

ARE PERIODONTAL TISSUES AND PERIODONTAL HEALTH IMPACTED BY FOOD SUPPLEMENTS (PROTEIN AND AMINOACIDS, NATURAL HERBAL PRODUCTS, MINERALS)? - REVIEW.

George Alexandru Maftel¹, Oana Ciurcanu^{2*}, Odette Luca^{3*}, Liliana Pasarin⁴, Cristina Popa¹, Mihaela Maris⁵, Maria Alexandra Martu⁴, Ionut Luchian⁴

¹“Gr.T.Popa”U.M.Ph., Iași, Romania, Faculty of Dentistry, Department of Oral Medicine

²“Gr.T.Popa”U.M.Ph., Iași, Romania, Faculty of Dentistry, Department of Dento-alveolar Surgery,

³“Gr.T.Popa”U.M.Ph. -Iași, Romania, Faculty of Dentistry, Department of Implantology, Removable Dentures, Dental Technology.

⁴ “Gr.T.Popa”U.M.Ph. -Iași, Romania, Faculty of Dentistry, Department of Periodontology.

⁵PhD Student “Dunarea de jos, Galati, Romania, Resident Doctor

* *Corresponding author* : Ciurcanu Oana: oana.ciurcanu@umfiasi.ro

Luca Odette: lucaodette@yahoo.com

All authors had an equal contribution equal with first author

Abstract:

The aim of this review is to provide an overview of the current evidence of some popular food supplements and superfoods that might be of interest in periodontology.

Although the number of publications investigating the effect of these products on human health and their possible use in medicine is increasing, only little is known so far regarding their effects on periodontal tissues and their possible use in periodontal treatment or medicine.

In summary, an increasing number of studies have revealed aspects and effects of these so-called lifestyle or fitness supplements and superfoods that may have an impact on periodontal health and healing after treatment. However, some the current evidence is of a very low quality, and more validated scientific data are required before their possible use in prevention or treatment of periodontal diseases can be made.

Keyword: *food supplements, periodontal tissues, prevention or treatment of periodontal diseases*

INTRODUCTION

The use of food supplements and so-called superfoods to increase fitness and regeneration or just to improve health and well-being is very popular these days, particularly in people living the fitness lifestyle. Some of the effects attributed to these supplements and superfoods involve tissues and processes that may also play a role in periodontal healing and regeneration. However, some the current evidence is of a very low quality, and more validated scientific data are required before their possible use in prevention or treatment of periodontal diseases can be made. Periodontitis is a dysbiotic inflammatory disease and the result of a host immuno-

inflammatory response to periodontopathic bacteria.

This review investigating the effect impact of health and lifestyle food supplements on periodontal tissues and health. (Protein and Aminoacid Supplements, Glucosamine and Chondroitin Sulfate, Natural herbal products and seeds, Minerals).[1]

1. Protein and Aminoacid Supplements

The most frequently used supplements in the fitness lifestyle are protein and amino acid supplements used to support muscle growth and muscle regeneration.

Possible beneficial effects of protein and amino acid supplements have been extensively studied in orthopedic and sports

medicine, and also in geriatric medicine, since proteins constitute an important structural and functional component of skeletal tissues.

However, some of these so-called muscle supplements might also have effects on periodontal tissues as well as on periodontal wound healing.

Alteration in protein turnover following tissue damage due to injury or extensive exercise is crucial to tissue repair. Increasing knowledge has indicated the need for increased protein intake during tissue repair based on its important roles supporting wound healing, maintaining tissue integrity, and promoting convalescence.[2]

An insufficient protein intake has been shown to delay wound healing and to reduce the integrity of the repaired tissue. [3-5]

Thus, milk can be considered as a natural biological liquid esculent providing nutrition at a time of rapid body and particularly muscular-skeletal growth.

Total protein intake and animal protein intake have been associated with higher bone mineral density and less bone mineral density loss over time.

The positive effects of dietary protein on bone mineral density may be due to increased levels of insulin-like growth factor 1 and suppression of parathyroid hormone.

Further investigation of these whey protein fractions revealed that lactoferrin was a constituent in many of these fractions.[6]

However, local concentrations can increase during inflammation. [6,7]

Studies of lactoferrin on human, rat, and mouse cell cultures of the osteoblast and osteoclast lineage and of bone marrow cultures showed that lactoferrin promotes osteoblast growth, inhibits osteoclastogenesis, and reduces osteoblast apoptosis.

