathione amounts [73].

In a study on rats, Sanbe et al. [74] showed that vitamin C decreased high cholesterol diet-induced alveolar bone resorption and decreased periodontal tissue damage.

Vitamin C has been shown to decrease the cytotoxic and apoptotic effects of *Porphyromonas gingivalis* (*P. gingivalis*) on gingival fibroblasts *in vitro* [75].

Akman et al. [76] showed that the administration of vitamin C with or without alpha lipoic acid was associated with a significant decrease in serum myeloperoxidase levels, increased bone alkaline phosphatase levels, decreased alveolar bone resorption, and decreased RANKL-positive cell count. In individuals with chronic periodontitis, vitamin C intake in addition to nonsurgical periodontal treatment has been shown to decrease the gingival bleeding index levels [77]. Furthermore, it was reported that low serum levels of vitamin C and vitamin E may be risk factors for periodontal disease in elderly individuals [78].

### 1.3.2 Vitamin E

Research on the relationship between vitamin E and periodontal diseases showed conflicting results. Cohen et al. [79] reported that 5% topical vitamin E gel, in addition to SRP, did not positively affect the formation of plaque and healing of the periodontal tissues. In another study, same researchers showed that vitamin E has a protective role against bone loss [49]. Another study reported that there was no statistically significant difference between the periodontitis patients and the healthy group in terms of serum vitamin E levels [80]. These contradictory results may be related to the study design, the dose of vitamin E, and the investigated different parameters.

In a study on rats, the combination of vitamin E and selenium has been shown to reduce collagen degradation [81]. In addition, vitamin E supplementation has been found to accelerate gingival wound healing [82].

A negative correlation was found between serum  $\alpha$ -tocopherol levels and the severity of periodontitis. While the level of  $\alpha$ -tocopherol increases, the severity of periodontitis decreases [83]. The use of vitamin E in addition to nonsurgical periodontal treatment has been shown to have positive effects on periodontal parameters [84].

### 1.3.3 Carotenoids

Carotenoids are highly potent antioxidants. Linden et al. [85] showed that  $\alpha$ -carotene,  $\beta$ -carotene,  $\beta$ -cryptoxanthin, and zeaxanthin levels were significantly lower in patients with moderate to severe periodontitis.

It has been shown that  $\beta$ -cryptoxanthin stimulates bone formation and may stop bone resorption by inhibiting gene expression of osteoclastic enzymes associated with bone resorption [86]. Therefore, it has been suggested that  $\beta$ -cryptoxanthin may reduce the risk of osteoporosis [87]. This may mean that it can slow and/or stop the alveolar bone destruction in periodontal diseases.

Systemic supplementation of 8 mg/day of lycopene was reported to decrease the gingival index in patients with gingivitis [88]. In individuals with chronic periodontitis, it was reported that the supplementation of 4 mg/day of oral lycopene in addition to SRP for 2 weeks resulted in a reduction in clinical attachment loss [89]. Arora et al. [90] found that, in individuals with CP, 8 mg/day of oral lycopene intake for 2 months in addition to SRP had positive effects in plaque index, modified gingival index, probing bleeding, and saliva IL-1 $\beta$  compared to the control group but reported that there was no significant difference in terms of a reduction in pocket depth, clinical attachment, and serum TNF- $\alpha$  levels.

In an animal study, vitamin A deficiency was shown to cause hyperkeratosis in the gingival epithelium, periodontal pocket formation, cement resorption, and osseous changes [91]. In another study, vitamin A deficiency was found to result in thickening of the cement, contraction of the periodontal ligament, irregularities in the periodontal ligament, thickening of the alveolar bone, and labial alveolar periosteum, and these results were shown to be reversible with replacement therapy [92]. In a study analyzing the relationship between the periodontal status and the serum antioxidant levels, it was shown that there was a relationship between the prevalence of increased periodontitis and the low serum levels of  $\beta$  cryptoxanthin and  $\beta$  carotene in men between the age of 60–70 years [85].

#### *1.3.4 Coenzyme Q10*

In periodontal disease, the amount of Coenzyme Q10 decreases in both blood and gingival tissues [93]. Oral intake of Coenzyme Q10 was found to cause an increase in the density of the gingiva and a decrease in the periodontal inflammation and microorganism amounts [94–96]. In another study, coadministration of Coenzyme Q10 and vitamin E orally was found to result in a decrease in plaque index, gingival index, sulcus bleeding index, and pocket depth [97].

#### *1.3.5 Polyphenols*

Polyphenols can increase the antioxidant activity of oral fluids. It has been reported that keeping green tea in the mouth for 2–5 minutes increases the antioxidant capacity of saliva [98], and the consumption of two grapefruits per day for 2 weeks increases the phagocytic capacity of the gingival crevicular fluid neutrophils [99]. Furthermore, *in vitro* studies have shown the antibacterial effect of polyphenols against periodontal pathogens [100].

