Chapter

Antioxidants and Periodontal Diseases

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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; α-tocopherol
- reducing the concentration of ROS directly; glutathione
• by neutralizing the primary radicals that initiate free radical production; superoxide 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].

1.1.1.4 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].

1.1.1.5 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 peroxyl 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 α-carotene, β-carotene, lycopene, crocetin, canthaxanthin, and fucoxanthin. β-carotene is a combination of two molecules of vitamin A (also known as retinol). When dietary β-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 α, β, and δ. The form of vitamin E with the highest biological activity is α-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
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-1α and interleukin-1β gene expression by more than twofolds compared to the control.

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-α, tumor necrosis factor-alpha; PDL, periodontal ligament; NF-kB, nuclear factor-kappa B; ROS, reactive oxygen species; PMNL, polymorphonuclear leukocyte; TIMP, tissue inhibitor of metalloproteinases; and MMP, matrix metalloproteinase.
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-hydroxodeoxyguanosine 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 α-tocopherol levels and the severity of periodontitis. While the level of α-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 α-carotene, β-carotene, β-cryptoxanthin, and zeaxanthin levels were significantly lower in patients with moderate to severe periodontitis.

It has been shown that β-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 β-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-1β 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-α 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 \( \geq 1 \text{ cup/day} \) 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

| Abbreviation | Definition |
|--------------|------------|
| 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$_2$O$_2$   | hydrogen peroxide |
| Lf           | lactoferrin |
| GSSG         | oxidized glutathione |
| PLA2         | phospholipase A2 |
| PUFA         | polyunsaturated fatty acids |
| P. gingivalis| Porphyromonas gingivalis |
| ROS          | reactive oxygen species |
| SRP          | scaling and root planning |
| Se           | selenium |
| O$_2^-$      | superoxide |
| SO           | superoxide dismutase |
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