Interestingly, besides its effects on bone metabolism, there are also reports of antimicrobial effects of lactoferrin,

attributed to its action as an iron chelator, as well as of an immunomodulatory function. Lactoferrin has been shown to decrease the secretion of interleukin-1 β and tumor necrosis factor alpha and to stabilize mast cells. [8-12]

A significant decrease in tumor necrosis factor alpha serum levels after administration of a high-caloric protein-rich oral supplement was also reported in a prospective randomized, double-blind, placebo-controlled study in patients with chronic heart failure and cachexia. [13]

This was also confirmed by a clinical trial in sarcopenic elderly patients where supplementation with whey protein, amino acids, and vitamin D increased serum insulin-like

growth factor 1 concentrations and lowered C-reactive protein. [14]

Furthermore, protein deficiency may also predispose patients to higher rates of infectious complications. [15]

Protein hydrolysates have the potential to promote different types of tissue repair and might be useful in situations where excess protein is needed, such as tissue repair, regeneration, or wound healing.

However, further well-controlled human trials are required to confirm these findings and assess the clinical relevance in *periodontal therapy*.

Lipopolysaccharide of gram-negative bacteria, like most of the main periodontal pathogens, is known to induce the release of proinflammatory cytokines such as interleukin-1 β , interleukin-6, interleukin, tumor necrosis factor-alpha, and nitric oxide in macrophages.

Furthermore, recent studies have also indicated that branched-chain amino acids may play a role in the development of insulin resistance and might be associated with incident cardiovascular disease. [16-18]

Glutamine has also been shown to simulate collagen synthesis through the conversion

process to proline and provides 75% of the intracellular free proline in fibroblasts.

Amman et al. [19] investigated the effect of essential amino acid supplements in adult osteoporotic rats.

Unfortunately, the number of studies investigating the effect of protein and amino acid supplements on periodontal disease or therapy is very limited.

Aral et al [20] investigated the effect of bodybuilding and protein supplements on periodontal tissues, comparing bodybuilders with gingivitis with nonexercising males with and without gingivitis.

They assessed clinical periodontal parameters and analyzed saliva and gingival crevicular fluid samples for interleukin-1 β , apoptosis-associated speck-like protein containing

C-terminal caspase-recruitment domain and caspase 1.

The authors indicated that bodybuilding and supplement usage may decrease gingival inflammation by downregulating caspase 1, interleukin-1 β , and apoptosis-associated speck-like protein containing C-terminal caspase-recruitment domain.

Lee et al [21] investigated the effects of a commercially available nutritional supplement drink on periodontal health or healing and tooth mobility after periodontal flap surgery.

Patients with a generalized moderate chronic periodontitis were, directly after periodontal flap surgery, randomly allocated to either the intervention or the control group.

After 8 weeks, tooth mobility returned to baseline levels again in both groups.

The authors concluded that the use of nutritional supplementation may improve early periodontal wound healing after periodontal surgery.

2. Glucosamine and Chondroitin Sulfate

Glucosamine is a naturally occurring amino monosaccharide that is present in the connective tissue and cartilage tissues as a

component of glycosaminoglycans and is involved in maintaining strength, flexibility, and elasticity of these tissues.

Numerous studies have shown the significant symptom-modifying effect of glucosamine in osteoarthritis and its beneficial effects on joint health. [22-24]

There are also an increasing number of studies investigating the effects of glucosamine in combination with chondroitin sulfate in osteoarthritis therapy. Supplementation with glucosamine has been shown to reduce inflammatory responses of joint cartilage by inhibiting the activation of nuclear factor kappa-light-chain- enhancer of activated B cells, which lies upstream of inflammatory processes or mediators such as interleukin-beta, interleukin-8, tumor necrosis factor alpha, and C-reactive protein.

Binding of proinflammatory cytokines to their respective receptors amplifies immune response by increasing proliferation of T cells, promoting leukocyte infiltration and facilitating cell-cell signaling. [25-28]

Cigarette smoking causes lung inflammation that is mainly regulated by redox-sensitive pathways.

It was recommended that glucosamine hydrochloride could be used as a pharmaceutical supplement to alleviate oxidative stress.[29]

Interleukin-8 plays an essential role in directing the sequential process of neutrophil rolling, adhesion, and transmigration into inflamed microvasculature.