#### *1.3.6 Flavonoids*

Catechin is an effective antioxidant found in green tea and was found to have protective effects against cancer and cardiovascular diseases. Catechins have also been shown to inhibit the growth of periodontal pathogens and prevent the periodontal tissue destruction [101].

In green tea users, the gingival bleeding index is decreased significantly [102]. Also, it was shown that green tea has an inverse relationship with average pocket depth, levels of bleeding during probing, and clinical attachment level [103]. In another study, it has been reported that green tea inhibits the activity of gingival crevicular fluid collagenase in aggressive periodontitis patients [104]. In an experimental periodontitis model in rats, flavonoids have been shown to prevent inflammatory bone resorption by lipopolysaccharides [105]. Chopra et al. [106] reported that green tea supplement in addition to the nonsurgical periodontal treatment resulted in improvements in the plaque index, gingival index, bleeding during probing, and clinical attachment loss parameters, and the gingival crevicular fluid antioxidant capacity was eight times higher than the control group. In contrast to these studies, in a study conducted in adults, it was found that the consumption of less than one cup of green tea per day was associated with a decrease in the prevalence of periodontal disease, and the consumption of one or more cups of green tea per day resulted in an increase in the prevalence of moderate and severe periodontitis [107].

Cocoa also contains flavonoids, and in an experimental study conducted in rats, a diet rich in cocoa has been shown to reduce periodontal disease-associated oxidative stress and periodontal destruction [108].



Coffee, which is a rich source of antioxidants due to its caffeine, caffeic acid, and chlorogenic acid content, has a modulating effect in natural and acquired immune response [109, 110]. In a study on adult males, coffee consumption has been shown to reduce alveolar bone loss [111]. Among periodontitis patients at the periodontal maintenance phase, there was a negative correlation between the coffee consumption [ $\geq 1$  cup/day] and the prevalence of severe periodontitis [112]. Han et al. [113] suggested that coffee consumption is higher in men with periodontitis, and it may be an independent risk factor for periodontal disease.

Quercetin is one of the most common flavonoids in dietary foods. It is a free radical scavenger found in many vegetables, fruits, olive oil, red wine, and tea. It has anti-inflammatory, antiallergic, antiviral, antithrombotic, antimutagenic, antineoplastic, and cytoprotective effects. In an experimental periodontitis study conducted on rats, 75 mg/kg/day oral quercetin administration was reported to decrease lipopolysaccharide-induced osteoclast formation, bone loss, and periodontal inflammation [114].

Curcumin also has antioxidant properties due to the phenolic compounds in its content. It has antitumor and anti-inflammatory properties [115]. Bakir et al. [116] reported that oral curcumin application reduced alveolar bone loss in rats.

Kaempferol is one of the flavonoids in vegetables (leek, cucumber, etc.), fruits, and tea. It has an immunomodulatory effect and has been suggested to be used as a host modulator agent in periodontal therapy [117]. In a study on rats, the administration of 10 mg/kg/day of oral kaempferol was reported to decrease the alveolar bone loss, attachment loss, and gingival tissue MMP-1 and MMP-8 levels [118].

The active ingredients of propolis are also flavonoids. In addition, it contains magnesium, calcium, iodine, potassium, sodium, copper, zinc, manganese and iron minerals, and vitamins B1, B2, B6, C, and E. The content that gives most of its antioxidant properties is the caffeic acid, which has phenolic properties. In an experimental periodontitis study performed in rats, it was shown that systemic propolis administration of 100 mg/kg/day for 21 days reduced alveolar bone loss [119]. In addition to SRP, 400 mg of daily propolis supplementation for 6 months was reported to significantly decrease HbA1C levels and pocket depth at 3 and 6 months compared to the control groups and to increase clinical attachment gain [120].

Proanthocyanidin is a potent antioxidant found in grape seed and red fruits like cranberries, blueberries, etc. In an experimental periodontitis model in rats, 30 mg/kg of proanthocyanidin was given for 30 days, and a decrease in reactive oxygen species in blood and a decrease in histopathologic inflammatory cell infiltration were reported [121].

Olive oil contains a large number of polyphenols, a high concentration of  $\alpha$ -tocopherols, and low concentrations of carotene and acts as a chain-breaking antioxidant through its oleuropein content. In a 24-month study conducted in rats, it was shown that alveolar bone loss was lower in the group that used olive oil compared to the groups that used sunflower oil and fish oil in addition to their regular diet [122].

### *1.3.7 Melatonin*

No significant difference was shown between saliva and plasma melatonin levels of healthy subjects and CP patients; however, melatonin levels were significantly lower in gingival tissues of individuals with CP [123]. It was reported that the levels of saliva melatonin increased after nonsurgical periodontal treatment and salivary melatonin levels correlated negatively with bleeding during probing [21].



1.3.8 Selenium

Serum selenium, glutathione, and catalase levels in diabetic individuals with periodontitis have been reported to be negatively correlated with the severity of periodontal inflammation and tissue destruction [124].

