Review Article

Dietary antioxidants and their indispensable role in periodontal health

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Abstract

Periodontitis is an increasing area of interest due to its global prevalence. This inflammatory condition results due to the loss of the critical balance between the virulence factors produced by microorganisms and the inflammatory host response. A number of efforts have been made in the past to address this condition and regain periodontal health. Targeting the root cause by nonsurgical debridement has been considered the gold standard. However, research has shown the possible effects of nutrient deficiency and an imbalanced diet on the periodontium. Therefore, an effort toward the maintenance of optimal conditions as well as improvement of the oral health necessities the introduction of adjunctive nutritional therapy, which can benefit the patients. Antioxidants in the diet have some remarkable benefits and valuable properties that play an irreplaceable role in the maintenance of periodontal health. These have emerged as excellent adjuncts that can enhance the outcomes of conventional periodontal therapy. The aim of this review article is to highlight some of these dietary antioxidants that can make a notable difference by striking a balance between health and disease.

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1. Introduction

Periodontitis is a ubiquitous chronic inflammatory disease affecting the supporting tissues of the teeth. It is one of the most common chronic diseases affecting humans. The disease is caused by infection induced by specific microorganisms or a group of microorganisms, which eventually causes progressive destruction of the periodontal ligament (PDL) and alveolar bone. The progression of this destructive disease appears to be dependent on abnormal host response to the biofilm organisms [1]. The periodontitis phenotype is characterized by hyperinflammation involving excess release of oxygen-free radicals by inflammatory cells, especially polymorphonuclear leucocytes (PMNLs) [1]. PMNLs are the first line of defense against any microbial invasion. In the event of a...
microbial attack, there is a burst of O$_2$ consumption (i.e., nonmitochondrial) at about 10 or 20 times that of resting consumption. This burst of oxygen consumption is the “respiratory burst” phenomenon, and the excessive uptake of oxygen in neutrophils and macrophages generates SO anion radicals, H$_2$O$_2$, hydroxyl radicals, and HOCl, all of which are capable of damaging either cell membranes or associated biomolecules. These are in fact the free radicals (FRs) or reactive oxygen species (ROS) capable of inducing tissue damage and cell destruction. Well-being of the organism depends on the activity of efficient defense mechanisms against oxidative damage induced by FRs/ROS. Antioxidants provide this defense and protection. They also counteract the destructive effects of ROS and help to maintain homeostasis in the body.

It is believed that although the primary etiological agent of the disease is specific, predominantly Gram-negative anaerobic or facultative bacteria within the subgingival biofilm [2], the majority of periodontal tissue destruction is caused by an inappropriate host response to those microorganisms and their products [3]. If this inappropriate host response is not addressed and disease is not promptly recognized and managed, it can cause tooth loss, resulting in compromised masticatory function and subsequent alterations in the dietary intake and malnutrition status.

Antioxidants, in particular, dietary antioxidants, have a protective effect on the periodontium. They neutralize the FRs, ROS, and reactive nitrogen species that can cause oxidative stress, which results in periodontal breakdown and excessive tissue damage. With growing age, vitamins and minerals, the essential constituents of food, are less efficiently absorbed and their production within the body declines, thereby increasing the risk of inflammatory burden. Dietary antioxidants include certain vital vitamins and minerals as well as certain important phytochemicals that help to keep the periodontal damage at bay. In fact, they can protect our cells from almost all of the diseases associated with inflammation and the aging process. Because of its association with several other systemic disorders, periodontitis has become a crucial area to deal with.

Many risk factors that modify the host response and thereby tip the balance from health to disease have been identified. These factors can be classified as genetic, environmental (e.g., stress, bacterial challenge), and lifestyle/behavioral (e.g., exercise, nutrition, smoking). Moreover, periodontal disease has been a prominent risk factor for a number of systemic diseases such as cardiovascular disease, diabetes, and rheumatoid arthritis [4–7]. Therefore, considering the significance of nutrition and the need to maintain optimal antioxidant levels for the maintenance of periodontal health, natural antioxidants as potential adjuncts are now gaining increased attention. These antioxidants, which are critical in maintaining an optimum level of health, can be easily obtained through our daily dietary intake. This adjunctive effort with appropriate nutritional supplementation is vital to halt the progression of this inflammatory condition. Thus, to appreciate the valuable effect of dietary antioxidants on periodontal health, we herein discuss the vital roles of few assorted antioxidants in the maintenance of optimum oral health; additionally, we also discuss how the nutritional status would assist in controlling the complex nature of the periodontal disease and striking a balance between health and disease.