Furthermore, proinflammatory mediators, such as interleukin-1 β , interleukin-6, and tumor necrosis factor alpha increase the expression of adhesion molecules on endothelial cells and neutrophils. [25,30]

However, glucosamine also seems to exhibit interesting effects on bone and collagen metabolism. These results indicate that glucosamine increases bone mineral density, induces osteoblastic differentiation, especially at middle and late

stages, and also suppresses osteoclastic cell differentiation, thereby increasing bone matrix deposition, decreasing bone resorption, and promoting bone formation. [23,31]

Furthermore, risk factors for diabetes development are elevated triglycerides, blood pressure, body mass index, and family history of diabetes.

The findings of this study indicate that there is no effect of glucosamine sulfate on mean hemoglobin A1c level or on obtaining a high hemoglobin A1c level or new-onset Diabetes mellitus over 6.5 years, especially in participants with a normal hemoglobin A1c level at baseline.

The results of an *in vitro* study using inferior nerve preparation in a rat mandible suggest that d-glucosamine hydrochloride has a pain relief effect on patients with dental pain. [32]

3. Natural herbal products and seeds “functional food or super food”(quinoa, spirulina),

In recent years, the increasing number of people suffering from cardiovascular diseases, obesity, diabetes mellitus, neurologic diseases, dementia, cancer, and other related diseases has shifted the focus from disease treatment to healthy lifestyle changes.

Epidemiologic studies have shown that physical inactivity and unhealthy diet containing high amounts of refined carbohydrates combined with saturated fatty acids but lacking fiber, minerals, and antioxidant micronutrients may be an important risk factor in the development of pathologic conditions.

Whereas pre-Neolithic oral bacterial ecosystems were more diverse and dominated by the nonpathogenic family of Ruminococcaceae, modern oral ecosystems are less diverse with an abundance of periodontopathogens, such as *P. gingivalis*, *Tannarella*, and *Treponema*, and cariogenic species, such as *Streptococcus mutans*. [33]

In 2009, Baumgartner et al. [34] illustrated that diet may have a significant impact on periodontal inflammatory status.

The Swiss study on 10 adults who were placed in a “Stone Age” environment and on

diet rich in fibers, fish oils, and micronutrients showed significant reduction in bleeding on probing and pocket depth compared with baseline, even in the absence of oral hygiene. [34,35] An evidence-based review, based on 31 human studies that explored the relationship between food supplements and periodontitis, showed substantial evidence of beneficial outcomes for treatment of periodontal diseases from nutritional intervention.

It also suggested guidelines for micronutrient supplement intake (mainly vitamins C and D) that may improve results in the treatment of periodontitis, especially in cases of refractory disease. [36]

Furthermore, it has been shown that the use of nutritional agents as adjuvants to nonsurgical periodontal therapy significantly reduced the periodontal disease severity, improved treatment prognosis in the short term (2-6 months), and reduced susceptibility toward periodontal disease.[37]

In the past few years, emerging evidence from the studies have increased the awareness of the industry and consumers related to the possible nutritional and health attributes of certain natural herbal products. Apart from that, it is a source of many vitamins (thiamin, riboflavin, niacin, and folic and ascorbic acids) and minerals (calcium, phosphorus, potassium, and magnesium), as well as compounds with antioxidant properties. [38,39]

Chia seeds extract has been tested in a recent *in vitro* study and demonstrated excellent antimicrobial efficacy against three periodontal pathogens: *P. gingivalis*, *Aggregatibacter actinomycetemcomitans*,

and *F. nucleatum*. Its inhibitory potential was similar to 0.2%

chlorhexidine, which was used as positive control. [40]

As there are no clinical trials related to the preventive or therapeutic properties of **chia** seeds on the diseases that affect oral mucosa and periodontium, we can only suggest that the systemic anti-inflammatory potential of chia seeds shown in some studies may play a role in the prevention and treatment of periodontal diseases.

It can also be stipulated that their antioxidative potential may have an effect on oxidative stress that orchestrates proinflammatory cascades that underpin tissue destruction in periodontitis and other inflammatory conditions associated with periodontitis, such as type 2 diabetes, cardiovascular disease, and obesity and related metabolic dysregulation.

The seeds' mineral content may also improve the quality of bone and prevent osteoporosis and its effect on the periodontal status of the patients.

Quinoa seeds, leaves, and sprouts are used as human and animal food owing to their nutritional values.

