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Micronutrients and bioactive compounds in oral inflammatory diseases

Kiranjit Kaur[a], Dean Sculley[b], Janet Wallace[c], Alexandria Turner[a], Celeste Ferraris[a], Martin Veysey[d,e], Mark Lucock[f], Emma L. Beckett[a,f,*]

[a] School of Environmental and Life Sciences, Australia
[b] School of Biomedical Sciences and Pharmacy, Australia
[c] School of Health Sciences, Australia
[d] School of Medicine & Public Health, The University of Newcastle, NSW, Australia
[e] Hull-York Medical School, University of York, Heslington, York, UK
[f] Hunter Medical Research Institute, NSW, Australia

HIGHLIGHTS

- Oral inflammatory diseases are multi-factorial with micronutrient intake being a crucial modifiable risk factor.
- Micronutrients, including vitamins C, E, D and A, omega-3 fatty acids and minerals have demonstrated anti-oxidant and anti-inflammatory functions.
- Oral mucosal lesions occur as a result of vitamin B deficiencies can help in early detection of specific anaemias.
- This review highlights the importance of micronutrients in oral inflammatory diseases causation, progression and prevention.

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ABSTRACT

Oral disorders are a significant public health concern. Oral inflammatory diseases are periodontal infections, oral mucosal lesions, pulpal and periapical lesions. The aetiology is multi-factorial and usually associated with a microbial origin, often driven by the overconsumption of free sugars. However, the role of micronutrients in these processes is now becoming apparent. Most of these studies have emphasised on systemic inflammation, but now the trends have shifted towards the role of micronutrients in oral inflammation. The progression of periodontal disease and healing of the periodontal tissues can be modulated by nutritional status. There are numerous degenerative changes in oral mucosa which have been observed during specific micronutrient deficiencies. Recent studies have advocated the use of dietary supplementation of particular micronutrients to treat the oral inflammatory lesions along with their standard treatment procedures. The micronutrient supplementation can be orally administered or locally delivered. Previously reviewed articles usually lacked compiled information regarding all oral inflammatory diseases. The current review provides an insight into the role of nutrition in oral inflammatory diseases, including periodontal disorders, oral mucosal lesions, pulpal and periapical lesions.

1. Introduction

Oral diseases are common public health concerns worldwide [1]. The oral diseases with inflammatory origin include the periodontal diseases gingivitis and periodontitis, inflammation of oral mucosa, pulpal and periapical lesions [2]. Periodontal disease is one of the most common chronic inflammatory disorders [3]. Periodontitis and untreated dental caries leading to pulpal and periapical lesions are the most common cause of tooth loss in adult life [4,5]. Oral inflammatory pathologies negatively influence the quality of life, leading to the deterioration of daily life activities [6].

The aetiology of oral inflammatory diseases is multi-factorial [7–9] and usually involves a microbial component [10,11]. Numerous potential modifiable and non-modifiable risk factors associated with oral inflammatory disorders have been identified, including smoking, alcohol consumption, stress, poor oral hygiene, systemic health, genetics and epigenetic factors [7,12–15]. The severity and progression of oral diseases depend on these risk factors [16].

Dietary habits are a ubiquitous modifiable determinant of oral health and play a significant role in the inflammatory processes

* Corresponding author. School of Environmental and Life Sciences, Australia.
E-mail address: emma.beckett@newcastle.edu.au (E.L. Beckett).

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underlying oral pathologies [17]. The role of macronutrients (carbohydrates, protein and fats), in particular, free sugars, in oral health is well-established and have been extensively reviewed [18–22]. More recently, the role of micronutrient imbalances found in various systemic inflammatory diseases has been of interest in oral and other inflammatory diseases [23]. Micronutrients found to modulate inflammatory responses include vitamins (many of which are anti-oxidants) and minerals [24,25]. Diet has also been found to influence the composition of the oral microbiome, which has been indirectly linked to increased risk of oral diseases [26–28].

This review will focus on the role of micronutrients and bioactive compounds in oral inflammatory conditions, including periodontal diseases, inflammatory lesions of the oral mucosa, and pulpal and periapical lesions.

