

# What is the use of nutraceuticals in dentistry? A scoping review

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**Abstract. – OBJECTIVE:** Recently, nutraceuticals have been widely explored in many medical fields and their use is also increasing in oral and dental problems. Since the nutraceutical evidence landscape in the literature has not been fully elucidated yet, this review aims to examine the effects of commercially available nutraceuticals and their potential evidence and applications in dentistry.

**MATERIALS AND METHODS:** A scoping review was conducted following the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR)” checklist. The electronic search was performed using PubMed/MEDLINE, EMBASE, the Cochrane Library, and Web of Science on March 2022. The inclusion criteria include humans, clinical trials, randomized controlled trials (RCT), reviews, and systematic reviews published over the last ten years.

**RESULTS:** 18 studies met the eligibility criteria. There were 2 RCTs, 11 systematic reviews, and four narrative reviews. In most studies, the clinical indications were oral leucoplakia, periodontitis, osseointegration of implants, oral mucositis, oral clefts, and oral health. Probiotics, prebiotics, polyunsaturated fatty acids, and vitamins A, B, C, D, and E were the most common nutraceuticals used in dentistry.

**CONCLUSIONS:** Nutraceuticals are foods that, according to the literature, may be useful for preventing and treating dental diseases.

*Key Words:*

Nutraceuticals, Fortified food, Oral health, Dentistry, Probiotic.

## Introduction

Biologically active molecules derived from food are often known as nutraceuticals because

they have characteristics similar to both nutrients and pharmaceuticals<sup>1</sup>. The term “nutraceutical” was coined in 1989 by Stephen L. Defelice, founder and president of “The Foundation for Innovation in Medicine” who defined “nutraceutical” as a food or part of a food that has a medical or health benefit<sup>2,3</sup>. In other words, nutraceuticals are natural bioactive or chemical compounds that, besides having a nutritional role, provide health-promoting, disease-curing, or prevention properties<sup>1</sup>. These foods are generally consumed as part of a regular diet and contain biologically active components that reduce the risk of developing various diseases<sup>4,5</sup>. Some examples of nutraceuticals include antioxidants or fortified foods, i.e., added at secondary times, and live active microorganisms or probiotics that provide particular benefits as described below<sup>6</sup>. Antioxidants are substances known to scavenge reactive oxygen species (ROS)<sup>7</sup>. The excess ROS generated in many chronic inflammatory conditions has a damaging effect known as oxidative stress, culminating in tissue damage in the absence or impairment of antioxidant mechanisms<sup>7,8</sup>. In periodontal diseases, this concept suggests that oxidative stress derived from ROS is primarily responsible for tissue destruction<sup>7</sup>. Among nutraceuticals, Vitamins C and E and, to a lesser extent, polyunsaturated fatty acids (PUFAs) have an antioxidant effect<sup>7,8</sup>.

Vitamin C is also considered an essential dietary antioxidant in the maintenance of periodontal health and has been shown to decelerate the rate of progression of periodontitis by stimulating the differentiation of progenitor cells of the periodontal ligament<sup>7</sup>. Therefore, it may represent a preventive agent for gingivitis and an adjunct to the non-surgical treatment of periodontitis. In addition, its antioxidant activity may be directly in-

involved in preventing oral cancer<sup>9</sup>. Vitamin E is a fat-soluble substance with potent antioxidant and anti-inflammatory properties that can prevent and treat oral mucositis and other diseases. It has various advantages including control of blood pressure, prevention of cardiovascular events, anti-tumor, anti-diabetic, and anti-obesogenic effects, and protection of the nervous system<sup>10</sup>.

PUFAs, n-6 and n-3 series with arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), are found in cell membranes where they act as precursors for cell signaling, gene expression, and inflammation. They also contribute to cell membrane integrity and fluidity. The n-6/n-3 ratio in tissues is largely determined by the proportion of PUFAs in the diet. PUFAs have fewer antioxidant effects than Vitamin C but have antimicrobial and anti-inflammatory properties for the treatment of periodontitis, as demonstrated by a recent study<sup>8</sup> that showed antibacterial activities for EPA and DHA, including inhibition of periodontal pathogens.

Vitamins, such as B and D, can improve oral health. Supplementing with Vitamin B (folate) during pregnancy may reduce the risk of facial defects in the fetus, like cleft palates and lips. Vitamin D impacts bone metabolism and regulates mineralization, making it effective for preventing osteoporosis and managing periodontitis and osseointegration of implants<sup>11-14</sup>.

Prebiotics and probiotics have been shown to be effective in promoting oral health. The oral cavity is a complex microbiological environment that needs to maintain homeostasis. Factors such as poor oral hygiene, diet, immunodeficiency, and other conditions can disrupt this balance and result in dysbiosis, inflammation, and infection. Biofilms formed by pathogenic bacteria on the hard and soft tissues of the oral cavity can lead to additional oral health issues, such as gingival bleeding and caries<sup>15-20</sup>.