2. Conclusion

Some systemic diseases and conditions that affect periodontal diseases including, cardiovascular disease, diabetes, dyslipidemia, hypertension, obesity, osteoporosis, and pregnancy are associated with antioxidants. Also, periodontitis is associated with low serum/plasma micronutrient levels. Nowadays, actual studies that investigate the effects of antioxidants on periodontal diseases have shown that antioxidants have anti-inflammatory properties. Although numerous studies demonstrated the relationship between antioxidants and periodontal diseases, and the number of studies in humans is limited. There are only a few cross-sectional studies that support the potential to improve periodontal outcomes by antioxidants. This chapter will discuss the possible role of antioxidants in the etiology and therapy of periodontal diseases.

Conflict of interest

The author has no conflicts of interest to disclose.

Abbreviations

AgP	aggressive periodontitis
AO	antioxidants
CP	chronic periodontitis
GSH and GSSG	glutathione
GSH-Px	glutathione peroxidase
GSH-Red	glutathione reductase
GSH-Tr	glutathione transferase
H <sub>2</sub> O <sub>2</sub>	hydrogen peroxide
Lf	lactoferrin
GSSG	oxidized glutathione
PLA2	phospholipase A2
PUFA	polyunsaturated fatty acids
<i>P. gingivalis</i>	<i>Porphyromonas gingivalis</i>
ROS	reactive oxygen species
SRP	scaling and root planning
Se	selenium
O <sub>2</sub> <sup>-</sup>	superoxide
SO	superoxide dismutase

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## References

- [1] Dennison DK, Dyke TE. The acute inflammatory response and the role of phagocytic cells in periodontal health and disease. *Periodontology* 2000. 1997;**14**(1):54-78
- [2] Chapple ILC, Matthews JB. The role of reactive oxygen and antioxidant species in periodontal tissue destruction. *Periodontology* 2000. 2007;**43**(1):160-232
- [3] Bansal N, Gupta ND. Role of dietary antioxidants in periodontitis: A preventive approach. *IOSR Journal of Dental and Medical Sciences*. 2014;**13**(9):81-84
- [4] Young IS, Woodside JV. Antioxidants in health disease. *Journal of Clinical Pathology*. 2001;**54**:176-186
- [5] Baskin SI, Salem H. Oxidants, Antioxidants, and Free Radicals. Washington DC: Taylor and Francis; 1997. pp. 79-120
- [6] Chapple IL. Role of free radicals and antioxidants in the pathogenesis of the inflammatory periodontal diseases. *Clinical Molecular Pathology*. 1996;**49**(5):M247-M255
- [7] Garewal HS. Antioxidants and Disease Prevention. Florida: CRC Press LLC; 1997. pp. 3-19
- [8] Ho YS, Magnenat JL, Gargano M, Cao J. The nature of antioxidant defense mechanisms: A lesson from transgenic studies. *Environmental Health Perspectives*. 1998;**106**(5):1219-1228
- [9] Patel SP, Rao NS, Pradeep AR. Effect of nonsurgical periodontal therapy on crevicular fluid and serum glutathione peroxidase levels. *Disease Markers*. 2012;**32**(1):1-7
- [10] Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. *Nature*. 2000;**408**:239-247
- [11] Villa-Correa YA, Isaza-Guzmán DM, Tobón-Arroyave SI. Influence of periodontal clinical status on salivary levels of glutathione reductase. *Journal of Periodontology*. 2016;**87**(6):716-724
- [12] Oakley AJ. Glutathione transferases: New functions. *Current Opinion in Structural Biology*. 2005;**15**(6):716-723
- [13] Dahiya P, Kamal R, Gupta R, Saini H. Evaluation of the serum antioxidant status in patients with chronic periodontitis. *Indian Journal of Multidisciplinary Dentistry*. 2016;**6**(1):3-6
- [14] Skaleric U, Manthey CM, Mergenhagen SE, Gaspirc B, Wahl SM. Superoxide release and superoxide dismutase expression by human gingival fibroblasts. *European Journal of Oral Sciences*. 2000;**108**(2):130-135
- [15] Wei D, Zhang XL, Wang YZ, Yang CX, Chen G. Lipid peroxidation levels, total oxidant status and superoxide dismutase in serum, saliva and gingival crevicular fluid in chronic periodontitis patients before and after periodontal therapy. *Australian Dental Journal*. 2010;**55**(1):70-78
- [16] Cooper CE, Brown GC. The inhibition of mitochondrial cytochrome oxidase by the gases carbon monoxide, nitric oxide, hydrogen cyanide and hydrogen sulfide: Chemical mechanism and physiological significance. *Journal of Bioenergetics and Biomembranes*. 2008;**40**(5):533-539
- [17] Maeda T, Sato O, Takano Y. Cytochrome oxidase activity as a marker for periodontal sensory receptors in the rat. *Archives of Oral Biology*. 1993;**38**(3):255-259
- [18] Ögüt S. Doğal antioksidanların önemi. *Journal of Adnan Menderes University, Agricultural Faculty*. 2014;**11**:25-30
- [19] Cutando A, Galindo P, Gómez-Moreno G, Arana C, Bolaños J, Acuña-Castroviejo

