ISSN: 2538-5887; Pathobiology Research. 2024; 27 (2): 43-57

Antioxidants Therapy in Oral Inflammatory Diseases: A Comprehensive Review

ARTICLE INFO

Article Type:
Narrative Review

Authors:
Hossein Malekzadeh [1]
Amir Danial Pour Ahmadiyeh [2*]

1. Department of Oral and Maxillofacial Medicine, School of Dentistry, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
2. Department of Oral and Maxillofacial Surgery, School of Dentistry, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

**** Corresponding author:***
Amir Danial Pour Ahmadiyeh
Email: dr.ad.pourahmadie@gmail.com

ABSTRACT

The current article seeks to review the published literature regarding the possible impacts of antioxidant therapy on the management of oral inflammatory conditions. Evidence for this review was systematically collected from reputable scientific databases, focusing on studies published between 2010 and 2024. To ensure a thorough exploration of the topic, broad keywords such as Antioxidants, Oxidative Stress, Inflammation, and Oral Diseases were employed, utilizing both "OR" and "AND" search strategies. The findings from the reviewed literature suggest that antioxidant therapy, whether derived from natural sources or synthesized, demonstrates statistically significant improvements in alleviating oral diseases associated with oxidative stress and inflammation. In conclusion, this review underscores the promise of antioxidant agents in both the prevention and treatment of inflammatory oral diseases, indicating that dietary changes and the intake of antioxidant supplements may be beneficial in managing these conditions.

Keywords:
Antioxidants, Oxidative Stress, Inflammation, Oral Diseases

INTRODUCTION

Oral inflammatory diseases, including periodontitis, gingivitis, and oral mucositis, are widespread conditions that affect millions of individuals globally. These ailments are marked by persistent inflammation, tissue damage, and discomfort, which not only compromise oral health but may also have implications for overall systemic health (1). Although traditional treatment options such as scaling and root planing, antibiotics, and surgical procedures are commonly employed, there is an increasing interest in investigating alternative therapies that aim to modulate the inflammatory processes involved (2). The role of oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) production and the antioxidant defense mechanisms, is significant in the pathogenesis of these oral inflammatory diseases (3). ROS, which are produced during normal cellular activities and can be intensified by factors such as smoking, infections, and inflammation, have the potential to harm cellular structures, resulting in tissue damage and inflammation (4). In the context of oral inflammatory diseases, ROS not only stimulate immune cells to produce pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 but also contribute to the degradation of collagen, a vital component of connective tissues, thereby facilitating periodontal tissue deterioration (5). Furthermore, excessive ROS production can enhance osteoclast activity, leading to bone resorption and the destruction of alveolar bone (6). Antioxidants play a crucial role in mitigating oxidative stress and present a promising therapeutic strategy for the management of oral inflammatory diseases (7). By donating electrons to reactive oxygen species (ROS), antioxidants transform these harmful entities into less detrimental molecules, thereby minimizing oxidative damage (8). Both natural and synthetic antioxidant agents have the capacity to inhibit the synthesis of pro-inflammatory cytokines while simultaneously encouraging the production of anti-inflammatory cytokines, which effectively attenuates the inflammatory response. Additionally, antioxidants safeguard collagen from ROS-induced degradation, thereby maintaining tissue integrity (9). Certain antioxidants have also been found to enhance osteoblast activity, facilitating bone regeneration

and repair in maxillofacial contexts. Numerous studies have explored the therapeutic potential of antioxidants in treating oral inflammatory diseases, highlighting their ability to improve clinical outcomes through various mechanisms (10). These include the reduction of oxidative stress, neutralization of free radicals, anti-inflammatory properties, modulation of inflammatory pathways, promotion of tissue repair, enhancement of immune function, improvement of salivary antioxidant capacity, microbial modulation, and reduction of gingival inflammation (11). In this context, certain antioxidants, notably Vitamin C and Vitamin E, have established roles in addressing oral inflammation (12). Research indicates that Vitamin C is vital for collagen synthesis, which is essential for maintaining the structural integrity and healing capacity of gingival tissue, often compromised during inflammatory processes. This vitamin plays a significant role in neutralizing reactive oxygen species (ROS) and free radicals, thereby alleviating oxidative stress within the oral environment (13). Additionally, Vitamin C has been identified as a modulator of the immune response, effectively lowering the levels of pro-inflammatory cytokines such as IL-1 and TNF-alpha, which are typically elevated in conditions of oral inflammation. Moreover, the synergistic effects of these vitamins have been documented, with Vitamin C enhancing the antioxidant capabilities of Vitamin E, thus providing a more effective defense against oxidative stress and inflammation in the oral cavity (14).

The clinical evidence regarding the application of antioxidants in the treatment of oral inflammatory diseases is still in a developmental stage, despite its promising nature. Numerous studies have indicated favorable outcomes in terms of inflammation reduction, tissue regeneration enhancement, and overall improvement in oral health. Nevertheless, this study seeks to conduct a comprehensive review of the existing literature concerning the potential impact of antioxidant therapy on the management and outcomes of oral inflammatory diseases.

Evidence Acquisition

The current review seeks to deliver an extensive evaluation of the effectiveness of antioxidants in the prevention and treatment of oral inflammatory diseases. The methodology for the database search is detailed in Table 1.

Table 1. Study evidence acquisition.

Keywords	Antioxidants, Oxidative Stress, Inflammation, Oral Diseases.
Database	Pubmed, Scopus, Web of Science, Embase, Cochrane Database of Systematic Reviews (CDSR), Online Library Wiley, Springer, Database of Abstracts of Reviews of Effects (DARE), Clinical Trial Results, World Health Organization International Clinical Trials Registry Platform (ICTRP), SID, Iranmedex, Magiran, Irandoc and Medlib.
Screening Strategy	"OR" and "AND"
Time Frame	2010 to 2024.
Inclusion Criteria	All types of original in vitro and in vivo research, on animal, children and adults including case–control, clinical trials, letters, case reports, organizational reports, opinions or editorial papers.
Exclusion Criteria	Conference papers, books, and short surveys, as well as publications written in languages other than English, were excluded.

RESULTS

Curcumin

Curcumin (CUM), a compound derived from the turmeric plant, scientifically known as Curcuma longa and part of the ginger family, is currently a focal point of extensive research. The therapeutic attributes of turmeric are primarily attributed to curcumin, the active constituent found in its rhizome, which imparts the characteristic yellow or orange hue. The hydroxy groups present in curcumin are crucial for its antioxidant properties, while the methoxy groups contribute to its anti-inflammatory and anti-proliferative effects (15). Curcumin is characterized by its insolubility in water and ether, yet it dissolves in solvents such as ethanol, dimethyl sulfoxide (DMSO), oil, and acetone. Historically, curcumin has been utilized in traditional medicine for approximately 5,000 years. As a potent antioxidant, curcumin enhances the expression of antioxidant enzymes, thereby providing a protective mechanism against free radicals. Its dual antioxidant and prooxidant

properties enable curcumin to inhibit the formation of reactive oxygen species and interact with thyroxine reductase (TR), facilitating its conversion to nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which subsequently leads to the generation of reactive oxygen species. Additionally, curcumin plays a role in preventing lipid oxidation and elevating intracellular glutathione levels. It exerts its antioxidant effects by chelating iron and mitigating oxidative stress through the induction of the enzyme heme oxygenase (HO-1) (16). Importantly, even at elevated doses, curcumin does not demonstrate significant adverse effects, and its antioxidant potency is comparable to that of vitamins C and E, exhibiting efficacy in both aqueous and lipid-soluble forms (17). The effectiveness of curcumin in the context of periodontal diseases is summarized in Table 2.