Prebiotics and probiotics can help restore balance to the oral microbiota and modulate the immune response. They have been shown to reduce post-operative pain and prevent and treat various oral diseases including gingivitis, caries, periodontitis, oral candidiasis, recurrent aphthous stomatitis, and even oral cancer. They do this by decreasing the count of cariogenic pathogens, competing with harmful bacteria, regulating innate and acquired immunity, releasing antioxidants and bacteriocins, and having antiproliferative effects on cancer cells<sup>21-25</sup>.

Therefore, this scoping review aimed to investigate the state-of-the-art and commercially avail-

able nutraceuticals and their therapeutic application in dental diseases. Overall, prebiotics and probiotics offer promising solutions for maintaining oral health and treating various oral conditions.

## Materials and Methods

### Search Strategy

The present systematic review followed the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) guidelines. An electronic search was conducted *via* PubMed/MEDLINE, EMBASE, Cochrane Library, and Web of Science on March 2022; the keywords used for the research were “nutraceuticals oral health dentistry” OR (“nutraceuticals/exp OR nutraceuticals) AND oral AND (“health/exp OR health) AND (“dentistry/exp OR dentistry)”. The review was registered on the open science framework (OSF) on <https://osf.io/rtsqv/>.

### Eligibility Criteria

The following inclusion criteria were applied: humans, clinical trial, randomized controlled trial, reviews, and systematic review, last ten years. All articles found were entered into EndnoteWeb<sup>®</sup> (available at: <https://access.clarivate.com/login?app=endnote>) referencing software to eliminate duplicates. One hundred forty-eight articles were selected. The first phase consisted in reading the titles and eliminating all those that were not relevant to the search topic. This led to the selection of 42 studies. Based on the following inclusion and exclusion criteria, 18 articles were eligible as illustrated in the flow chart (Figure 1).