2. The role of micronutrients in periodontal diseases

Periodontal diseases are chronic inflammatory diseases involving the destruction of supporting structures of the teeth [2,20,29–31]. It has been estimated that periodontal diseases impact up to 90% of the world's population [30]. The overall prevalence of periodontal diseases increases with age [32], and in 2016, it was estimated to be responsible for approximately 4.8 million years lived with disability impacting the quality of life [33]. The disease incidence rises sharply in adults aged 30–40 years [32,34]. Understanding the nutritional factors contributing to this considerable burden of disease may inform new strategies for prevention and management of these conditions [20,35].

Periodontal diseases are comprised of inflammation of the gingiva, termed as gingivitis, and inflammation of periodontal tissues, known as periodontitis [29]. Gingivitis is the mildest form of periodontal disease and is reversible [36] while periodontitis involves the destruction of connective tissue and bone, which is irreversible [37,38]. Periodontal diseases are characterised by host inflammatory responses to bacteria, including *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* present in dental plaque [39–41]. The destruction of periodontal tissues is caused by the production of inflammatory factors released by immune cells, followed by the accumulation of polymorphonuclear leukocytes [42,43]. It results in the release of reactive oxidative species with antimicrobial properties [44]. However, this inflammatory response may also damage host tissue, and in this way, oxidative stress is associated with an increased risk for periodontal diseases [45–47]. Inflammation is therefore established as a key driver in the pathology of these oral diseases.

Nutrition has a significant role to play in the development of periodontal diseases. Dietary inadequacies have been found to impact prognosis with malnutrition attributed to a more rapid progression [48–50]. The inflammatory response, characteristic of the disorders, can be attenuated by increasing consumption of vitamins C and D [19,20,51]. Research has established dietary factors contribute to the modulation of the microbes in the oral cavity that has been linked to periodontal infections [28,52–55].

The inflammatory processes involved in periodontal diseases appear to be fuelled by nutrient imbalances, and dietary factors contribute to the dysbiotic oral cavity linked to these conditions. Research on anti-oxidant nutrients, vitamin D and calcium in periodontal diseases has been conducted in human and animal models and primarily highlights their anti-inflammatory and anti-oxidant roles.

2.1. Vitamins and antioxidants

Anti-oxidant nutrients prevent free radical production and stabilise and scavenge existing free radicals [56,57]. Free radicals cause an oxidative chain reaction that leads to cellular damage and death [57–59]. Anti-oxidants interrupt this chain reaction modulating the oxidative stress found to be significantly associated with periodontal diseases [60–64]. A wide variety of studies, including longitudinal, cross-sectional and randomised clinical trials, have explored the role of anti-oxidants in oral inflammatory diseases [65–68].

2.2. Vitamin B complex

The vitamin B complex refers to eight water-soluble vitamins, which perform many essential functions in the body. The B complex vitamins include thiamine (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), vitamin B_6 (pyridoxine), folate (B_9), biotin (B_7) and cobalamin (B_{12}) [69]. The research shows a role for each of the B vitamins in periodontal disease progression and severity. B_2, B_3, B_6 and B_{12} deficiencies have been linked with haemorrhagic gingivitis and periodontitis [54,70]. Regarding periodontal disease, folic acid deficiency leads to the absence of keratinisation of the gingival surface, decreased cell turnover rate, diminished resistance to infections and destruction of gingival and periodontal tissues [71]. A case study linked Vitamin B_{12} deficiency and acute necrotising ulcerative gingivitis [72]. It can be explained by the role of vitamin B_{12} in the modulation of cellular immunity [73,74]. Furthermore, data obtained from a US population-based, a cross-sectional study reported that lower serum levels of folate independently affect the status of periodontal diseases in older adults [75].

Additionally, it has been reported that folate deficiency in smokers increases the risk of periodontitis [76,77]. In smokers, folic acid deficiency can occur even with regular dietary intake due to the additional utilisation of folic acid required to convert the compounds present in cigarette smoke into biologically inactive compounds [71]. Furthermore, a clinical trial conducted on 30 individuals showed that Vitamin B supplementation after apical flap surgery that commonly occurs in the treatment of periodontal diseases increased clinical attachment levels as compared to placebo [78]. Overall, there is an observed increase in periodontitis in smokers, which may be due to folic acid deficiency.