- D, et al. Relationship between salivary melatonin and severity of periodontal disease. *Journal of Periodontology*. 2006;**77**(9):1533-1538
- [20] Srinath R, Acharya AB, Thakur SL. Salivary and gingival crevicular fluid melatonin in periodontal health and disease. *Journal of Periodontology*. 2010;**81**(2):277-283
- [21] Bertl K, Schoiber A, Haririan H, Laky M, Steiner I, Rausch WD, et al. Non-surgical periodontal therapy influences salivary melatonin levels. *Clinical Oral Investigations*. 2013;**17**(4):1219-1225
- [22] Soriani M, Pietraforte D, Minetti M. Antioxidant potential of anaerobic human plasma: Role of serum albumin and thiols as scavengers of carbon radicals. *Archives of Biochemistry and Biophysics*. 1994;**312**(1):180-188
- [23] Harshavardhana B, Rath SK, Mukherjee M. Evaluation of serum ceruloplasmin in aggressive and chronic periodontitis patients. *Journal of Indian Society of Periodontology*. 2013;**17**(3):333-337
- [24] Shirmohamadi A, Chitsazi MT, Faramarzi M, Salari A, Alavi FN, Pashazadeh N. Effect of non-surgical periodontal treatment on transferrin serum levels in patients with chronic periodontitis. *Journal of Dental Research, Dental Clinics, Dental Prospects*. 2016;**10**(3):169-175
- [25] Battino M, Ferreiro MS, Gallardo I, Newman HN, Bullon P. The antioxidant capacity of saliva. *Journal of Clinical Periodontology*. 2002;**29**(3):189-194
- [26] Lourenço AG, Nakao C, Machado AA, Motta AC, Tonani L, Candido RC, et al. Lactoferrin, a marker for periodontal disease. *Current HIV Research*. 2013;**11**(3):220-225
- [27] Maher P, Lewerenz J, Lozano C, Torres JL. A novel approach to enhancing cellular glutathione levels. *Journal of Neurochemistry*. 2008;**107**:690-700
- [28] Bains VK, Bains R. The antioxidant master glutathione and periodontal health. *Dental Research Journal*. 2015;**12**(5):389-405
- [29] Halliwell B. Reactive oxygen species in living systems: Source, biochemistry, and role in human disease. *American Journal of Medicine*. 1991;**91**(3):14-22
- [30] Tassi C, Lotito M. Levels of salivary cysteine in periodontitis patients with and without hopeless teeth: Diagnostic validity of the assay. *Journal of Osseointegration*. 2010;**1**(2):24-27
- [31] Sinha S, Singh SN, Ray US. Total antioxidant status at high altitude in lowlanders and native highlanders: Role of uric acid. *High Altitude Medicine & Biology*. 2009;**10**(3):269-274
- [32] Rizal MI, Vega S. Level of salivary uric acid in gingivitis and periodontitis patients. *Journal of Dental Sciences*. 2017;**1**(1):7-10
- [33] Hunt JV, Dean RT, Wolff SP. Hydroxyl radical production and autoxidative glycosylation. Glucose autoxidation as the cause of protein damage in the experimental glycation model of diabetes mellitus and ageing. *The Biochemical Journal*. 1988;**256**(1):205-212
- [34] Almas K, Al-Qahtani M, Al-Yami M, Khan N. The relationship between periodontal disease and blood glucose level among type II diabetic patients. *The Journal of Contemporary Dental Practice*. 2001;**2**(4):18-25
- [35] Kaur N, Kaur N, Sarangal V. A study to evaluate the correlation of serum albumin levels with chronic periodontitis. *Indian Journal of Dental Research*. 2015;**26**(1):11-14
- [36] Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. Bilirubin



is an antioxidant of possible physiological importance. *Science*. 1987;**235**(4792):1043-1046

[37] Chapple ILC, Milward MR, Dietrich T. The prevalence of inflammatory periodontitis is negatively associated with serum antioxidant concentrations. *The Journal of Nutrition*. 2007;**137**(3):657-664

[38] Higdon J. Carotenoids. In: *An Evidence-Based Approach to Dietary Phytochemicals*. New York: Thieme; 2006. pp. 47-61

[39] Moore T. Effects of vitamin A deficiency in animals: Pharmacology and toxicology of vitamin A. In: Sebrell WH, Harris RS, editors. *The Vitamins*. Vol. 1967. New York: Academic Press. pp. 245, 280-266, 294

[40] Rowe NH, Gorlin RJ. The effect of vitamin A deficiency upon experimental oral carcinogenesis. *Journal of Dental Research*. 1959;**38**(1):72-83

[41] Stanford TW, Rees TD. Acquired immune suppression and other risk factors/indicators for periodontal disease progression. *Periodontology* 2000. 2003;**32**(1):118-135