Green Tea

Green tea is obtained from the leaves of the Camellia sinensis plant. The health benefits associated with green tea extract, particularly its catechin polyphenols, have prompted numerous scientific studies aimed at exploring its potential in the prevention and treatment of various diseases. Among the key constituents of green tea are epigallocatechin (EC) and epicatechin (EGC), which have been identified by researchers as possessing antioxidant properties and the ability to neutralize free radicals (25). Furthermore, green tea is rich in carotenoids, tocopherols, ascorbic acid, and essential minerals such as zinc, selenium, and chromium, in addition to a variety of other phytochemical compounds (26). A summary of the findings regarding the effectiveness of green tea in managing periodontal diseases is presented in Table 2.

Resveratrol

Resveratrol, scientifically known as 3,5,4'-trihydroxy-trans-stilbene, is a naturally occurring phytoalexin identified in over 27 different plant species. Numerous studies have indicated that resveratrol exhibits significant anti-inflammatory, antioxidant, and anti-diabetic properties. Its capacity to diminish lipid peroxidation is notably more potent compared to other phenolic compounds such as epicatechin, catechin, and quercetin. This compound is present in various sources, including the plant Polygonum cuspidatum, the bark of certain trees, dried fruits like nuts and peanuts, as well as in flowers and red fruits, particularly in fermented grapes, mulberries, red wine, and blueberries (35). Resveratrol exists in two isomeric forms: trans-resveratrol and cis-resveratrol, with the latter being less stable. This compound is recognized for its wide range of biological activities, which encompass antioxidant, antimicrobial, anti-inflammatory, antitumor, antiviral, anti-aging, antifungal, and antithrombotic effects. Furthermore, it has demonstrated potential benefits for various health conditions, including diabetes, cardiovascular diseases, neurodegenerative disorders, and certain aspects of bone metabolism (36). The effectiveness of resveratrol in the context of periodontal diseases is summarized in Table 2.

Triphala

Triphala is a traditional herbal formulation composed of the dried fruits of three Indian medicinal plants: Haritaki (Terminalia chebula), Amalaki (Phyllanthus emblica), and Bibhitaki (Terminalia bellirica), each contributing equally to its preparation. This remedy is highly regarded within the framework of Ayurvedic medicine, one of the oldest healthcare systems globally, which has its origins in the Indian subcontinent. The term Ayurveda translates to the "science of life" or "science of complete health," focusing on disease prevention and health promotion (42). Within Ayurvedic classification, triphala is categorized as one of the eight essential components of medicine, particularly associated with longevity and rejuvenation. The formulation is abundant in various bioactive compounds, including tannins (such as gallic acid, ellagic acid, and chebulinic acid), flavonoids (like quercetin and luteolin), fatty acids (including linoleic and oleic acids), ascorbic acid, and other phytochemicals, which have been linked to numerous biological effects. These effects encompass antioxidant properties, anti-inflammatory actions, antimicrobial activity, modulation of immune function, anti-cancer effects, prevention of tooth decay, reduction of fever, and cardiovascular protection (43). Triphala is particularly noted for its strong antimicrobial, antioxidant, and anti-collagenase capabilities. The efficacy of triphala in treating periodontal diseases is summarized in Table 2.

Table 2. The summary of antioxidants in periodontist diseases.

Author	Year	subjects	Materials	Pathology	Outcomes
Gao et al. (19)	2023	Human	Curcumin	Dental Caries	Curcumin was efficient and safe techniques for caries prevention and treatment, thereby expanding treatment options in clinical dentistry and promoting oral health
Laurindo et al. (20)	2023	Human	Curcumin		Curcumin was improved inflammatory factors and could effectively be used as adjuvants in dental inflammatory diseases
Pan et al. (21)	2023	P. Gingivalis/ A. Actinomycete mcomitans	Curcumin	Gingivals	Curcumin at a low concentration and irradiated with medium power dental curing light can inhibit the growth of periodontal bacteria
Malekzadeh et al. (23)	2021	Human	Curcumin	Mild Periodontitis	Nano-curcumin has positive effects on the decrease of inflammation and gingival bleeding in patients with gingivitis and mild periodontitis
Malhotra et al. (22)	2019	Human	Curcumin	Oral Malignant Disorders	Curcumin is a potent, safe and inexpensive modality for the management of PMDS
Maghsoudi et al. (18)	2017	Human	Curcumin	Dental Decay	Curcumin-loaded chitosan nanoparticles hold promises for being used in dental decay fighting products
Pan et al. (29)	2023	Mice	Green Tea	Oral Inflammation	Green tea promoted the growth of probiotics Lactobacillus and Bacillus, inhibited the reproduction of pathogens Achromobacter, reversing the microbiota disorders in oral cavity.
Kong et al. (32)	2022	Human	Green Tea	Oral Infectious Diseases	Green tea improved the mechanical and antibacterial properties of GIC without affecting its fluorine release property
Mazur et al. (35)	2021	Human	Green Tea	Periodontitis And Caries	Green tea showed positive effect in reducing gingivitis
Gartenmann et al. (31)	2020	Human	Green Tea	Plaque And Gingival Inflammation	Green tea resulted in lower plaque generation
Prashant et al. (34)	2020	Human	Green Tea	Chronic Periodontitis	Green tea showed reduction in the total colony count from base line
Sharma et al. (26)	2017	Human	Green Tea	Periodontal Diseases	Green tea has shown the antioxidant, antimicrobial, and anticollagenase activities on periodontal health
Hormozi et al. (27)	2016	Human	Green Tea	Periodontal Diseases	Green tea products can be effective for plaque control and prevention of periodontitis
Fournier et al. (28)	2016	Human	Green Tea	Porphyromonas Gingivalis	Green tea was found to decrease the expression of genes coding for the major virulence factors
Anand et al. (30)	2016	Human	Green Tea	Oral Microbial Onditi ons	Green tea showed a significant reduction of Streptococcus mutans count
Hrishi et al. (33)	2016	Human	Green Tea	Periodontitis	Green tea showed reduction of gingival inflammation and improved periodontal parameters
Zheng et al. (40)	2024	Human	Resveratrol	Oral Malodor	Resveratrol inhibited the whole process of Pg and Fn growth
Li et al. (39)	2021	Human	Resveratrol	Gingival Fibroblasts	Resveratrol significantly inhibited the PI3K/AKT and Wnt/β-catenin signaling pathways
Berger et al. (41)	2018	Human	Resveratrol	Chronic Periodontitis	Resveratrol demonstrated conclusively to be effective, to help to reduce surgical need
Corrêa et al. (37)	2017	Rat	Resveratrol	Periodontitis	Resveratrol was capable of reducing alveolar bone loss in an animal model of periodontitis
Shahidi et al. (38)	2017	Human	Resveratrol	Gingival Fibroblasts	Resveratrol significantly inhibited LPS-induced IL-6 and IL-8 secretion by HGFs
Bharathi et al. (46)	2024	Human	Triphala	Gingivitis	Triphala reduced gingival inflammation.
Baratakke et al. (47)	2017	Human	Triphala	Gingival Inflammation	Triphala showed significant reduction in plaque and gingival scores
Mishra et al. (45)	2016	Emblica Officinalis / Te rminalia Belerica/ Term inalia Chebula	Triphala	Oral Microbial Conditions	Antioxidant, antimicrobial activities of Triphala caused to poses microbial growth
Biswas et al. (44)	2014	Human	Triphala	Gingivitis	Triphala showed to effective in decreases plaque induced gingivitis
Wang et al. (51)	2023	Ligament Cells	Vitamin A	Periodontal Disease	Vitamin A promoted proliferation and osteogenic differentiation