2.2.1. Vitamin C

Vitamin C, also known as L-ascorbic acid, is a water-soluble vitamin requiring regular intake [79]. Vitamin C performs crucial roles in numerous biochemical functions, including the quenching of free radicals and modulation of inflammatory responses [80,81]. Plasma levels of vitamin C decrease during times of infection and post-surgical stress [82], due to the additional vitamin C needed for tissue repair and regeneration in these cases [81,83–85]. Therefore, additional intake may be required in these situations. The anti-inflammatory, anti-oxidant and regenerative actions of vitamin C are well-established [62,86–91], which suggest a role for this nutrient in modulating inflammatory responses in periodontal diseases.

Vitamin C deficiency has been identified as a significant risk factor in periodontal diseases [86,87]. It is well established that dietary vitamin C deficiency leads to scurvy, an inflammatory disease of the gingiva, which causes bleeding gums [89,90,92,93]. Multiple epidemiological studies have shown that vitamin C status correlates to periodontitis risk [86–89]. Cross-sectional studies involving Korean and Japanese populations have found that the dietary intake and serum levels of vitamin C are independently related to periodontitis [86,87]. A study using combined Finnish and Russian cohorts revealed that vitamin C deficiency was associated with periodontitis, and vitamin C levels were also negatively correlated with levels of antibodies to *Porphyromonas gingivalis* [89], gram-negative bacteria causing gingivitis. Furthermore, results from the third National Health and Nutrition Examination Survey (NHANES III, representative of the USA population) showed a weak but statistically significant relationship between lower dietary intake of vitamin C and periodontal diseases in the general population and specifically in tobacco users [88]. These studies suggest that inadequate Vitamin C intake increases risk and association with periodontal diseases across diverse cultural demographics.

Vitamin C may also be used therapeutically to reduce the severity of periodontal diseases and improve treatment outcomes. A longitudinal

study linked the consumption of vitamin C rich grapefruit to improved plasma concentrations of vitamin C and decreased sulcus bleeding scores [68]. The lower prevalence of deep periodontal pockets has also been linked with higher intake of citrus fruits [94]. While saturation of plasma vitamin C levels may occur at high doses [41], local application may also influence oral health. It has also been reported that local intradermal and sub-epithelial vitamin C injections could be used as an adjunct with surgical and non-surgical treatment of periodontal diseases [95,96]. Furthermore, local administration of vitamin C helps in the reduction of inflammation, promotes healing, increases the production of collagen and improves gingival circulation [95]. Oral supplementation of vitamin C as an adjunct to non-surgical treatment of chronic periodontitis has also found to be effective against periodontal inflammation [97]. Overall, vitamin C appears to have anti-inflammatory properties and therapeutic potential in the treatment of periodontal diseases.

2.3. Vitamin D

Vitamin D plays a vital role in immune responses and bone homeostasis [98,99]. Research has suggested that deficiency of vitamin D could impact periodontal tissues [100–102]. Individuals receiving regular periodontal treatments along with vitamin D supplements demonstrated a better trend in the maintenance of periodontal therapy. It may be due to its indirect role in the reduction of gingival inflammation [103]. The Third National Health and Nutrition Examination Survey (NHANES III), a representative study involving a US population, concluded that optimal vitamin D status reduced gingival inflammation [104]. The same survey highlighted a link between the high prevalence of periodontitis and vitamin D deficiencies [105]. A case-control study established that vitamin D inadequacy is associated with periodontal diseases in women during pregnancy [106]. Furthermore, results from a longitudinal study in older men suggested that vitamin D intake protects against the progression of periodontal disease [107]. A systematic review found that while the literature was mixed and scarce, that some data did support a protective role for vitamin D in periodontal disease [108]. It is possible that this impact on periodontal health is due to its anti-inflammatory effects [109–111].

Epidemiological data from a Danish population suggested that consumption of dairy products containing vitamin D, along with calcium, casein and whey proteins, have a protective effect against periodontitis. However, these studies lacked information about dietary supplementation [112,113]. Therefore, it could not be determined if the vitamin D, other dairy components, or the displacement of other less healthful foods by dairy, was responsible for the effect. Hence, further studies are needed to confirm the protective effects of vitamin D in periodontitis.