[42] Flora SJ. Structural, chemical and biological aspects of antioxidants for strategies against metal and metalloid exposure. *Oxidative Medicine and Cellular Longevity*. 2009;**2**(4):191-206

[43] Mazzotta MY. Nutrition and wound healing. *Journal of the American Podiatric Medical Association*. 1994;**84**(9):456-462

[44] Amaliya, Timmerman MF, Abbas F, Loos BG, Van der Weijden GA, Van Winkelhoff AJ, et al. Java project on periodontal diseases: The relationship between vitamin C and the severity of periodontitis. *Journal of Clinical Periodontology*. 2007;**34**(4): 299-304

[45] Brigelius-Flohe R, Traber MG. Vitamin E: Function and metabolism. *The FASEB Journal*. 1999;**13**(10):1145-1155

[46] Maxwell SR. Prospects for the use of antioxidant therapies. *Drugs*. 1995;**49**(3):345-361

[47] Zaidi SM, Banu N. Antioxidant potential of vitamins A, E and C in modulating oxidative stress in rat brain. *Clinica Chimica Acta*. 2004;**340**(1-2):229-233

[48] Horwitt MK. Interpretations of requirements for thiamin, riboflavin, niacin-tryptophan, and vitamin E plus comments on balance studies and vitamin B-6. *The American Journal of Clinical Nutrition*. 1986;**44**(6):973-985

[49] Cohen ME, Meyer DM. Effect of dietary vitamin E supplementation and rotational stress on alveolar bone loss in rice rats. *Archives of Oral Biology*. 1993;**38**(7):601-606

[50] Derviş E. Oral antioksidanlar. *Dermatoloji Akademisi Dernegi*. 2011;**2**:263-267

[51] Tapas AR, Sakarkar DM, Kakde RB. Flavonoids as nutraceuticals: A review. *Tropical Journal of Pharmaceutical Research*. 2008;**7**(3):1089-1099

[52] Kozłowska A, Szostak-Wegierek D. Flavonoids--food sources and health benefits. *Roczniki Państwowego Zakładu Higieny*. 2014;**65**(2):79-85

[53] Ercan P, El SN. Koenzim q10'un beslenme ve sağlık açısından önemi ve biyoyararlılığı. *TÜBAV Bilim Dergisi*. 2010;**3**:192-200

[54] Sumien N, Heinrich KR, Shetty RA, Sohal RS, Forster MJ. Prolonged intake of coenzyme Q10 impairs cognitive functions in mice. *The Journal of Nutrition*. 2009;**139**(10):1926-1932

- [55] Hanioka T, Tanaka M, Ojima M, Shizukuishi S, Folkers K. Effect of topical application of coenzyme Q10 on adult periodontitis. *Molecular Aspects of Medicine*. 1994;**15**:241-248
- [56] Velioğlu S. Doğal antioksidanların insan sağlığına etkileri. *Gıda Bilim ve Teknoloji Dergisi*. 2000;**25**(3):167-176
- [57] Chapple ILC. Reactive oxygen species and antioxidants in inflammatory diseases. *Journal of Clinical Periodontology*. 1997;**24**:287-296
- [58] Tsai CC, Chen HS, Chen SL, Ho YP, Ho KY, Wu YM, et al. Lipid peroxidation: A possible role in the induction and progression of chronic periodontitis. *Journal of Periodontal Research*. 2005;**40**(5):378-384
- [59] Steinbeck MJ, Appel WH Jr, Verhoeven AJ. NADPH-oxidase expression and in situ production of superoxide by osteoclasts actively resorbing bone. *The Journal of Cell Biology*. 1994;**126**(3):765-772
- [60] Chapple IL, Brock G, Eftimiadi C, Matthews JB. Glutathione in gingival crevicular fluid and its relation to local antioxidant capacity in periodontal health and disease. *Molecular Pathology*. 2002;**55**(6):367-373
- [61] Halliwell B. How to characterize an antioxidant: An update. *Biochemical Society Symposium*. 1995;**61**:73-101
- [62] Gumus P, Huseyinalemдарoglu B, Buduneli N. The role of oxidative stress in the interaction of periodontal disease with systemic diseases or conditions. *Oxidants and Antioxidants in Medical Science*. 2016;**5**(2):33-38
- [63] Borutta A. Vitamin C intake and periodontal disease. *British Dental Journal*. 2005;**199**:210
- [64] Chapple IL, Milward MR, Ling-Mountford N, Weston P, Carter K, Askey K, et al. Adjunctive daily supplementation with encapsulated fruit, vegetable and berry juice powder concentrates and clinical periodontal outcomes: A double-blind RCT. *Journal of Clinical Periodontology*. 2012;**39**(1):62-72
- [65] McCall MR, Frei B. Can antioxidant vitamins materially reduce oxidative damage in humans? *Free Radical Biology & Medicine*. 1999;**26**(7-8):1034-1053
- [66] Leggott PJ, Robertson PB, Rothman DL, Murray PA, Jacob RA. The effect of controlled ascorbic acid depletion and supplementation on periodontal health. *Journal of Periodontology*. 1986;**57**(8):480-485
- [67] Leggott PJ, Robertson PB, Jacob RA, Zambon JJ, Walsh M, Armitage GC. Effects of ascorbic acid depletion and supplementation on periodontal health and subgingival microflora in humans. *Journal of Dental Research*. 1991;**70**(12):1531-1536
- [68] Nishida M, Grossi SG, Dunford RG, Ho AW, Trevisan M, Genco RJ. Dietary vitamin C and the risk for periodontal disease. *Journal of Periodontology*. 2000;**71**(8):1215-1223
- [69] Jacob RA, Omaye ST, Skala JH, Leggott PJ, Rothman DL, Murray PA. Experimental vitamin C depletion and supplementation in young men. Nutrient interactions and dental health effects. *Annals of the New York Academy of Sciences*. 1987;**498**(1):333-346
- [70] Rai B, Anand SC. Serum and salivary vitamin C in periodontal disease. *Advances in Medical and Dental Sciences*. 2008;**2**(2):26-27
- [71] Meyle J, Kapitzka K. Assay of ascorbic acid in human crevicular fluid from clinically healthy gingival sites by high-performance liquid chromatography. *Archives of Oral Biology*. 1990;**35**(4):319-323