Author	Year	subjects	Materials	Pathology	Outcomes
Luo et al. (52)	2018	Human	Vitamin A	Periodontal Disease	Negative correlation between adequate intake of vitamin A, and the risk of periodontal disease
Park et al. (53)	2017	Human	Vitamin A	Periodontitis	Vitamin A significantly decreases the incidence of periodontitis
Hans et al. (57)	2023	Human	Vitamin B	Periodontal Disease	Serum micronutrient levels especially Vitamin A, Vitamin B 12, and Vitamin D may be modifiable risk factors for periodontal disease
Neiva et al. (56)	2017	Human	Vitamin B	Gingivitis	Vitamin B showed significant reduction of systemic inflammatory burden
Zong et al. (58)	2015	Human	Vitamin B	Periodontal Progression and Loss	vitamin B was inversely associated with changes in risk ratios of tooth loss
Warad et al. (59)	2014	Human	Vitamin B	Chronic Periodontitis	Serum VB12 levels are directly related while serum FA levels are inversely related to inflammation and tissue destruction in periodontium
Kunsongkeit et al. (63)	2019	Human	Vitamin C	Nonsurgical Periodontal Therapy	Vitamin C administration caused to all periodontal parameters were significantly improved from baseline
Chitsazi et al. (64)	2017	Human	Vitamin C	Chronic Periodontitis	Vitamin c administration showed a significant improvement in periodontal indexes scores
Shimabukuro et al. (61)	2015	Human	Vitamin C	Gingival Inflammation	Regular application of vitamin c dentifrice could reduce gingival inflammation
Gokhale et al. (62)	2013	Human	Vitamin C	Gingivitis	Dietary ascorbic acid supplementation with root planing improves the sulcus bleeding index in subjects with gingivitis
Weimin Gao et al. (68)	2020	Human	Vitamin D	Moderate Or Severe Periodontitis	Significant decrease in depth (PD), bleeding index (BI), plaque index (PLI), attachment loss (AL) in vitamin D group was reported
Gaetano Isola et al. (66)	2020	Human	Vitamin D	Periodontitis	Vitamin D adminestration showed anti-inflammatory and antimicrobial activity
Meghil et al. (69)	2019	Human	Vitamin D	Periodontitis	Vitamin D administrated had reduced peripheral blood CD3 and CD3+CD8+ cytotoxic T lymphocyte (CTLs) counts and reduced pro-inflammatory salivary cytokines
Garcia et al. (67)	2011	Human	Vitamin D	Chronic Periodontitis	Vitamin D supplementation (≤1,000 IU/day) had a modest positive effect on periodontal health, and consistent dental care improved clinical parameters of periodontal disease
Roja et al. (72)	2022	Subgingival Plaque Samples	Tinospora Cordifolia	Subgingival Microbiota	Tinospora cordifolia extract had significant antimicrobial activities
Nair et al. (73)	2020	Human	Tinospora Cordifolia	Plaque And Gingivitis	Tinospora cordifolia showed significant reduction inplaque score, gingival score, and colony forming units of gram-negative organisms and S. mutans
Morgana et al. (77)	2019	Rat	Piperine	Periodontitis	Piperine increased the TGF-β level, significantly improved the collagen repair, and decreased the cellularity and activation of NF-κB in the periodontal tissues
Kaur et al. (78)	2017	Rat	Piperine	Scaling And Root Planing	Piperine improved clinical parameters such as plaque index, gingival index and probing pocket depth
Y Dong et al. (76)	2015	Rat	Piperine	Periodontitis	Piperine displays significantly protective effects on inflammation, alveolar bone loss, bone microstructures and collagen fiber degradation
Torshabi et al. (83)	2024	Gram-Positive Strains/ Gramnegative Strain	Sumac	Oral Microbial Condition	Sumac mouthwash showed no cytotoxicity and demonstrated significant antioxidant effects
Sağlam et al. (81)	2015	Rat	Sumac	Periodontitis	Systemic administration of sumac extract reduced alveolar bone loss by affecting RANKL/OPG balance
Y Dong et al. (82)	2015	Rat	Sumac	Periodontitis	Piperine inhibited alveolar bone loss and reformed trabecula microstructures
Namratha Nayak et al. (87)	2019	Human	Psidium Guajava	Gingival Inflammation	Guava mouth showed gradual reduction in GI, PI and microbial counts
Singla et al. (86)	2018	Rat	Psidium Guajava	Oral Streptococci	The aqueous extracts of the Guajava showed an acceptable antibacterial efficacy against oral streptococci
Shetty et al. (89)	2018	P. Gingivalis /A. Actinomycete mcomitans	Psidium Guajava	Periodontal Pathogens	Antimicrobial activity of guava extracts against periodontal pathogens A. actinomycetemcomitans and P. gingivali
Carina Denny et al. (88)	2013	Mice	Psidium Guajava	Peritoneal Cavity	Guava showed anti-inflammatory activity by carrageenan, dextran, serotonin, histamine-induced paw edema and neutrophils migration

Vitamin A

Vitamin A, a fat-soluble vitamin derived from both plant and animal sources, is classified within the carotenoid family, which encompasses over 600 varieties. It is predominantly found in yellow, orange, and red vegetables and possesses strong antioxidant properties, playing a crucial role in maintaining epithelial integrity as well as promoting the development of teeth and bones (48). This vitamin is utilized as a supplement in the treatment of periodontal diseases due to its restorative effects on epithelial cells (49). The advised daily intake is a minimum of 1000 IU (international units). However, excessive consumption of retinol, particularly β-carotene, may lead to teratogenic effects during pregnancy and cause skin hypopigmentation (50). The summary of item selection on efficacy of vitamin A in periodontal diseases is demonstrated in Table 2.

Vitamin B

The B complex vitamins are widely found in a variety of everyday foods. For example, vitamin B1 can be sourced from fruits, vegetables, pork, and beef, while vitamin B2 is particularly concentrated in animal liver and fish. It is feasible to acquire the essential vitamins needed by the human body through a balanced diet. Thus, during the treatment process, it is crucial not only to provide scientifically sound vitamin supplementation but also to educate patients about mouth ulcers to help them modify their dietary and lifestyle habits (54). Specifically, increasing the intake of vegetables, fruits, and vitamin B-rich meats, along with adequate hydration and regular physical activity, can significantly boost immunity and overall health, thereby facilitating quicker recovery and minimizing the likelihood of recurrence (55). The summary of item selection on efficacy of vitamin B in periodontal diseases is demonstrated in Table 2.