2.3.1. Vitamin E

Vitamin E is a fat-soluble vitamin existing in various forms, mostly tocopherols and tocotrienols [114]. Major dietary sources include nuts and plant oils [115]. One of the nutrients roles is to scavenge peroxyl free radicals, assisting in the stabilisation of membrane structures, by inhibiting the free radical reaction [56,116]. This function of vitamin E is relevant to periodontal diseases that are characterised by oxidative stress. A cross-sectional study conducted on an adult US population showed an inverse relationship between serum tocopherol levels and the severity of periodontitis [65]. In addition to scavenging free radicals, research has suggested that the beneficial role of vitamin E in periodontal inflammation may be due to its intrusion in the synthesis of prostaglandins [117]. Importantly, several rat studies have shown that a vitamin E rich diet reduces periodontal and gingival inflammation and improves wound healing [118–120]. These studies highlight the role of vitamin E in periodontal diseases and indicate that dietary sources may be an area for future human research.

2.3.2. Carotenoids and flavonoids

Carotenoids and flavonoids such as β-carotene, lycopene and polyphenols are antioxidants usually obtained from vegetables and fruits [57,121–123]. Research has shown these phytochemicals to be effective in the prevention and treatment of periodontal diseases. A recent review of antioxidant nutrients suggests the increased intake of flavonoids and carotenoids may be beneficial for the prevention of periodontitis [58]. More specifically, deficiency of the vitamin A precursor β-carotene [124], has been linked to periodontitis and gingivitis [67,125]. When vitamin A is supplemented alongside other therapies, studies have shown treatment outcomes for periodontal diseases to improve [60,126]. The research supports the importance of adequate intake of carotenoids and flavonoids to prevent and manage periodontal diseases.

Carotenoids and flavonoids are well known to have anti-oxidant properties and to modulate anti-inflammatory processes [116]. For example, lycopene, a bright red carotenoid, has been shown to stimulate the release of an anti-inflammatory cytokine, IL-10 and reduction of TNF-α *in vitro* [127]. This anti-inflammatory effect was demonstrated in a placebo-controlled randomised clinical trial that tested the efficacy of orally administered lycopene (8 mg/day for two weeks) with and without dental prophylaxis [128]. Lycopene alone and in combination with dental prophylaxis significantly decreased gingival inflammation at the end of the study period [128]. Similar results were found for the efficacy of lycopene supplements in mild-moderate, but not more severe gingivitis in another intervention study [129]. While these intervention trials suggest that lycopene supplementation may be useful for reducing inflammation in periodontal disease, it is important to note that these trials were small (~20 participants each). It has also been shown that lycopene delivered locally through an orally administered gel reduced markers of oxidative stress and gingival inflammation in periodontal diseases [130].

Flavonoids present in green tea, coffee and cocoa may be also beneficial in reducing the inflammation associated with periodontal diseases. Green tea supplements successfully reduced inflammation as an adjunct to mechanical periodontal therapy in a human intervention trial [131]. In a large prospective cohort study of men, it was found that higher coffee consumption was associated with a small but significant reduction in the number of teeth with the periodontal bone loss [132]. Mechanistically this is supported by animal models of experimentally induced periodontitis, where reduced oxidative stress markers were seen in rats fed a cocoa-enriched diet [133]. While these studies are indicative of a benefit to flavonoid consumption, additional research is needed to form specific recommendations or therapeutic guidelines to be developed.

2.4. Minerals

2.4.1. Zinc

Zinc is the second most abundant trace mineral in the human body and is involved in the protection of cellular elements from oxidative damage [57,134]. Therefore, zinc may play an essential role in the maintenance of periodontal health. Zinc deficiency can cause gingival inflammation by the aggregation of IL-1 [135]. A study conducted on 14 Sprague-Dawley rats fed with a zinc-deficient diet for four weeks following weaning has revealed an increase in plaque and gingival index and depth of periodontal pockets. Hence, dietary deficiency of zinc can be a potential risk factor for periodontal diseases [136].