2. Discussion

2.1. Neutrophils as mediators of inflammation

PMNLs play a vital role in host defense and constitute the first line of defense against microbial invasion and infection in the body. In the oral cavity, following plaque accumulation and the development of clinical inflammation, 90% of leukocytes that enter the gingival crevicular fluid (GCF) and 50% of those that infiltrate junctional epithelium are PMNLs [1]. These neutrophils help in controlling the microbial invasion by several intracellular and extracellular oxidative and non-oxidative killing mechanisms [8]. This oxidative killing mechanism of neutrophils leads to the formation of ROS/FRs.

2.2. Free radicals

An FR may be defined as an atomic or molecular species capable of independent existence with one or more unpaired electrons in its structure [9]. These FRs at low concentrations are involved in performing various cell signaling functions but at higher concentrations, they react with certain cellular components such as DNA, proteins, lipids exerting an oxidative stress in the gingival tissues, PDL, and alveolar bone and mediate tissue damage. Hence, to maintain the biological balance, antioxidants come into play.

2.3. Antioxidants

An antioxidant is any substance that when present at concentrations below those of their oxidizable substrate significantly delays or prevents oxidation of that substrate [10]. Several biologically important compounds have been shown to possess antioxidant properties, including vitamin C (ascorbic acid), vitamin E (α-tocopherol), vitamin A, β-carotene, metallothionein, polyamines, melatonin, nicotinamide adenine dinucleotide phosphate, adenosine, co-enzyme Q-10, urate, ubiquinol, polyphenols, flavonoids, phytoestrogens, cysteine, homocysteine, taurine, methionine, S-adenosyl-L-methionine, resveratrol, nitroxides, reduced glutathione (GSH), glutathione peroxidase, superoxide dismutase [11], catalase, nitric oxide synthase, heme oxygenase-1, and eosinophil peroxidase [12].

These are essential for a range of biological processes important in supporting optimal health. Baumgartner et al [13] carried out a study on the effect of Stone Age diet on the oral conditions in the absence of any oral hygiene measures. Ten volunteers residing in a Stone Age setup were included in the study for a period of 4 weeks. The volunteers were placed on a primitive diet, which was high in fiber, antioxidants, and fish oils, but low in refined sugars and with no oral hygiene measures. Clinical parameters such as bleeding on probing, gingival and plaque indices, and probing depth were studied and reported at baseline and at 4 weeks. As would be expected, plaque levels increased significantly and classic periodontal pathogens emerged within the biofilm, but...
unexpectedly gingival bleeding significantly reduced from 35% to 13%. This study supports an intrinsic role of nutrition in maintaining periodontal health.

2.3.1. Implications of antioxidants in general health
Antioxidants that prevent oxidation of other substances are widely available as dietary supplements with a range of health claims. One important characteristic that is frequently attributed to the role of antioxidants is their ability to decrease the risk of cancer. However, numerous studies have raised doubt on this claim in the past few years, as increased evidence has suggested that antioxidants may actually increase the risk of some forms of cancer. A study carried out by Sayin et al. [14] indicated that antioxidants may have a harmful effect in the development of lung cancer. When mice with mutations that increased their risk of lung cancer were subjected to antioxidants, their early precancerous lesions progressed at a faster rate, and the mice developed multiple tumors and at more advanced levels. The antioxidants reduced the oxidative stress and DNA damage as expected, but also reduced the expression of p53, a key tumor suppressor protein. This work was carried out in cells and in mice, but the authors tried to correlate the findings with humans as well. Therefore, the mice were treated with different types and doses of the antioxidants (vitamin E and acetylcysteine) that healthy humans generally consume, and the results were confirmed in human lung cancer cells. Thus, the evidence for a procarcinogenic role of antioxidants in people who are at a greater risk of cancer, such as smokers, was established [14].