- [72] Suomalainen K, Sorsa T, Lindy O, Saari H, Konttinen YT, Uitto VJ. Hypochlorous acid induced activation of human neutrophil and gingival crevicular fluid collagenase can be inhibited by ascorbate. *Scandinavian Journal of Dental Research*. 1991;**99**(5):397-405
- [73] Tomofuji T, Ekuni D, Sanbe T, Irie K, Azuma T, Maruyama T, et al. Effects of vitamin C intake on gingival oxidative stress in rat periodontitis. *Free Radical Biology & Medicine*. 2009;**46**(2):163-168
- [74] Sanbe T, Tomofuji T, Ekuni D, Azuma T, Tamaki N, Yamamoto T. Oral administration of vitamin C prevents alveolar bone resorption induced by high dietary cholesterol in rats. *Journal of Periodontology*. 2007;**78**(11):2165-2170
- [75] Staudte H, Guntsch A, Volpel A, Sigusch BW. Vitamin C attenuates the cytotoxic effects of porphyromonas gingivalis on human gingival fibroblasts. *Archives of Oral Biology*. 2010;**55**(1):40-45
- [76] Akman S, Canakci V, Kara A, Tozoglu U, Arabaci T, Dagsuyu IM. Therapeutic effects of alpha lipoic acid and vitamin C on alveolar bone resorption after experimental periodontitis in rats: A biochemical, histochemical, and stereologic study. *Journal of Periodontology*. 2013;**84**(5):666-674
- [77] Gokhale NH, Acharya AB, Patil VS, Trivedi DJ, Thakur SL. A short-term evaluation of the relationship between plasma ascorbic acid levels and periodontal disease in systemically healthy and type 2 diabetes mellitus subjects. *Journal of Dietary Supplements*. 2013;**10**(2):93-104
- [78] Iwasaki M, Manz MC, Taylor GW, Yoshihara A, Miyazaki H. Relations of serum ascorbic acid and  $\alpha$ -tocopherol to periodontal disease. *Journal of Dental Research*. 2012;**91**(2):167-172
- [79] Cohen RE, Ciancio SG, Mather ML, Curro FA. Effect of vitamin E gel, placebo gel and chlorhexidine on periodontal disease. *Clinical Preventive Dentistry*. 1991;**13**(5):20-24
- [80] Slade EW Jr, Bartuska D, Rose LF, Cohen DW. Vitamin E and periodontal disease. *Journal of Periodontology*. 1976;**47**(6):352-354
- [81] Asman B, Wijkander P, Hjerpe A. Reduction of collagen degradation in experimental granulation tissue by vitamin E and selenium. *Journal of Clinical Periodontology*. 1994;**21**(1):45-47
- [82] Kim JE, Shklar G. The effect of vitamin E on the healing of gingival wounds in rats. *Journal of Periodontology*. 1983;**54**(5):305-308
- [83] Zong G, Scott AE, Griffiths HR, Zock PL, Dietrich T, Newson RS. Serum  $\alpha$ -tocopherol has a nonlinear inverse association with periodontitis among US adults. *The Journal of Nutrition*. 2015;**145**(5):893-899
- [84] Singh N, Chander Narula S, Kumar Sharma R, Tewari S, Kumar SP. Vitamin E supplementation, superoxide dismutase status, and outcome of scaling and root planing in patients with chronic periodontitis: A randomized clinical trial. *Journal of Periodontology*. 2014;**85**(2):242-249
- [85] Linden GJ, McClean KM, Woodside JV, Patterson CC, Evans A, Young IS, et al. Antioxidants and periodontitis in 60-70-year-old men. *Journal of Clinical Periodontology*. 2009;**36**(10):843-849
- [86] Yamaguchi M. Role of carotenoid  $\beta$ -cryptoxanthin in bone homeostasis. *Journal of Biomedical Science*. 2012;**19**(1):36
- [87] Sugiura M, Nakamura M, Ogawa K, Ikoma Y, Ando F, Yano M. Bone mineral density in post-menopausal female subjects is associated with serum



antioxidant carotenoids. *Osteoporosis International*. 2008;**19**(2):211-219

[88] Chandra RV, Prabhuji ML, Roopa DA, Ravirajan S, Kishore HC. Efficacy of lycopene in the treatment of gingivitis: A randomised, placebo-controlled clinical trial. *Oral Health & Preventive Dentistry*. 2007;**5**(4):327-336