Case-control and cross-sectional studies have also established a link between serum zinc levels and periodontitis in both healthy and diabetic patients [137–140]. Maintenance of periodontal health in diabetic patients is a crucial consideration as periodontitis is one of the significant complications of diabetes mellitus [139,141,142]. The lowered plasma levels of zinc have also been associated with the further deterioration of periodontal disease in patients with type 2 diabetes mellitus as compared to healthy individuals [143]. These studies confirm that

zinc deficiency is not only a risk factor for periodontal diseases but exacerbates periodontitis in type 2 diabetes.

2.4.2. Selenium

Selenium's association with periodontal diseases is not as well researched to date. However, it is known that selenium is essential for immune responses, and serum levels are inversely related to inflammation and tissue destruction [144]. Selenium-containing glutathione peroxidase acts as a preventive antioxidant by suppressing the formation of free radicals [57]. It has also been reported that lower serum levels of selenium can be associated with the severity of periodontal diseases [141]. Although studies are limited, maintaining selenium levels in periodontal diseases may aid in their management.

2.5. Calcium

Calcium is known for its role in promoting bone health [145]. Periodontitis involves the destruction of alveolar bone [145,146], and hence, calcium may be beneficial in this condition. The emerging evidence suggests that this is the case, showing calcium status to be vital in determining the risk for periodontal disease [147–149]. The data from NHANES III suggested that lower dietary intake of calcium resulted in progression of periodontal diseases. Furthermore, it has been shown that low calcium intake may indirectly affect periodontal disease; however, further studies are needed to confirm this [150].

Many intervention trials have observed the beneficial effect of combined calcium and vitamin D supplementation on the progression and maintenance of periodontal diseases [109,111,151]. A randomised clinical trial involving healthy adults (> 65years) also indicated that the use of calcium supplementation improved periodontal health and retention of teeth compared to placebo [110]. However, the trial also involved a combination of vitamin D, which may confound the results.

3. The role of micronutrients in oral mucosal lesions

Oral mucosal lesions are usually characterised by inflammation of the lips and mucosa and defoliation of tongue [152]. The inflammatory lesions of oral mucosa include aphthous ulcers, glossitis, cheilitis and stomatitis [153]. These inflammatory lesions usually result from either local trauma or systemic pathologies [154]. Regardless of origin, all of these inflammatory pathologies are characterised by the accumulation of polymorphonuclear leukocytes, which lead to the secretion of specific chemical mediators and are responsible for host immune and inflammatory responses [2,20,155,156]. The most commonly produced chemical mediators include cytokines, chemokines and lipid mediators [2,155,157]. These inflammatory mediators play a vital role in tissue homeostasis by anabolic and catabolic processes [158]. Even though nutritional deficiencies in iron are a predisposing factor in oral mucosal lesions, the research focuses on the roles of B vitamins such as folic acid and vitamin B_{12} [159–161].

3.1. Vitamin B complex

The B-complex vitamins act as co-factors in energy metabolism and are essential for the production of new cells and tissue maintenance during development and healing [71,162]. Thus, deficiency of these vitamins can result in disruption of the oral mucosa [71]. The first signs of insufficiency of some of the B group vitamins are seen in the oral cavity and can be characterised by specific oral manifestations, as shown in Table 1 [54,163–167].

Some of these oral manifestations including angular cheilitis, glossitis, stomatitis, diffuse erythematous mucositis and ulcerative mucosal lesion, are symptoms of early pernicious anaemia (B_{12} deficiency) and megaloblastic anaemia (B_{12} and folic acid deficiency) [168,169]. Vitamin B_{12} deficiency may be a contributing factor in recurrent aphthous stomatitis (RAS), a chronic inflammatory disease of oral mucosa characterised by painless and recurrent ulcers, however, the exact aetiology is unknown [164]. Overall, B vitamins play an essential role in the health of the oral mucosa and their deficiency contributes to the occurrence of common oral conditions.

Table 1
Effect of deficiency of vitamin B complex on oral structures.