Quinoa has been described as "one of the grains of the 21st century," and its production, preservation, and consumption were promoted by the Food and Agriculture Organization of the United Nations in 2013. Quinoa is superior to many grains, such as rice, rye, barley, and oat, in relation to protein and lipid content. It contains 13.1%-16.7% of high-quality proteins with well-balanced essential amino acid content that satisfies the amino acid requirements for adults suggested

by the Food and Agriculture Organization of the United Nations/

World Health Organization/United Nations University.

It contains a significant amount of essential amino acids, such as lysine, methionine, and threonine, that is higher than in essential cereals, such as wheat and maize. [41]

The content of micronutrients, such as vitamins and minerals, is also of great importance, as the seed is rich in pyridoxine (vitamin B6), folic acid, ascorbic acid (vitamin C), and vitamin E. Mineral content, such as calcium, iron, and magnesium, is considerably higher than in other commonly used grains, such as wheat and corn.

These components are known to exhibit a wide range of health benefits, such as *antifungal, antiviral, antibacterial, and cancer-suppressing effects*.

They also exhibit hypoglycemic, antithrombotic, diuretic, anti-inflammatory, anabolic, antidiabetic, anti-osteoporotic, and anti-obesity properties. [42]

The evidence of some of these benefits is demonstrated in limited numbers of animal and human studies.

Vitamins: thiamine, riboflavin, niacin, folic and ascorbic acids Minerals: calcium, phosphorus, potassium, and magnesium

Antioxidants: polyphenols, chlorogenic acid, caffeic

acid, quercetin, kaempferol Fatty acids: omega-3 and omega-6 fatty acids [38,39]

Improvement of lipid profile; reduction of risk of diabetes and cardiovascular diseases. [43]

Quinoa (*Cenopodium quinoa* Wild.)

Vitamins: pyridoxine (vitamin B6), folic acid, ascorbic acid, and vitamin E

The antibacterial activity of quinoa against oral bacteria has rarely been reported. A recent *in vitro* study showed that alkali-transformed saponins derived from quinoa husk were efficient

against three halitosis-related bacteria: *P. gingivalis*, *Clostridium perfringens*, and *F. nucleatum*.

The saponins altered membrane potential and morphology, as well as interfered with its permeability, causing leakage of nucleic acids and proteins.

The results of the study indicated that saponins derived from quinoa husk may have an important role in a new drug

delivery system against oral halitosis caused by oral microorganisms.[44]

Spirulina. *Arthrospira platensis* is a microscopic single-cell alga that inhabits fresh and marine waters.

Spirulina contains up to 70% of proteins; it is also rich source of vitamins (B-complex, β -carotenes, and vitamin K) and minerals (iron, magnesium, zinc, copper, selenium, and chromium). It can be easily cultivated, harvested, and processed into a variety of final products, such as powder, tablets, flakes, and other edible profiles. [45]

Owing to the high content of carotenoids and the protein-bound pigment C-phycoocyanin

this blue-green algae has been shown to have antioxidant and immunomodulatory properties in *in vitro* and *in vivo* studies.

These substances may act as scavengers of reactive oxygen species mainly generated by host defense cells during an inflammatory reaction and increased oxidative stress. [45]

Oxidative stress was first described by Sies in 1985, and some years later it was revealed that it underpins the pathogenesis of numerous of inflammatory diseases, such as periodontitis, diabetes, cardiovascular disease, and obesity/metabolic dysregulation. [36,46]

The antioxidative potential of spirulina has been demonstrated in several human studies conducted on geriatric patients and on healthy individuals after exercise.

Food supplemented by spirulina for 16 weeks showed significantly increased levels of antioxidant status in plasma of geriatric patients. [47]

In addition to its unproven role as an antioxidant and immunomodulator, spirulina has been reported to improve blood lipid profile, which may be of importance in prevention of diabetes and cardiovascular diseases. [45]

Recently, **Spirulina** (*Arthrospira*) *maxima* was tested on rats as a potential agent in treatment of periodontitis.

Gingival tissue of rats treated with *S. maxima* showed reduced concentrations of proinflammatory cytokines, such as tumor necrosis factor alpha, interleukin-1 β , interleukin-6,

and inflammatory transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells. Activity of myeloperoxidase and expression of matrix metalloproteinases were also decreased in periodontal tissue of test rats.