2.3.2. Implications of antioxidants in periodontal health
Antioxidants may have beneficial effects on functional mechanisms regulating fibroblast migration and proliferation during gingival healing or periodontal repair. They work by the following three mechanisms (Fig. 1):

1. By reducing the production of cytokines, chemokines, and proinflammatory proteins by leukocytes, which are responsible for causing the destruction of cells and other structures.
2. By neutralizing ROS, they protect the fibroblasts from toxic substances that release ROS and help in reversing the effect of oxidative damage.
3. By promoting the process of wound healing

2.4. Vitamin C

2.4.1. Significance and role in periodontal health
The importance of vitamin C or ascorbic acid in periodontal health has been known since long. Vitamin C is a potent antioxidant radical scavenger and is found to be in the aqueous phase [15].

Severe vitamin C deficiency leads to a severe periodontal condition called “scorbutic gingivitis” or “scurvy,” which is characterized by ulcerative gingivitis and rapid periodontal pocket formation and attachment loss. Ascorbic acid is a significant nutrient, showing rapid intestinal absorption [16]. Vitamin C is required for the synthesis of collagen in humans. It plays a vital role in collagen hydroxylation and is important for the formation of norepinephrine from dopamine and plays an active role in tyrosine metabolism [17].

Inadequate consumption of vegetables and fruits, which are two key sources of vitamin C, can lead to depletion or deficiency of this vital vitamin in the body [18]. Ascorbic acid is rapidly depleted and oxidized within the extracellular fluids during oxidative stress [19]. However, adequate glutathione (GSH) levels prevent the oxidation of ascorbic acid. GSH is, therefore, a chain-breaking antioxidant, which controls the inflammatory reactions and maintains appropriate vitamin C levels.

Vitamin C helps in the synthesis of collagen by preventing the iron-dependent oxidation of lysyl and prolyl hydroxylase. Like the osteoblastic cells, bone-forming PDL cells lining the lamina dura may undergo differentiation in the presence of ascorbic acid. The fibroblastic PDL cells respond to vitamin C by accelerating the expression of both collagen and

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![Fig. 1 - Interrelationship between free radicals and antioxidants (de novo). PMNL = polymorphonuclear leucocytes.](image-url)
collagenase-1, thereby maintaining a high level of matrix turnover important for a tissue like PDL to undergo active remodeling [20].

Certain cells such as PMNLs, mononuclear cells, platelets, and endothelial cells accumulate high concentrations of ascorbic acid [21]. PMNLs and macrophages contain vitamin C concentrations that are 10–40 times higher than those in the plasma. It has been thought that the high ascorbic acid levels in these cells contribute to their ability to respond to inflammatory stimuli [22]. The ascorbic acid influence was also seen in the phagocytic ability of neutrophils [23].

Melnick et al [24] reported that there is an interrelationship between ascorbic acid deficiency and necrotizing gingivitis. Vogel and Wechsler [25] reported that the everyday intake of vitamin C in a group of periodontitis patients studied was considerably less than that in the control group. Based on the National Health and Nutrition Examination Survey (NHANES) I study, Ismail et al [26] found an inverse relationship between dietary vitamin C and periodontal disease taking into consideration all the confounding factors such as age, sex, race, education, income, and the oral hygiene status.

Blignaut and Grobler [27] reported that deeper pockets (CPITN Codes 3 and 4) were seen less frequently in people who consumed vitamin C-rich foods. Amarasena et al [28], in an elderly group of Japanese volunteers, showed a definite negative correlation between serum vitamin C levels and attachment loss regardless of habits, systemic status (e.g., diabetes), sex, and the number of teeth present.

2.4.2. Sources of vitamin C
Sources rich in vitamin C are natural fruits and vegetables such as gooseberry, broccoli, kiwi fruit, paprika, Brussels sprouts, grapefruits, citrus fruits, pepper, cauliflower, strawberries, pineapple, cherries, and potatoes. Gooseberry contains 20 times the amount of vitamin C than in oranges. Gooseberry contains 720 mg of vitamin C/100 g of fresh fruit pulp, or up to 900 mg/100 g of pressed juice, which aids in metabolism [29]. Green kiwifruit is a rich source of vitamin C and contains 93 mg vitamin C/100 g of fruit; oranges, by contrast, contain up to 53 mg vitamin C/100 g of fruit [30].