[89] Belludi SA, Verma S, Banthia R, Bhusari P, Parwani S, Kedia S, et al. Effect of lycopene in the treatment of periodontal disease: A clinical study. *The Journal of Contemporary Dental Practice*. 2013;**14**(6):1054-1059

[90] Arora N, Avula H, Avula JK. The adjunctive use of systemic antioxidant therapy [lycopene] in nonsurgical treatment of chronic periodontitis: A short term evaluation. *Quintessence International*. 2013;**44**(6):395-405

[91] Frandsen AM. Periodontal tissue changes in vitamin A deficient young rats. *Acta Odontologica Scandinavica*. 1963;**21**:19-34

[92] Schour I, Hoffman MM, Smith MC. Changes in the incisor teeth of albino rats with vitamin a deficiency and the effects of replacement therapy. *The American Journal of Pathology*. 1941;**17**(4):529-562

[93] Soni S, Pk A, Sharma N, Chander S. Coenzyme Q10 and periodontal health: A review. *International Journal of Oral and Maxillofacial Pathology*. 2012;**3**(2):21-26

[94] McRee JT, Hanioka T, Shizukuishi S, Folkers K. Therapy with coenzyme Q10 for patients with periodontal disease. 1. Effect of coenzyme Q10 on subgingival microorganisms. *Jjournal of Dental Health*. 1993;**43**:659-666

[95] Shizukuishi S, Hanioka T, Tsunemitsu A, Fukunaga Y, Kishi T, Sato N. Clinical Effect of Coenzyme 10 on Periodontal Disease; Evaluation

of Oxygen Utilisation in Gingiva by Tissue Reflectance Spectrophotometry. Amsterdam: Elsevier; 1986. pp. 359-368

[96] Wilkinson EG, Arnold RM, Folkers K, Hansen I, Kishi H. Bioenergetics in clinical medicine. II. Adjunctive treatment with coenzyme Q in periodontal therapy. *Research Communications in Chemical Pathology and Pharmacology*. 1975;**12**(1):111-123

[97] Matthews-Brzozowska T, Kurhańska-Flisykowska A, Wyganowska-Swiatkowska M, Stopa J. Healing of periodontal tissue assisted by coenzyme Q10 with Vitamin E—clinical and laboratory evaluation. *Pharmacological Reports*. 2007;**59**(1):257-260

[98] Lee MJ, Lambert JD, Prabhu S, Meng X, Lu H, Maliakal P, et al. Delivery of tea polyphenols to the oral cavity by green tea leaves and black tea extract. *Cancer Epidemiology, Biomarkers & Prevention*. 2004;**13**(1):132-137

[99] Staudte H, Sigusch BW, Glockmann E. Grapefruit consumption improves vitamin C status in periodontitis patients. *British Dental Journal*. 2005;**199**(4):213-217

[100] Petti S, Scully C. Polyphenols, oral health and disease: A review. *Journal of Dentistry*. 2009;**37**(6):413-423

[101] Makimura M, Hirasawa M, Kobayashi K. Inhibitory effect of tea catechins on collagenase activity. *Journal of Periodontology*. 1993;**64**:630-636

[102] Nănescu S, Mârțu S, Ciomaga G, Toma V, Forna D, Foia L, et al. Dual effects of flavonoids on dyslipidemia and periodontal disease. *Romanian Journal of Oral Rehabilitation*. 2011;**3**(4):38-46

[103] Kushiya M, Shimazaki Y, Murakami M, Yamashita Y. Relationship between intake of green tea and periodontal disease. *Journal of Periodontology*. 2009;**80**:372-377