Vitamin C

Ascorbic acid, commonly referred to as vitamin C, is primarily acquired through dietary sources. The human body requires only small quantities of this water-soluble vitamin to support essential physiological functions. Vitamin C is widely acknowledged as a crucial hydrophilic antioxidant and serves as a specific cofactor in numerous enzymatic processes. While most plants and animals possess the ability to synthesize vitamin C from D-glucose and D-galactose, certain species, including humans, monkeys, guinea pigs, bats, and birds, lack the enzyme L-gulonolactone oxidase (GLO), rendering them incapable of producing this vitamin endogenously (66). Consequently, it is imperative for humans to obtain vitamin C through their diet or supplements, as a complete deficiency can lead to serious health issues such as swollen and bleeding gums, dry skin, open sores, fatigue, delayed wound healing, and depression. A deficiency in vitamin C can result in scurvy, particularly when individuals consume less than 10 mg of the vitamin daily. Furthermore, insufficient levels of vitamin C have been associated with various health conditions, including certain cancers, anemias, and infections (67). The summary of item selection on efficacy of vitamin C in periodontal diseases is demonstrated in Table 2.

Vitamin E

The fat-soluble vitamin E, known as tocopherol, possesses significant antioxidant properties and is the most commonly utilized vitamin that supports cellular function. Vitamin E as an antioxidant, inhibits the detrimental effects of free radicals that can lead to tissue oxidation and damage. The presence of antioxidants in the oral cavity may adversely affect the gingival tissue, thereby contributing to the onset of periodontal disease (65). The summary of item selection on efficacy of vitamin E in periodontal diseases is demonstrated in Table 2.

Cordifolia

Cordifolia L., a member of the Rubiaceae family, exhibits a wide geographical distribution. In India, it is commonly known as Indian Madder, Manjith, or Manjistha, while in China, it is referred to as Qiancao. The root's natural red hue serves as both a food coloring agent and a dye for textiles. Its application in phytomedicine is well-documented within the traditional medical frameworks of Ayurveda and Siddha in India, as well as in traditional Chinese medicine (70). The extracts derived from this plant have been utilized to address various blood-related ailments, including hematemesis, epistaxis, spotting, traumatic bleeding, and amenorrhea. The preparation of these extracts can be achieved through aqueous methods or by employing

organic solvents such as methanol, ethanol, chloroform, and dichloromethane (71). The summary of item selection on efficacy of Cordifolia in periodontal diseases is demonstrated in Table 2.

Piperine

Piperine as a phenolic compound in Piper longum and Piper nigrum, has a critical role in traditional medicine and is widely regarded as both a spice and a preservative in various Pacific islands and Asian nations. Its remarkable therapeutic properties have been demonstrated across a range of cell types and in various inflammatory conditions linked to chronic pain, including osteoarthritis (OA), melanoma, and rheumatoid arthritis (RA) (74). Research has highlighted the in-vitro capabilities of piperine, such as its ability to inhibit enzymes involved in the synthesis of prostaglandins and leukotrienes, alongside it demonstrated in-vivo anti-inflammatory effects in rat models (75). The summary of item selection on efficacy of piperine in periodontal diseases is demonstrated in Table 2.

Sumac

Rhus coriaria L., widely recognized as sumac, is a plant native to the Mediterranean region and is classified within the Anacardiaceae family. This plant has a long-standing tradition of being utilized as a spice and flavoring agent. The fruits of sumac are round and turn a reddish hue as they ripen. When dried and ground into a dark red powder, these fruits possess an acidic and astringent flavor, making them a popular spice in various Mediterranean and Middle Eastern nations, including Lebanon, Syria, Jordan, Turkey, and Iran (79). Beyond its culinary applications and use in tanning, Rhus coriaria has been employed for millennia in Middle Eastern and South Asian cultures as a traditional remedy for numerous ailments, including cancer. The fruits have been utilized in folk medicine to address a range of health issues, such as liver disease, diarrhea, urinary tract problems, and ulcers (80). The summary of item selection on efficacy of sumac in periodontal diseases is demonstrated in Table 2.

Psidium Guajava

Guava is renowned for its remarkable antioxidant properties, largely attributed to its high Vitamin C (Ascorbic acid) content. Additionally, it contains quercetin, carotenoids, and polyphenols, which enhance its antioxidant effects (84). Mouthwash formulated with aqueous extracts of guava leaves demonstrated significant efficacy against Staphylococcus aureus and Escherichia coli, likely due to the presence of various bioactive compounds. The mouthrinse containing guava leaf extract exhibited a notable impact on gingivitis (85). The summary of item selection on efficacy of Guava in periodontal diseases is demonstrated in Table 2.

DISCUSSION

The review of the literatures that fulfilled the criteria of the present study indicates that the administration of antioxidants demonstrates significant effectiveness in managing periodontal disease, mucositis, oral submucosal fibrosis, candidiasis, caries, and oral potentially malignant disorders (3). Antioxidants are compounds capable of preventing or mitigating oxidative damage to target molecules. Research has shown that oxidative stress linked to periodontitis is detectable in both saliva and serum (4). A key characteristic of periodontal diseases is the generation of free radicals, which originate from both bacterial activity and immune responses. It has been observed that an increase in free radical production correlates with a reduction in antioxidant defenses. An imbalance between the antioxidant and pro-oxidant systems can result in heightened oxidative damage and subsequent harm to oral tissues (12).

Flavonoids represent the most extensive group of plant polyphenols and are recognized as some of the most effective antioxidants available (10). These compounds can be found in a wide range of sources, including fruits, vegetables, grains, roots, stems, flowers, and tea (11). Notably, flavanols and catechins are distinguished for their exceptional antioxidant capabilities, which play a crucial role in protecting the body from free radicals and preserving oxygen. Research conducted by Pal et al. has demonstrated that catechins, particularly those that include gallate, such as epicatechin gallate and epigallocatechin gallate, have the ability to inhibit collagenase produced by eukaryotic cells (12).

Resveratrol, a polyphenolic compound that occurs naturally and is derived from the seeds of Vitis vinifera, is widely recognized for its substantial immunomodulatory properties, which

encompass anti-inflammatory, antioxidant, antimicrobial, and anti-carcinogenic effects (39). These advantageous attributes are essential for addressing a range of clinical issues that stem from microbial and inflammatory sources, particularly concerning periodontal disease. Research conducted by Lim et al. illustrated the clinical effectiveness of administering resveratrol directly into periodontal pockets of patients with generalized periodontitis, underscoring its potential as an adjunctive therapy alongside scaling and root planing (SRP) in the treatment of periodontal disease (38).

The results of this study advocate for the integration of resveratrol concentrate with SRP to improve clinical results related to periodontal health. It is important to acknowledge that the efficacy of resveratrol is contingent upon its dosage and concentration; consequently, a 4% resveratrol solution was employed in the research (37). Curcumin is acknowledged as a powerful herbal ingredient in mouthwash products, especially when utilized in its nano form, which improves absorption and allows for faster outcomes with lower dosages (16). Studies have shown that curcumin significantly reduces periodontal inflammation by blocking the release and activity of several cytokines, such as TNF alpha and interleukins 1, 2, 6, 8, and 12. Additionally, it decreases the expression of pro-inflammatory enzymes like NF-κB in immune cells (18). The evaluation of the antioxidants under consideration highlights significant similarities and distinctions in their therapeutic attributes, mechanisms of action, and prospective uses in the treatment of oral inflammatory diseases. Curcumin, extracted from Curcuma longa, is a highly effective antioxidant renowned for its anti-inflammatory properties. Its bioactive mechanisms involve the suppression of reactive oxygen species (ROS) production and the enhancement of antioxidant enzyme expression, which is crucial for mitigating oxidative stress in periodontal tissues (21). Although curcumin is primarily recognized as an antioxidant, it may display prooxidant effects in specific circumstances, thereby complicating its overall function in cellular metabolism. Notably, curcumin is associated with minimal adverse effects, even at elevated doses, rendering it particularly attractive for clinical use. Green tea, especially its catechin polyphenols such as epigallocatechin (EGC) and epicatechin, presents considerable therapeutic promise, distinguished by its antioxidant properties. Rich in antioxidants, green tea effectively scavenges free radicals and reduces inflammation. Furthermore, green tea contains vital minerals and compounds that may enhance its health benefits, potentially amplifying its anti-inflammatory effects (35).