2.4.3. Recommended dietary allowance
In 2000, the recommended daily intake of vitamin C was increased by the Food and Nutrition Board (FNB), based on certain biochemical, molecular, epidemiological, and clinical data (FNB 2000). The recommended dietary allowance (RDA) for men was increased from 60 mg to 90 mg and for women from 60 mg to 75 mg daily [30]. Levine et al [31] reported that the optimal intake of vitamin C should be 200 mg daily from a range of fresh fruits and vegetables.

2.5. Vitamin D and calcium

2.5.1. Significance and role in periodontal health
There is limited evidence signifying the relationship between vitamin D/calcium and periodontal health. Some studies say that periodontal bone loss is more in individuals with osteoporosis [32]. According to the NHANES III, it has been shown that the low daily consumption of calcium results in more severe periodontal disease [33].

In a previous study, Van der Velden and colleagues [34] administered calcium and vitamin D at doses higher than 800–1000 IU daily and reported reduced severity of periodontal disease. The studies carried out on vitamin E are less than those on vitamin C; thus, the exact interrelationship is difficult to establish [35].

The possible effect of vitamin E in the management of periodontal disease is based on its ability to interfere with the synthesis of prostaglandins, which are vital in the development of inflammation. Parrish et al in 1977 conducted a study on the effect of a diet rich in vitamin E on ligature-induced periodontitis in rats. Three groups were selected for the study and these groups received diet, which was low, medium and high in Vitamin E for 8 weeks, then 6 weeks of ligature-induced periodontitis. At the end of this period, no differences were observed histologically [36]. In another study by Kim and Shaklar, the effect of vitamin E on gingival wound healing in rats was analyzed. More rapid healing of gingivectomy wounds was seen in rats that received the supplements with complete healing noted at 7 days [37]. Further, Cohen et al analyzed the effect of stress, periodontal status, and vitamin E on disease progression. Vitamin E supplements were found to have significant beneficial effects on bone loss [38].

However, a specific correlation between vitamin E deficiency and periodontal disease is difficult to determine. This is due to the wide distribution of the vitamin in oils, fats, and grains and the high prevalence of periodontal disease occurrence.

Alpha-tocopherol is located within cell membrane phospholipids and is a major chain-breaking antioxidant, but has limited mobility, which confines its efficacy [39]. However, many ROS are generated in the aqueous solution, particularly those from phagocytes and the vascular endothelium, and the role of α-tocopherol in causing periodontal disease is thus likely to have no major significance. In a study by Slade [40], no differences were detected in plasma vitamin E concentrations in patients with and without periodontal disease, and in another, its prostaglandin-inhibitory properties were credited in reducing periodontal inflammation [41]. Thus, no definite role of vitamin E deficiency in the pathogenesis of periodontal disease has been identified.

Vitamin D is known to play a significant role in bone and calcium homeostasis and acts as an anti-inflammatory agent because it inhibits immune cell cytokine expression and causes monocyte/macrophages to secrete molecules that have a strong antibiotic effect. Indeed, vitamin D deficiency may be linked to increased risk of infectious diseases. Hence, vitamin D is beneficial in the treatment of periodontitis, not only because of its direct effects on bone metabolism, but also because it may have antibiotic effects on periodontopathogens and inhibit inflammatory mediators that contribute to the periodontal destruction [42].

Using the NHANES III data, Dietrich et al [43] reported that levels of 25-hydroxycholecalciferol [25(OH)D] showed an inverse relationship with attachment loss in men and women aged 50 years or older, independent of their bone mineral density [43].

In the same study, they also concluded that low levels of 25(OH)D were associated with a higher percentage of bleeding
on probing. This was observed due to the anti-inflammatory effect of vitamin D, which reduced the susceptibility to gingival inflammation [43].

In a study by Miley et al [44], the consumption of calcium and vitamin D oral supplements by patients attending periodontal disease maintenance programs was assessed. Patients who were consuming vitamin D (≥400 IU/day) and calcium (≥1000 mg/day) for a period of more than 18 months were compared with patients who were consuming neither vitamin D nor calcium. Patients who received periodontal maintenance therapy along with adjunctive vitamin D and calcium supplements had better periodontal health status in contrast to the other group. In addition, vitamin D produces calcium supplements had better periodontal health status in maintenance therapy along with adjunctive vitamin D and vitamin D nor calcium. Patients who received periodontal were compared with patients who were consuming neither vitamin D (\[47,48\]) and prevent the inhibition of collagenase in GCF in aggressive periodontitis patients. It was also demonstrated that flavonoids may restore the alveolar bone by their inhibitory effect on lipopolysaccharides. Therefore, increased intake of flavonoids may prove to be beneficial in the prevention of periodontal disease. Hence, an inverse association was found between the consumption of flavonoids and periodontal disease.