Deficient Vitamin	Oral Manifestation(s)
Vitamin B_1	Cracked lips, angular cheilosis
Vitamin B_2,B_3	Angular cheilosis, glossitis
Vitamin B_6	Burning sensation in the oral cavity related with glossitis and stomatitis, and cheilosis
Vitamin B_9	Recurrent aphthous stomatitis (RAS)
Vitamin B_{12}	Angular cheilosis, painful ulcers in the oral cavity, glossodynia (sore tongue) and RAS

4. The role of micronutrients in pulpal and periapical lesions

Pulpal and periapical lesions are usually linked with infections associated with dental caries. There are two types of pulpal lesions: reversible and irreversible pulpitis, result from inflammation of pulpal tissue as sequelae of traumatic injury or dental caries [170–174]. These pulpal lesions also cause periapical lesions often termed as endodontic-periodontic lesions [175]. The periapical lesions include periapical cysts such as peri-radicular cysts, periapical abscesses and granulomas [170,176].

Exposure of the pulp occurs as a consequence of deep dental caries, dental fractures, or dental procedures, and triggers an inflammatory response. It is termed pulpitis and is characterised by a marked inflammatory infiltrate, with the secretion of IL-6 and other cytokines [177]. The progression of pulpal inflammation to the periapical region leads to host immune responses and, causes the destruction of periapical alveolar bone and formation of periapical lesions [2,175]. To date, few studies have shown a link between micronutrients and pulpal and periapical inflammation. The limited research that has been conducted has focused on the anti-inflammatory roles vitamin E and copper in these oral conditions. The intervention studies have been conducted on rats, while human studies have presented associations to nutrient deficiency states. Therefore, further investigations are needed to understand the role of nutrients in risk and therapies.

4.1. Vitamin E

Vitamin E supplementation may be beneficial in repair of, and protection against, pulpal inflammation. An experimental study conducted on adult male Sprague-Dawley rats has shown that vitamin E supplementation, along with dental pulp therapy, can enhance pulp healing and repair [178]. It has also been revealed that an isomer of vitamin E, α-tocopherol is beneficial to protect the pulp cells against toxicity resulting in pulpal inflammation caused by H_2O_2 *in vitro* [179]. However, research is still limited.

4.2. Copper

Copper is known for its anti-inflammatory function [180,181]. The altered serum levels of copper are indicative of chronic inflammatory conditions, such as the elevations in serum copper associated with periodontitis [138]. A case-control study involving a small Indian population has shown a highly significant ($p < 0.001$) correlation to copper deficiency in individuals with periapical inflammation in comparison to healthy individuals [182]. However, further research to confirm the anti-inflammatory properties of copper in periapical inflammation is needed.

5. Interactions between micronutrients and salivary function

Saliva is an important part of the oral environment, dysfunction of the salivary glands or altered composition of saliva can have implications for oral health [183]. It is well-established that Vitamin C deficiency influences salivary gland function [184] and iron deficiency commonly results in reduced salivary secretion [185]. Studies in rodents also suggest that calcium, and vitamin D deficiency may result in dysfunction of salivary glands [186–188]. This may further exacerbate oral inflammation or diseases, and may further promote malnutrition through a reduced sense of taste and appetite [189].

6. Conclusion

The symptoms and treatment of oral inflammatory diseases are influenced mostly by micronutrient intake or supplementation. Micronutrients are necessary for the maintenance of the health of oral mucosa and structures as they possess anti-oxidant and anti-inflammatory properties. Deficiency of certain micronutrients can modulate the risk for oral inflammatory diseases. Also, the insufficiency of some of the B-complex vitamins aids in the early detection of certain anaemias. Research has also confirmed that deficiency of particular trace minerals also aggravates certain oral diseases in the presence of chronic systemic pathologies.

Vitamins C, D, E, A, B-complex, and minerals also show therapeutic potential for the prevention of oral inflammatory disorders. Systemic and local administration of the micronutrients can promote tissue healing and result in the better prognosis of periodontal diseases. Given the known role of micronutrients in oral health, studies are still limited, especially regarding the importance of micronutrients in pulpal and periapical lesions. Further investigations are still needed to expand the body of knowledge, which may help in the prevention of oral inflammatory diseases and the development of future therapeutic aids.

Author contributions

K.K., D.S., J.W., A.T., C.F., M.V., M.L. and E.L.B. were involved in writing the draft. All authors were involved in reviewing and editing the manuscript.

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Declaration of competing interest

The authors declare no conflict of interest.

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