In vivo studies indicate that green tea extract may play a significant role in the prevention of various diseases, including periodontal disorders (33-36). The diverse advantages of green tea position it as a strong candidate for the management of oral inflammatory diseases, primarily due to its combined effects on inflammation and oxidative stress. Resveratrol, a compound found in numerous plants and commonly linked to red wine, is recognized for its exceptional antioxidant properties (39-41). Research demonstrates that resveratrol significantly outperforms other phenolic compounds in reducing lipid peroxidation. Its wide array of characteristics, particularly its anti-inflammatory, antimicrobial, and potential anti-cancer properties, highlights its adaptability in addressing various health issues, including those related to oral health. A thorough understanding of the stability of trans- and cis-resveratrol is essential for its effective use, as the trans form exhibits greater stability and biological activity. The comprehensive biological effects of resveratrol may pave the way for innovative approaches in periodontal therapy, especially by targeting the complex aspects of disease pathology (37). The analysis of these compounds reveals that the evaluated natural antioxidants possess significant antioxidant and anti-inflammatory properties, each with distinct characteristics that may affect their effectiveness in treating oral inflammatory diseases. Although all compounds are effective against oxidative stress and inflammation, their mechanisms of action differ. Curcumin, for instance, serves a dual purpose as both an antioxidant and a potential prooxidant, which warrants careful consideration when used in high concentrations. Green tea highlights the importance of catechins, whereas resveratrol is noted for its strong ability to reduce lipid peroxidation (18). Curcumin is particularly notable for its well-documented safety profile, even at elevated doses, making it a promising candidate for prolonged use. In

contrast, green tea and resveratrol may necessitate more precise dosing to mitigate the risk of adverse effects or interactions with other therapies. The potential for combining these compounds could lead to a synergistic effect, enhancing their antioxidant capabilities while reducing inflammatory responses. Future research could investigate the impact of such combinations on periodontal health, potentially leading to the development of innovative adjunctive therapies. Vitamin A is crucial for maintaining the integrity of epithelial tissues, facilitating the development of teeth and bones, and assisting in the management of periodontal diseases. The recommended daily intake of vitamin A is at least 1000 IU; however, excessive consumption, especially of β-carotene, may result in teratogenic effects during pregnancy and skin hypopigmentation. In contrast, vitamin B plays a significant role in the healing of mouth ulcers, enhancing immune function, and promoting overall health (52). Research underscores the importance of dietary changes, particularly increasing the consumption of vitamin B-rich foods, and highlights the necessity of educating patients about their dietary choices and lifestyle habits to improve recovery outcomes (56). Vitamin C is recognized as a vital hydrophilic antioxidant and a cofactor in various enzymatic reactions, preventing serious health complications such as scurvy, bleeding gums, and delayed wound healing (65). Insufficient intake of vitamin C can lead to severe health issues, including fatigue and depression, and it is essential for maintaining periodontal health, emphasizing the importance of adequate dietary consumption. Conversely, vitamin E functions as an antioxidant that protects cellular activities but may have adverse effects on oral tissues. While antioxidants are generally beneficial, an excess in the oral cavity could potentially exacerbate gingival conditions (32).

Vitamins play essential and varied roles in the maintenance of periodontal health. Vitamin A is particularly noted for its restorative effects on epithelial cells, which are crucial for the health of the gums (21). On the other hand, Vitamin B highlights the importance of dietary balance and patient education, both of which are critical in preventing mouth ulcers and enhancing immune function. Vitamin C is indispensable as it helps avert severe deficiency-related issues, underscoring the necessity of regular consumption for the preservation of dental health (62). Additionally, while Vitamin E offers beneficial antioxidant properties, it also prompts inquiries about the equilibrium between antioxidant consumption and its possible impacts on gingival tissue (71). A thorough understanding of these vitamins reveals the complex interplay between diet and oral health. Achieving a balanced intake from diverse sources can significantly improve periodontal health, whereas both deficiencies and excessive supplementation may result in adverse effects. The current analysis indicates a notable correlation between deficiencies in various vitamins and a heightened occurrence of periodontitis, especially when not accounting for factors such as gender, education, income, diabetes, and alcohol use.

A research study by Mehta et al. examined the effects of curcumin gel on Candida populations among individuals who use tobacco, recognizing the harmful impact of tobacco on oral health and its contribution to modifications in the oral microbiome, particularly through elevated levels of Candida (23). The results revealed a notably higher occurrence of Candida colonization in smokers when compared to healthy subjects, with Candida tropicalis being the most commonly identified species within the smoking demographic, whereas Candida albicans was more frequently found in the control group (19). Importantly, the group of smokers displayed significant alterations in nuclear diameter and micronuclei counts following treatment with curcumin. After quitting smoking and receiving curcumin, there was a significant decrease in Candida colonies, with Candida albicans becoming the predominant species in the experimental group (22).

CONCLUSION

Antioxidants play a vital role in maintaining oral health by providing protection against oxidative stress and inflammation caused by free radicals. These beneficial compounds can be found in a variety of dietary sources and supplements, each offering unique benefits for oral hygiene. Key antioxidants such as vitamins A, B, C, and E, along with polyphenols found in green tea, resveratrol, and curcumin, support anti-inflammatory processes in the teeth and gums, help prevent oral diseases, and reduce

inflammation. Incorporating these antioxidants into one's diet, whether through supplements or as part of an oral care routine, can significantly bolster the mouth's defenses, aiding in the prevention and treatment of oral health issues.

ACKNOWLEDGMENT

The current systematic review was conducted without the support of any grants from funding agencies or external sources.

CONFLICT OF INTEREST

There is not any conflict of interest.

REFERENCES

[1] Girisa S, Kumar A, Rana V, Parama D, Daimary UD, Warnakulasuriya S, Kumar AP, Kunnumakkara AB. From simple mouth cavities to complex oral mucosal disorders—Curcuminoids as a promising therapeutic approach. ACS pharmacology & translational science. 2021 Mar 17;4(2):647-65.

[2] Nwizu NN. Periodontal disease and cancer: Chronic inflammation-the oral-systemic link. State University of New York at Buffalo; 2014.

[3] Martu MA, Maftei GA, Luchian I, Stefanescu OM, Scutariu MM, Solomon SM. The effect of acknowledged and novel anti-rheumatic therapies on periodontal tissues—a narrative review. Pharmaceuticals. 2021 Nov 23;14(12):1209.

[4] Sczepanik FS, Grossi ML, Casati M, Goldberg M, Glogauer M, Fine N, Tenenbaum HC. Periodontitis is an inflammatory disease of oxidative stress: We should treat it that way. Periodontology 2000. 2020 Oct;84(1):45-68.

[5] Scannapieco FA, Cantos A. Oral inflammation and infection, and chronic medical diseases: implications for the elderly. Periodontology 2000. 2016 Oct;72(1):153-75.