2.6.2. Sources of flavonoids

Foods with a high flavonoid content include parsley, onions, blueberries and other berries, black tea, green tea and oolong tea, bananas, all citrus fruits, Ginkgo biloba, red wine, sea buckthorns, and dark chocolates (with a cocoa content of ≥70%).

2.7. Carotenoids

2.7.1. Significance and role in periodontal health

Carotenoids (alpha-carotene, beta-carotene, cryptoxanthin, lutein, lycopene, and zeaxanthin) are a set of naturally colored pigments. They are antioxidant in nature and have protective effects on vitamins C and E. They also show synergistic effects by scavenging reactive nitrogen species. Beta-carotene is the main source of provitamin A in the diet. Carotenoids have a significant influence on other antioxidants, and hence they are considered vital in antioxidant defense mechanisms. Svilaas et al [52] reported that carotenoids are predictors of the overall antioxidant status. The authors aimed to determine the contribution of a variety of foods to total antioxidant intake and to assess the correlation of the total antioxidant intake from these food groups with the antioxidants in plasma. The daily intakes of total antioxidants, beta-carotene, vitamin A, vitamin C, and energy in the 7-day weighed dietary records are presented. Among various food substances, coffee, wine, and vegetables had a significant correlation with dietary zeaxanthin, beta-carotene, and alpha-carotene. The data presented agree with the hypothesis that dietary antioxidants contribute significantly to antioxidant defense.

Lindner et al [53] assessed the correlation between periodontal health and the serum levels of various antioxidants including carotenoids, retinol, and vitamin E in a homogenous group of Western European men. The authors noticed that low serum levels of carotenoids, beta-carotene, cryptoxanthin and alpha-carotene, were associated with an increased prevalence of periodontitis in these patients.

Walton et al [54] found that patients with low levels of z- and beta-carotene and total carotenoids were more likely to have high interleukin-6. Beta-Cryptoxanthin has an anabolic effect on
bone metabolism. It has been shown to stimulate bone formation and inhibit bone resorption [55].

Among all the carotenoids, lycopene has been found to be one of the most effective antioxidants. There is an association between periodontitis and the risk of congestive heart failure, with high consumption of lycopene affecting this relationship significantly in periodontitis patients [56]. Lycopene has also been associated with malondialdehyde, an important marker for oxidative stress, and is reported to significantly decrease the stress levels [57].

2.7.2. Sources of carotenoids
Lycopene, a carotenoid phytonutrient, is the most powerful antioxidant present in a number of fruits and vegetables. It has reparative properties in the presence of vitamin C. Tomatoes constitute the main source of dietary lycopene, accounting for up to 85% of the daily consumption [58]. Besides, apricots, guavas, watermelons, papayas, and pink grapefruits are also considered major sources.

2.7.3. Recommended dietary allowance
Vitamin A is one of the major carotenoids. The RDA for vitamin A varies for each individual. For infants, the RDA at 0–6 months of age is 400 μg/day, whereas at 7–12 months it is 500 μg/day. For children, the RDA is 400 μg/day. Adult males have an RDA of 900 μg/day and adult females have an RDA of 700 μg/day. During pregnancy, the recommended allowance is up to 770 μg/day, whereas for lactating women it is about 1300 μg/day [59].

In addition to the aforementioned antioxidants, there are a number of other micronutrients and macronutrients, which may play a significant role in periodontal health and disease prevention. A number of food sources contain antioxidants as their major beneficial component in the prevention of disease process. Among these, Aloe vera is a prominent plant source, which has enumerable properties and beneficial effects attributed to its antioxidant, antibacterial, immune-boosting, wound-healing capabilities, among many others. This review also focuses on the therapeutic significance and antioxidant properties of this miraculous plant, which has loads of rewards to offer.