- [104] Balbin M, Fueyo A, Tester AM, Pendás AM, Pitiot AS, Astudillo A, et al. Loss of collagenase-2 confers increased skin tumour susceptibility to male mice. *Nature Genetics*. 2003;**35**(3):252-257
- [105] Tominari T, Hirata M, Matsumoto C, Inada M, Miyaura C. Polymethoxy flavonoids, nobiletin and tangeretin, prevent lipopolysaccharide-induced inflammatory bone loss in an experimental model for periodontitis. *Journal of Pharmacological Sciences*. 2012;**119**:390-394
- [106] Chopra A, Thomas BS, Sivaraman K, Prasad HK, Kamath SU. Green tea intake as an adjunct to mechanical periodontal therapy for the management of mild to moderate chronic periodontitis: A randomized controlled clinical trial. *Oral Health & Preventive Dentistry*. 2016;**14**:293-303
- [107] Han K, Hwang E, Park JB. Excessive consumption of green tea as a risk factor for periodontal disease among Korean adults. *Nutrients*. 2016;**8**(7):408
- [108] Tomofuji T, Ekuni D, Irie K, Azuma T, Endo Y, Tamaki N, et al. Preventive effects of a cocoa-enriched diet on gingival oxidative stress in experimental periodontitis. *Journal of Periodontology*. 2009;**80**(11):1799-1808
- [109] Leon-Carmona JR, Galano A. Is caffeine a good scavenger of oxygenated free radicals? *The Journal of Physical Chemistry. B*. 2011;**115**:4538-4546
- [110] Horrigan LA, Kelly JP, Connor TJ. Immunomodulatory effects of caffeine: Friend or foe? *Pharmacology & Therapeutics*. 2006;**111**:877-892
- [111] Ng N, Kaye EK, Garcia RI. Coffee consumption and periodontal disease in males. *Journal of Periodontology*. 2014;**85**(8):1042-1049
- [112] Machida T, Tomofuji T, Ekuni D, Azuma T, Takeuchi N, Maruyama T, et al. Severe periodontitis is inversely associated with coffee consumption in the maintenance phase of periodontal treatment. *Nutrients*. 2014;**6**(10):4476-4490
- [113] Han K, Hwang E, Park JB. Association between consumption of coffee and the prevalence of periodontitis: The 2008-2010 Korea National Health and Nutrition Examination Survey. *PLoS One*. 2015;**13**:e0134784
- [114] Cheng WC, Huang RY, Chiang CY, Chen JK, Liu CH, Chu CL, et al. Ameliorative effect of quercetin on the destruction caused by experimental periodontitis in rats. *Journal of Periodontal Research*. 2010;**45**(6):788-795
- [115] Aggarwal BB, Sung B. Pharmacological basis for the role of curcumin in chronic diseases: An age-old spice with modern targets. *Trends in Pharmacological Sciences*. 2009;**30**:85-94
- [116] Bakır B, Yetkin Ay Z, Büyükbayram Hİ, Kumbul Doğuç D, Bayram D, Candan IA, et al. Effect of curcumin on systemic T helper 17 cell response; gingival expressions of interleukin-17 and retinoic acid receptor-related orphan receptor  $\gamma$ ; and alveolar bone loss in experimental periodontitis. *Journal of Periodontology*. 2016;**87**(11):183-191
- [117] Choi IS, Choi EY, Jin JY, Park HR, Choi JI, Kim SJ. Kaempferol inhibits *P. intermedia* lipopolysaccharide-induced production of nitric oxide through translational regulation in murine macrophages: Critical role of heme oxygenase-1-mediated ROS reduction. *Journal of Periodontology*. 2013;**84**:545-555
- [118] Balli U, Cetinkaya BO, Keles GC. Assessment of MMP-1, MMP-8 and TIMP-2 in experimental periodontitis treated with kaempferol. *Journal*

of Periodontal & Implant Science.  
2016;**46**:84-95

[119] Aral CA, Kesim S, Greenwell H, Kara M, Çetin A, Yakan B. Alveolar bone protective and hypoglycemic effects of systemic propolis treatment in experimental periodontitis and diabetes mellitus. *Journal of Medicinal Food*. 2015;**18**:195-201

[120] El-Sharkawy HM, Anees MM, Van Dyke TE. Propolis improves periodontal status and glycemic control in patients with type 2 diabetes mellitus and chronic periodontitis: A randomized clinical trial. *Journal of Periodontology*. 2016;**87**(12):1418-1426

[121] Govindaraj J, Emmadi P, Deepalakshmi, Rajaram V, Prakash G, Puvanakrishnan R. Protective effect of proanthocyanidins on endotoxin induced experimental periodontitis in rats. *Indian Journal of Experimental Biology*. 2010;**48**(2):133-142

[122] Bullon P, Battino M, Varela-Lopez A, Perez-Lopez P, Granados-Principal S, Ramirez-Tortosa MC, et al. Diets based on virgin olive oil or fish oil but not on sunflower oil prevent age-related alveolar bone resorption by mitochondrial-related mechanisms. *PLoS One*. 2013;**8**(9):e74234

[123] Balaji TM, Vasanthi HR, Rao SR. Gingival, plasma and salivary levels of melatonin in periodontally healthy individuals and chronic periodontitis patients: A pilot study. *Journal of Clinical and Diagnostic Research*. 2015;**9**:ZC23-ZC25

[124] Thomas B, Ramesh A, Suresh S, Prasad BR. A comparative evaluation of antioxidant enzymes and selenium in the serum of periodontitis patients with diabetes mellitus type 2. *Contemporary Clinical Dentistry*. 2013;**4**:176-180