[6] Babiuch K, Kuśnierz-Cabala B, Kęsek B, Okoń K, Darczuk D, Chomyszyn-Gajewska M. Evaluation of proinflammatory, NF-kappaB dependent cytokines: IL-1α, IL-6, IL-8, and TNF-α in tissue specimens and saliva of patients with oral squamous cell carcinoma and oral potentially malignant disorders. Journal of Clinical Medicine. 2020 Mar 21;9(3):867.

[7] Vo TT, Chu PM, Tuan VP, Te JS, Lee IT. The promising role of antioxidant phytochemicals in the prevention and treatment of periodontal disease via the inhibition of oxidative stress pathways: Updated insights. Antioxidants. 2020 Dec 1;9(12):1211.

[8] Ramesh A, Varghese SS, Doraiswamy JN, Malaiappan S. Herbs as an antioxidant arsenal for periodontal diseases. Journal of intercultural ethnopharmacology. 2016 Jan;5(1):92.

[9] Tiku ML, Madhan B. Preserving the longevity of long-lived type II collagen and its implication for cartilage therapeutics. Ageing research reviews. 2016 Jul 1;28:62-71.

[10] Abedi N, Sajadi-Javan ZS, Kouhi M, Ansari L, Khademi A, Ramakrishna S. Antioxidant materials in oral and maxillofacial tissue regeneration: a narrative review of the literature. Antioxidants. 2023 Feb 27;12(3):594.

[11] Vyas T, Sood P, Kaur M. Antioxidants in oral diseases and future prospects and their application in dentistry. Journal of Advanced Medical and Dental Sciences Research. 2018 May 1;6(5):53-62.

[12] Jiang Q. Natural forms of vitamin E: metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. Free Radical Biology and Medicine. 2014 Jul 1;72:76-90.

[13] Bivona III JJ, Patel S, Vajdy M. Induction of cellular and molecular Immunomodulatory pathways by vitamin E and vitamin C. Expert Opinion on Biological Therapy. 2017 Dec 2;17(12):1539-51.

[14] Malcangi G, Patano A, Ciocia AM, Netti A, Viapiano F, Palumbo I, Trilli I, Guglielmo M, Inchingolo AD, Dipalma G, Inchingolo F. Benefits of natural antioxidants on oral health. Antioxidants. 2023 Jun 20;12(6):1309.

[15] Abou Sulaiman AE, Shehadeh RM. Assessment of total antioxidant capacity and the use of vitamin C in the treatment of non-smokers with chronic periodontitis. Journal of periodontology. 2010 Nov;81(11):1547-54.

[16] Cagetti MG, Wolf TG, Tennert C, Camoni N, Lingström P, Campus G. The role of vitamins in oral health. A systematic review and meta-analysis. International journal of environmental research and public health. 2020 Feb;17(3):938.

[17] Palaska I, Papathanasiou E, Theoharides TC. Use of polyphenols in periodontal inflammation. European journal of pharmacology. 2013 Nov 15;720(1-3):77-83.

[18] M Varoni E, Lodi G, Sardella A, Carrassi A, Iriti M. Plant polyphenols and oral health: old phytochemicals for new fields. Current medicinal chemistry. 2012 Apr 1;19(11):1706-20.

[19] Chainoglou E, Hadjipavlou-Litina D. Curcumin analogues and derivatives with anti-proliferative and anti-inflammatory activity: Structural characteristics and molecular targets. Expert opinion on drug discovery. 2019 Aug 3;14(8):821-42.

[20] Abrahams S, Haylett WL, Johnson G, Carr JA, Bardien S. Antioxidant effects of curcumin in models of neurodegeneration, aging, oxidative and nitrosative stress: A review. Neuroscience. 2019 May 15;406:1-21.

[21] Soleimani V, Sahebkar A, Hosseinzadeh H. Turmeric (Curcuma longa) and its major constituent (curcumin) as nontoxic and safe substances. Phytotherapy Research. 2018 Jun;32(6):985-95.

[22] Maghsoudi A, Yazdian F, Shahmoradi S, Ghaderi L, Hemati M, Amoabediny G. Curcumin-loaded polysaccharide nanoparticles: Optimization and anticariogenic activity against Streptococcus mutans. Materials Science and Engineering: C. 2017 Jun 1;75:1259-67.

[23] Gao Z, Chen X, Wang C, Song J, Xu J, Liu X, Qian Y, Suo H. New strategies and mechanisms for targeting Streptococcus mutans biofilm formation to prevent dental caries: a review. Microbiological Research. 2023 Oct 14:127526.

[24] Laurindo LF, de Carvalho GM, de Oliveira Zanuso B, Figueira ME, Direito R, de Alvares Goulart R, Buglio DS, Barbalho SM. Curcumin-based nanomedicines in the treatment of inflammatory and immunomodulated diseases: An evidence-based comprehensive review. Pharmaceutics. 2023 Jan 10;15(1):229.

[25] Pan H, Wang D, Zhang F. In vitro antimicrobial effect of curcumin-based photodynamic therapy on Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans. Photodiagnosis and Photodynamic Therapy. 2020 Dec 1;32:102055.

[26] Malhotra M, Rai A, Malhotra V. Curcumin in the Management of Oral Potentially Malignant Disorders. World J. Pharm. Res. 2019 Aug 3;8:1-21.

[27] Malekzadeh M, Kia SJ, Mashaei L, Moosavi MS. Oral n ano-curcumin on gingival inflammation in patients with gingivitis and mild periodontitis. Clinical and experimental dental research. 2021 Feb;7(1):78-84.

[28] Musial C, Kuban-Jankowska A, Gorska-Ponikowska M. Beneficial properties of green tea catechins. International journal of molecular sciences. 2020 Mar 4;21(5):1744.

[29] Vishnoi H, Bodla RB, Kant R, Bodla RB. Green tea (Camellia sinensis) and its antioxidant property: A review. International Journal of Pharmaceutical Sciences and Research. 2018 May 1;9(5):1723-36.

[30] Sharma S, Bhuyan L, Ramachandra S, Sharma S, Dash KC, Dhull KS. Effects of green tea on periodontal health: A prospective clinical study. Journal of International Oral Health. 2017 Mar 1;9(2):39-44.

[31] Hormozi M. Effects of green tea and its products on dental caries and periodontal diseases: A review. International Journal of

Contemporary Dental & Medical Reviews. 2016;2016.

[32] Fournier-Larente J, Morin MP, Grenier D. Green tea catechins potentiate the effect of antibiotics and modulate adherence and gene expression in Porphyromonas gingivalis. Archives of Oral Biology. 2016 May 1;65:35-43.

[33] Pan Y, Lv H, Zhang F, Chen S, Cheng Y, Ma S, Hu H, Liu X, Cai X, Fan F, Gong S. Green tea extracts alleviate acetic acid-induced oral inflammation and reconstruct oral microbial balance in mice. Journal of Food Science. 2023 Dec;88(12):5291-308.

[34] Anand PS, Athira S, Chandramohan S, Ranjith K, Raj VV, Manjula VD. Comparison of efficacy of herbal disinfectants with chlorhexidine mouthwash on decontamination of toothbrushes: An experimental trial. Journal of International Society of Preventive and Community Dentistry. 2016 Jan 1;6(1):22-7.

[35] Gartenmann SJ, Steppacher SL, von Weydlich Y, Heumann C, Attin T, Schmidlin PR. The Effect of Green Tea on plaque and gingival inflammation: A systematic review. Journal of Herbal Medicine. 2020 Jun 1;21:100337.