2.8. Therapeutic significance of A. vera
A. vera contains 75 active components: vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids, and amino acids. The plant contains vitamins A (β-carotene), C, and E, which are powerful antioxidants. It also contains vitamins such as vitamin B12, folic acid, and choline. A. vera has antioxidant effects, which neutralize FRs. It contains eight enzymes, namely, aliase, alkaline phosphatase, amylase, bradykinase, carboxypeptidase, catalase, cellulase, lipase, and pectoxidase. It provides calcium (Ca), chromium (Cr), copper (Cu), selenium (Se), magnesium (Mg), manganese (Mn), potassium (K), sodium (Na), and zinc (Zn).

Some of these enzymes are antioxidants and are crucial for the proper functioning of the various enzyme systems in numerous metabolic pathways. A. vera provides monosaccharides (glucose and fructose) and polysaccharides (glucomannans/polymannose). They are obtained from the mucilage layer of the plant and are referred to as “mucopolysaccharides” [60]. Swishing A. vera juice a few minutes before consuming food may help in keeping the mouth healthy. Bhat and colleagues [61] applied A. vera gel in the periodontal pocket after thorough scaling and root planing. A highly significant improvement in periodontal parameters was seen after the therapy. Hence, A. vera is known for its significant antioxidant properties. A recent randomized controlled trial demonstrated A. vera gel as an adjunct to mechanotherapy in the treatment of chronic periodontitis patients with Type 2 diabetes mellitus [62].

2.8.1. Effects on wound healing
Along with the maintenance of periodontal health, some studies have shown that diet may have an adjunctive role in wound healing after a few periodontal procedures. These studies have shown that micronutrients (vitamins D and B) [63–65] and macronutrients [docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)] [66,67] can assist in patient recovery after periodontal therapy. A vitamin D-rich diet (serum 25(OH)D > 50 nmol/L) before open-flap debridement surgery showed greater clinical attachment levels and reductions in probing depths postsurgery as compared with patients with lower levels of serum 25(OH)D. In addition, vitamin B complex benefited patients after an access flap surgery (50 mg thiamine HCl, riboflavin, niacinamide, β-calcium pantothenate, pyridoxine HCl; 50 μg d-biotin cyanocobalamin; and 400 μg folate). In patients requiring curative treatment, a combination of acetylsalicylic acid (81 mg) and fish oil (containing 900 mg DHA and EPA) decreased the probing depths while increasing clinical attachment and reducing the levels of salivary Receptor activator of nuclear factor kappa-B ligand (RANKL) and MMP-8, which are prominent markers of inflammation [66]. In patients with a furcation defect requiring a bone allograft, a combination of acetylsalicylic acid (75 mg) and DHA (900 mg) and EPA (450 mg) showed a significant increase in clinical attachment levels, probing depth reductions, and reduction in interleukin-1β present in the GCF. Overall, these studies signify the importance of dietary supplements before and after periodontal procedures in improving periodontal outcomes.

Many studies so far have highlighted the role of topically applied antioxidants in decreasing the wound-healing time [68]. Antioxidants facilitate wound healing by promoting fibroblast migration and lowering inflammatory markers when used in combination. Their use may be primarily effective in patients who smoke, as nicotine increases the production of ROS which results in an increased degree of oxidative damage to human fibroblasts [69,70].

3. Conclusion
In conclusion, periodontitis is a slowly progressive chronic inflammatory disorder, which generally occurs in response to an imbalance between the antioxidant defense mechanisms and repair efforts by ROS. If this balance is tipped toward the increased generation of FRs, then there is cell damage and tissue destruction. Therefore, for prevention of this tissue damage and maintenance of optimal oral health, sufficient
antioxidant levels are to be present in the oral fluids. Many of these nutrients cannot be manufactured by the body, and therefore, they must be supplied in the diet.

Dietary antioxidants play a vital role in the maintenance of oral health and have a potential to influence periodontal disease management, which positively affects clinical outcomes. A strong association exists between periodontal health and antioxidants, both of which have an inverse interrelationship. Thus, obtaining enough antioxidants through our diet to promote healthier tissues is essential to reduce the unwanted effects of these FRs. This explains the indispensable role of dietary antioxidants in periodontal health.

**Conflicts of interest**

All contributing authors declare no conflicts of interest.

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