In addition, treatment with *S. maxima* increased concentration of anti-inflammatory

cytokine interleukin-4 and the osteoprotegerin/ RANKL expression ratio. *S. maxima*-treated

groups showed reduced numbers of osteoclasts and less bone loss, as well as increased production of osteoblasts and osteogenesis-related factors. [48]

Scarce evidence so far exists on the effect of spirulina on periodontal health and disease. One randomized controlled clinical study tested the benefits of local application of spirulina-based

Gel as adjunct to nonsurgical treatment (scaling and root planing) of chronic periodontitis.

The results showed significant improvement of clinical parameters, such as probing depth reduction and clinical attachment gain, in the experimental group when compared with the control group (scaling and root planing alone).

During the course of treatment, spirulina gel did not cause any side or adverse effects.[49]

As this study is one of the first to use spirulina as a local adjunct agent in the treatment of periodontitis, further studies, including more relevant clinical and biochemical parameters, are necessary to confirm the findings and explore underlying mechanisms.

Turmeric is a dietary spice whose active ingredient, curcumin, is isolated from the rhizomes of *Curcuma longa*, a plant that

belongs to the ginger family. Turmeric is yellow in color and is most used in Asian and Indian cuisine.

Curcumin has been approved by the US Food and Drug Administration to be a safe food supplement, and a daily intake of curcumin at a dose of 0.1-3 mg/kg body weight has been considered as an acceptable dose by the Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives, 1996.[50]

Curcumin (mainly its analogues) has shown chemopreventive and chemotherapeutic properties in different cancer studies.

It has been shown *in vivo* (paw edema model) to have analgesic and anti-inflammatory activity through suppression of gene expression and inhibition of secretion of proinflammatory substances, such as tumor necrosis factor alpha, monocyte chemoattractant protein-1, interleukin-10, and interleukin-6.

It has been delivered in the form of nanoparticles, tablets, capsules, powder, or solution in doses from 0.18 to 8 g/d. [51]

In clinical trials, patients with periodontal diseases usually use curcumin as adjuvant therapy following subgingival instrumentation.

All trials were conducted in India, with the main objective to compare the efficacy of turmeric and chlorhexidine, formulated either as a mouthwash or gel, in the prevention and treatment of gingivitis. [52] Three studies on prevention showed that, as an adjunct to mechanical plaque control, turmeric-based mouthwash significantly reduced plaque accumulation and gingival inflammation after the experimental period (14-21 days).

However, when compared with chlorhexidine, it was less efficient. [52,53]

Two studies tested the therapeutical efficacy of turmeric and chlorhexidine as an adjunct to mechanical treatment of gingivitis and compared them with mechanical treatment alone.

It has been widely used in photodynamic therapy of cancers owing to its low cost and high efficacy. De Paula Zago et al. [54] have shown that curcumin can significantly inhibit the growth of oral pathogens while used as a photosensitizer.

In a clinical study, Sreedhar et al. [55] used curcumin gel as a photosensitizer in photodynamic therapy following subgingival instrumentation with ultrasonic scaling in 15 patients with deep periodontal pockets.

Curcumin showed enhanced antimicrobial properties against *P. gingivalis*, *A. actinomycetemcomitans*, and *Prevotella intermedia*.

These results were improved when the multiple applications of photodynamic therapy were performed. The curcumin binds to the cell wall of periodontal pathogens and when irradiated with light of specific wavelength produces reactive oxygen species, which can destroy the pathogens in the immediate vicinity. [55]

This and other preliminary *in vivo* studies provide initial evidence that curcumin may offer periodontists a complementary approach to the conventional periodontal therapy through either systemic or local application.[56]

Açai-berry, the fruit of the Amazonian palm, *Euterpe oleracea* Martius, has been extensively studied not only for its nutritional properties but also its anti-inflammatory, antioxidant, and bioactivity properties. Açai pulp fraction contains a remarkable number of phytochemicals and mono- and polyunsaturated fatty acids.[57] Phytochemical analyses indicate that açai extract is rich in anthocyanins and possesses a high number of polyphenols, especially flavonoids, that exhibit promising therapeutic potential.

Earlier *in vitro* studies demonstrated that açai extract may exhibit potent anti-inflammatory, neuroprotective, and anticarcinogenic properties. [57]

These findings may be of importance for further testing and development of novel therapeutic agents with potential to reduce inflammatory bone loss that occurs as a result of periodontitis.

4. Minerals

Minerals belong to the group of minor/micronutrients that are present in food in small amounts, measured by microgram quantities.