[36] Kong C, Zhang H, Li L, Liu Z. Effects of green tea extract epigallocatechin-3-gallate (EGCG) on oral disease-associated microbes: A review. Journal of Oral Microbiology. 2022 Dec 31;14(1):2131117.

[37] Ghosh N, Ali A, Ghosh R, Das S, C Mandal S, Pal M. Chronic inflammatory diseases: progress and prospect with herbal medicine. Current Pharmaceutical Design. 2016 Jan 1;22(2):247-64.

[38] Hrishi TS, Kundapur PP, Naha A, Thomas BS, Kamath S, Bhat GS. Effect of adjunctive use of green tea dentifrice in periodontitis patients–A Randomized Controlled Pilot Study. International Journal of Dental Hygiene. 2016 Aug;14(3):178-83.

[39] Prashant S, Dayal M, Zeeshan M, Chatterjee S, Verma K, Khan SF. Evaluation of the Therapeutic Efficacy of Green Tea Catechin Strips as an Antimicrobial Agent Local Delivered Drug in the Management of Chronic Periodontitis.

[40] Hameed AH, Soud SA, Ali MA. Resveratrol: Properties, Sources, Production and Their Medical Applications A Review. Journal of University of Babylon for Pure and Applied Sciences. 2021 Jul 1(2):45-66.

[41] Berman AY, Motechin RA, Wiesenfeld MY, Holz MK. The therapeutic potential of resveratrol: a review of clinical trials. NPJ precision oncology. 2017 Sep 25;1(1):35.

[42] Inchingolo AD, Inchingolo AM, Malcangi G, Avantario P, Azzollini D, Buongiorno S, Viapiano F, Campanelli M, Ciocia AM, De Leonardis N, de Ruvo E. Effects of resveratrol, curcumin and quercetin supplementation on bone metabolism—a systematic review. Nutrients. 2022 Aug 26;14(17):3519.

[43] Corrêa MG, Pires PR, Ribeiro FV, Pimentel SZ, Casarin RC, Cirano FR, Tenenbaum HT, Casati MZ. Systemic treatment with resveratrol and/or curcumin reduces the progression of experimental periodontitis in rats. Journal of periodontal research. 2017 Apr;52(2):201-9.

[44] Quaresma JA. Organization of the skin immune system and compartmentalized immune responses in infectious diseases. Clinical microbiology reviews. 2019 Sep 18;32(4):10-128.

[45] Shahidi M, Vaziri F, Haerian A, Farzanegan A, Jafari S, Sharifi R, Shirazi FS. Proliferative and anti-inflammatory effects of resveratrol and silymarin on human gingival fibroblasts: a view to the future. Journal of Dentistry (Tehran, Iran). 2017 Jul;14(4):203.

[46] Li L, Li J, Wang Y, Liu X, Li S, Wu Y, Tang W, Qiu Y. Resveratrol prevents inflammation and oxidative stress response in LPS-induced human gingival fibroblasts by targeting the PI3K/AKT and Wnt/β-catenin signaling pathways. Genetics and Molecular Biology. 2021 Jul 2;44(3):e20200349.

[47] Ansari S. Overview of traditional systems

of medicine in different continents. InPreparation of Phytopharmaceuticals for the Management of Disorders 2021 Jan 1 (pp. 431-473). Academic Press.

[48] Belapurkar P, Goyal P, Tiwari-Barua P. Immunomodulatory effects of triphala and its individual constituents: a review. Indian journal of pharmaceutical sciences. 2014 Nov;76(6):467.

[49] Peterson CT, Denniston K, Chopra D. Therapeutic uses of triphala in ayurvedic medicine. The Journal of Alternative and Complementary Medicine. 2017 Aug 1;23(8):607-14.

[50] Malik T, Madan VK, Prakash R. Herbs that heal: Floristic boon to the natural healthcare system. Ann. Phytomed. 2020;9(2):6-14.

[51] Biswas G, Anup N, Acharya S, Kumawat H, Vishnani P, Tambi S. Evaluation of the efficacy of 0.2% chlorhexidine versus herbal oral rinse on plaque induced gingivitis-A randomized clinical trial. J Nurs Health Sci. 2014 Mar;3(2):58-63.

[52] Mishra S, Anuradha J, Tripathi S, Kumar S. In vitro antioxidant and antimicrobial efficacy of Triphala constituents: Emblica officinalis, Terminalia belerica and Terminalia chebula. Journal of Pharmacognosy and Phytochemistry. 2016;5(6):273-7.

[53] Carazo A, Macáková K, Matoušová K, Krčmová LK, Protti M, Mladěnka P. Vitamin A update: forms, sources, kinetics, detection, function, deficiency, therapeutic use and toxicity. Nutrients. 2021 May 18;13(5):1703.

[54] Mi N, Zhang M, Ying Z, Lin X, Jin Y. Vitamin intake and periodontal disease: a meta-analysis of observational studies. BMC Oral Health. 2024 Jan 20;24(1):117.

[55] Carazo A, Macáková K, Matoušová K, Krčmová LK, Protti M, Mladěnka P. Vitamin A update: forms, sources, kinetics, detection, function, deficiency, therapeutic use and toxicity. Nutrients. 2021 May 18;13(5):1703.

[56] Cagetti MG, Wolf TG, Tennert C, Camoni N, Lingström P, Campus G. The role of vitamins in oral health. A systematic review and meta-analysis. International journal of environmental research and public health. 2020 Feb;17(3):938.

[57] Huang Z, Liu Y, Qi G, Brand D, Zheng SG. Role of vitamin A in the immune system. Journal of clinical medicine. 2018 Sep;7(9):258.

[58] Levine R, Stillman-Lowe CR. The scientific basis of oral health education. Cham, Switzerland: Springer International Publishing; 2019.

[59] Hrubša M, Siatka T, Nejmanová I, Vopršalová M, Kujovská Krčmová L, Matoušová K, Javorská L, Macáková K, Mercolini L, Remião F, Máťuš M. Biological properties of vitamins of the B-complex, part 1: Vitamins B1, B2, B3, and B5. Nutrients. 2022 Jan 22;14(3):484.

[60] Jolfayi AG, Jafari A, Rahmani F, Taghizadeh N, Mohammadi S, Rasaei N. Deciphering the Influence of Lifestyle Factors on Immunotherapy Efficacy in Cancer Patients. InHandbook of Cancer and Immunology 2024 Jan 18 (pp. 1-56). Cham: Springer International Publishing.

[61] Chaudhury S. Effects of Vitamin Deficiencies on Oral Health. Indian Journal of Public Health Research & Development. 2019 Nov 1;10(11).

[62] Dommisch H, Kuzmanova D, Jönsson D, Grant M, Chapple I. Effect of micronutrient malnutrition on periodontal disease and periodontal therapy. Periodontology 2000. 2018 Oct;78(1):129-53.

[63] Maldonado E, Martínez-Sanz E, Partearroyo T, Varela-Moreiras G, Pérez-Miguelsanz J. Maternal folic acid deficiency is associated to developing nasal and palate malformations in mice. Nutrients. 2021 Jan 16;13(1):251.

[64] Bačun B, Galić D, Pul L, Tomas M, Kuiš D. Manifestations and Treatment of Hypovitaminosis in Oral Diseases: A Systematic Review. Dentistry Journal. 2024 May 21;12(6):152.

[65] Drouin G, Godin JR, Pagé B. The genetics of vitamin C loss in vertebrates. Current

genomics. 2011 Aug 1;12(5):371-8.

[66] Putchala MC, Ramani P, Sherlin HJ, Premkumar P, Natesan A. Ascorbic acid and its pro-oxidant activity as a therapy for tumours of oral cavity–A systematic review. Archives of oral biology. 2013 Jun 1;58(6):563-74.

[67] Malcangi G, Patano A, Ciocia AM, Netti A, Viapiano F, Palumbo I, Trilli I, Guglielmo M, Inchingolo AD, Dipalma G, Inchingolo F. Benefits of natural antioxidants on oral health. Antioxidants. 2023 Jun 20;12(6):1309.

[68] Doseděl M, Jirkovský E, Macáková K, Krčmová LK, Javorská L, Pourová J, Mercolini L, Remião F, Nováková L, Mladěnka P, Oemonom. Vitamin C—sources, physiological role, kinetics, deficiency, use, toxicity, and determination. Nutrients. 2021 Feb 13;13(2):615.

[69] Carr AC, Rowe S. Factors affecting vitamin C status and prevalence of deficiency: A global health perspective. Nutrients. 2020 Jul 1;12(7):1963.

[70] Tada A, Miura H. The relationship between vitamin C and periodontal diseases: a systematic review. International journal of environmental research and public health. 2019 Jul;16(14):2472.

[71] Vo TT, Chu PM, Tuan VP, Te JS, Lee IT. The promising role of antioxidant phytochemicals in the prevention and treatment of periodontal disease via the inhibition of oxidative stress pathways: Updated insights. Antioxidants. 2020 Dec 1;9(12):1211.

[72] Gerreth P, Maciejczyk M, Zalewska A, Gerreth K, Hojan K. Comprehensive evaluation of the oral health status, salivary gland function, and oxidative stress in the saliva of patients with subacute phase of stroke: a case-control study. Journal of Clinical Medicine. 2020 Jul 15;9(7):2252.

[73] Singh N, Chander Narula S, Kumar Sharma R, Tewari S, Kumar Sehgal P. Vitamin E supplementation, superoxide dismutase status, and outcome of scaling and root planing in patients with chronic periodontitis: a randomized clinical trial. Journal of periodontology. 2014 Feb;85(2):242-9.

[74] Desai SJ, Prickril B, Rasooly A. Mechanisms of phytonutrient modulation of cyclooxygenase-2 (COX-2) and inflammation related to cancer. Nutrition and cancer. 2018 Apr 3;70(3):350-75.

[75] Shahidi F, De Camargo AC. Tocopherols and tocotrienols in common and emerging dietary sources: Occurrence, applications, and health benefits. International journal of molecular sciences. 2016 Oct 20;17(10):1745.

[76] Humbare RB, Sarkar J, Kulkarni AA, Juwale MG, Deshmukh SH, Amalnerkar D, Chaskar M, Albertini MC, Rocchi MB, Kamble SC, Ramakrishna S. Phytochemical characterization, antioxidant and anti-proliferative properties of Rubia cordifolia L. extracts prepared with improved extraction conditions. Antioxidants. 2022 May 20;11(5):1006.

[77] Humbare RB, Sarkar J, Kulkarni AA, Juwale MG, Deshmukh SH, Amalnerkar D, Chaskar M, Albertini MC, Rocchi MB, Kamble SC, Ramakrishna S. Phytochemical characterization, antioxidant and anti-proliferative properties of Rubia cordifolia L. extracts prepared with improved extraction conditions. Antioxidants. 2022 May 20;11(5):1006.

[78] Baek JM, Kim JY, Jung Y, Moon SH, Choi MK, Kim SH, Lee MS, Kim I, Oh J. Mollugin from Rubea cordifolia suppresses receptor activator of nuclear factor-κB ligand-induced osteoclastogenesis and bone resorbing activity in vitro and prevents lipopolysaccharide-induced bone loss in vivo. Phytomedicine. 2015 Jan 15;22(1):27-35.

[79] Udagawa N, Koide M, Nakamura M, Nakamichi Y, Yamashita T, Uehara S, Kobayashi Y, Furuya Y, Yasuda H, Fukuda C, Tsuda E. Osteoclast differentiation by RANKL and OPG signaling pathways. Journal of bone and mineral metabolism. 2021 Jan;39:19-26.

[80] Chopra B, Dhingra AK, Kapoor RP, Prasad DN. Piperine and its various

physicochemical and biological aspects: A review. Open Chemistry Journal. 2016 Dec 30;3(1).

[81] Zou R, Zhou Y, Lu Y, Zhao Y, Zhang N, Liu J, Zhang Y, Fu Y. Preparation, pungency and bioactivity transduction of piperine from black pepper (Piper nigrum L.): A comprehensive review. Food Chemistry. 2024 Jun 4:139980.

[82] Yadav V, Krishnan A, Vohora D. A systematic review on Piper longum L.: Bridging traditional knowledge and pharmacological evidence for future translational research. Journal of ethnopharmacology. 2020 Jan 30;247:112255.

[83] Madka V, Rao CV. Anti-inflammatory phytochemicals for chemoprevention of colon cancer. Current cancer drug targets. 2013 Jun 1;13(5):542-57.

[84] Dong Y, Huihui Z, Li C. Piperine inhibit inflammation, alveolar bone loss and collagen fibers breakdown in a rat periodontitis model. Journal of periodontal research. 2015 Dec;50(6):758-65.

[85] Alsamri H, Athamneh K, Pintus G, Eid AH, Iratni R. Pharmacological and antioxidant activities of Rhus coriaria L.(Sumac). Antioxidants. 2021 Jan 8;10(1):73.

[86] Elagbar ZA, Shakya AK, Barhoumi LM, Al-Jaber HI. Phytochemical diversity and pharmacological properties of Rhus coriaria. Chemistry & Biodiversity. 2020 Apr;17(4):e1900561.

[87] Sağlam M, Köseoğlu S, Hatipoğlu M, Esen HH, Köksal E. Effect of sumac extract on serum oxidative status, RANKL/OPG system and alveolar bone loss in experimental periodontitis in rats. Journal of Applied Oral Science. 2015 Jan;23:33-41.

[88] Lim YY, Lim TT, Tee JJ. Antioxidant properties of guava fruit: comparison with some local fruits. Sunway Academic Journal. 2006;3:9-20.

[89] Singla S, Malhotra R, Nd S, Saxena S. Antibacterial efficacy of mouthwash prepared from pomegranate, grape seed and guava extracts against oral streptococci: An in vivo study. Journal of Clinical Pediatric Dentistry. 2018 Jan 1;42(2):109-13.

[90] Mosaddad SA, Hussain A, Tebyaniyan H. Green alternatives as antimicrobial agents in mitigating periodontal diseases: a narrative review. Microorganisms. 2023 May 11;11(5):1269.

[91] Ravi K, Divyashree P. Psidium guajava: A review on its potential as an adjunct in treating periodontal disease. Pharmacognosy reviews. 2014 Jul;8(16):96.

[92] Belibasakis GN, Maula T, Bao K, Lindholm M, Bostanci N, Oscarsson J, Ihalin R, Johansson A. Virulence and pathogenicity properties of Aggregatibacter actinomycetemcomitans. Pathogens. 2019 Nov 6;8(4):222.

[93] Ravi K, Divyashree P. Psidium guajava: A review on its potential as an adjunct in treating periodontal disease. Pharmacognosy reviews. 2014 Jul;8(16):96.