Minerals act as catalysts in a variety of enzyme systems, either as ionic enzymatic cofactors or metalloenzymes.

Regular daily intake of food rich in minerals is usually sufficient to maintain health; however, in some cases, pharmacological supplements are used to maintain satisfactory levels or treat deficiencies. [58] *Sodium* is the cation and main major mineral in extracellular fluid. It plays a key role in cellular membrane potential and nerve conduction, and together with calcium, potassium, and magnesium has an important influence on cardiac output and peripheral vascular resistance, the main determinants of blood pressure level. [59]

Sodium is mainly consumed as sodium chloride, "dietary salt," but may be found in food additives, too.

Potassium is the key cation in intracellular fluid with a similar role to sodium. Potassium is known to have a protective effect on the cardiovascular system, and its anti-atherosclerotic properties have attracted attention in the recent years.

Other health benefits of potassium may be related to diabetic patients and improvement of their glucose tolerance. [58]

Calcium is the main component of hydroxyapatite, a mineral that is present in our skeletal system and teeth. It is important for normal bone turnover, nerve conduction, and blood coagulation. [59]

Metabolism of calcium is regulated by parathyroid hormone and calcitonin, and its

active resorption through intestinal wall is highly dependent on vitamin D.

Numerous clinical studies have emphasized the importance of calcium intake in bone mineral density maintenance and tooth retention, especially in the elderly population.

Vitamin D deficiency is common in the world, with an estimate that more than 1 billion people suffer from its insufficiency or deficiency. [60]

The beneficial effect of supplementation with vitamin D and calcium has been well documented and recognized in the treatment of rickets, osteomalacia, and osteoporosis.

In recent times, vitamin D and calcium have also been considered as candidates to modulate periodontal disease, as some studies have found that their intake may reduce alveolar bone loss, gingival inflammation, and attachment loss.

Caution should be considered with patients reporting a risk of bowel cancer. [61]

The Third National Health and Nutrition Examination Survey large cohort of up to 12 000 subjects suggested that low dietary intake of calcium results in more severe periodontal disease and progressive attachment loss in a dose-dependent manner. [60]

Another study that used data from the Third National Health and Nutrition Examination Survey reported an inverse association between the prevalence of periodontal disease and the intake of dairy products, a common dietary source of calcium and vitamin D. [62]

A recent cross-sectional study on 51 subjects on periodontal maintenance therapy resulted in a trend toward better clinical (gingival inflammation, probing depth, and attachment loss and furcation involvement) and radiological parameters (cemento-enamel junction to alveolar crest distance) of periodontal disease in patients who were voluntarily taking calcium (at least 1000 mg/day) and vitamin D (at least 400 IU/day) supplements for more than 18

months (average of 10.6 years) prior to commencement of the study. [60]

Although some studies implied benefits of daily supplementation with vitamin D and calcium, use of these microelements in healthy patients with periodontal disease requires further evidence.

Recommended daily intake of calcium for adults ranges from 1000 to 1300 mg/day. [63]

Magnesium is second most prominent intracellular cation and is present in all tissues, with majority (two-thirds) stored in bones. Imbalances in magnesium metabolism may be associated with different pathologic conditions such as cardiovascular diseases, diabetes, pre-eclampsia, eclampsia, and sickle cell disease.[36] Low magnesium intake has been linked to periodontitis. [64]

In a cross-sectional epidemiologic study involving 4290 subjects from 20 to 80 years of age, periodontal health was determined and correlated to concentrations of serum magnesium and calcium. In a matched study, the periodontal status of 60 subjects from the same population using magnesium drugs was compared with 120 nonusers. Subjects taking magnesium showed less

attachment loss ($P < 0.01$) and a higher number of remaining teeth than did their counterparts. The findings of the study indicate that magnesium supplementation may improve periodontal status and improve tooth retention. [65]

CONCLUSION

In summary, an increasing number of studies have revealed aspects and effects of these so-called lifestyle or fitness supplements and superfoods that may have an impact on periodontal health and healing after treatment. Against the background of periodontal disease

as a chronic inflammatory disease involving bone and connective tissue degradation, a deeper insight and understanding of the potential anti-inflammatory effects of supplements and their effects on bone and connective tissue metabolism could help to develop new prevention and treatment strategies.

However, some the current evidence is of a very low quality, and more validated scientific data are required before their possible use in prevention or treatment of periodontal diseases can be made.

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