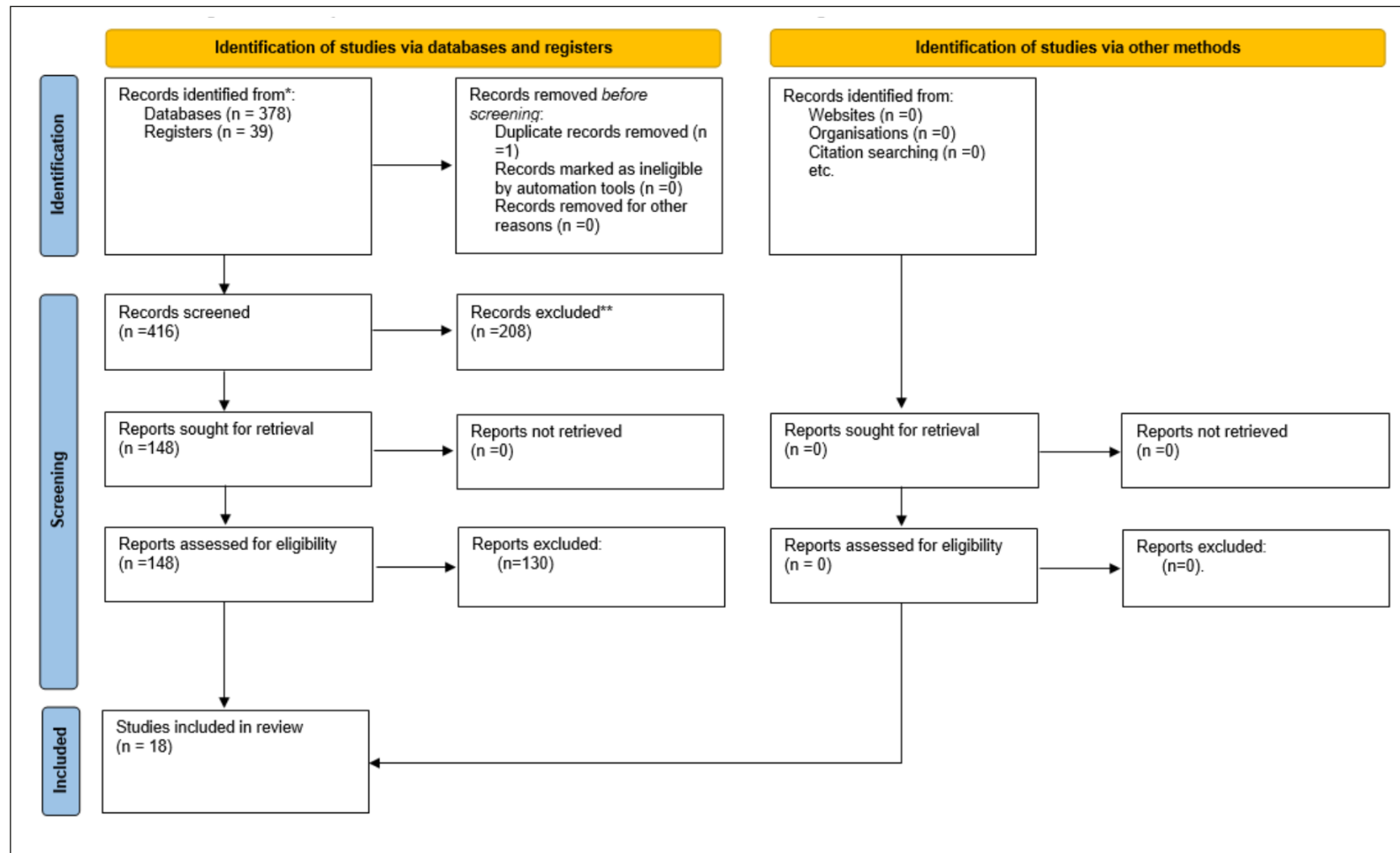
### Inclusion Criteria

- Studies investigating the effect of nutraceuticals in the dental field.
- Studies whose bioactive compounds are of food origin.
- Humans, clinical trial, randomized controlled trial, reviews and systematic review, last ten years.

### Exclusion Criteria

- Studies whose nutraceuticals have exclusively systemic effects.
- Systematic reviews carried out on the same nutraceuticals with overlapping results (redundant reviews).
- Studies involving the introduction of substances beneficial to oral health through toothpaste or mouthwashes.

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**Figure 1.** Literature search flowchart (PRISMA 2020) From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n 71. For more information, visit: <http://www.prisma-statement.org>

- Studies dealing with a specific bacterium for probiotic use.
- Studies where the full text was not available.

### **Data Extraction**

This scoping review included all types of studies, including both pre-clinical (*in vitro* and *in vivo*) and clinical studies. The data extraction from the included articles involved author names, year, country, funding, journal name, type of article, subject or area of interest, clinical indication, and conclusions. In addition, if there were randomized trials, we extracted the information on the risk of bias (Cochranes 5 domains), personal habits, age, gender, type of intervention in both the groups and the method used for detecting the primary endpoints, doses, etc. The data were extracted by two reviewers, N.C and S.K. The data reported in the graphical form would be excluded as it is difficult to remove the numerical data from the graphs unless the data was provided in numerical form in separate files by the authors.

### **Data Analysis**

The data were extracted using a single Microsoft Excel sheet 2010 for data validation and coding. For scoping review only, qualitative analysis of the data was done. No quantitative data were used.

### **Outcome Variables**

A defined outcome was considered for clinical trials. For example, in the presence of oral cancer lesions or oral cancer tumors, the following outcomes were recorded: complete response (CR), if completely regressed, partial response (PR) with a 50% reduction or more in size, no response or no change (NR/NC) in case of reduction (50%) in size, progressive disease (PD) in the presence of a carcinoma 25% increase in size. Other outcomes include systemic inflammation and immune modulation.

## **Results**

An initial search identified 378 articles on the topic within the PubMed database and 39 in other databases. Fifteen eligible review articles were considered for this scoping review (Table I).

The analysis of the articles showed that the components of nutraceuticals found in dentistry are: probiotics, prebiotics, PUFAs, and vitamins A, B, C, D, E. Specifically:

A review of the state-of-the-art and commercially available nutraceuticals for their therapeutic application in dental diseases was performed. This review analyzed 8 articles<sup>16,22,24-28</sup>, examining the effects of probiotics, with one article<sup>15</sup> also evaluating the use of prebiotics to rebalance the oral flora. Chee<sup>29</sup> analyzed the effects of polyunsaturated fatty acids (PUFAs) on oral health. The review also looked at Nagao et al<sup>9</sup> and Fageeh et al<sup>7</sup> that evaluated the effects of vitamin C, with one of them assessing the use of vitamin C in combination with vitamin A (beta-carotene). Nasri et al<sup>30</sup>, Meghil et al<sup>31</sup> and Javed et al<sup>32</sup> focused on the effects of vitamin D, and de Sousa Melo et al<sup>10</sup> considered the effects of vitamin E.

There were two RCTs<sup>9,32</sup> and one cohort study<sup>33</sup> (Table II) found in the literature whose main objective was to determine the effectiveness of nutraceuticals in oral leukoplakia<sup>33</sup> and periodontitis<sup>32</sup>. The study received funding from NIH-NIDCR [R01 DE014328 (to CWC)] to carry out the trial. Nagao et al<sup>9</sup> trial used 25(OH)D vitamin D supplementation and compared it with the placebo (Table II).

These authors considered N=69 patients, including patients with smoking and alcohol habits, and tobacco chewers and a follow-up of 6 and 4 months, respectively, were conducted in both studies. The overall response rate was 17.40% for the test group and 4.30% for the control group. The risk of bias in both studies was low. Other characteristics of the studies are mentioned in Table I.

## **Discussion**

The main goal of this study was to identify the most used nutraceuticals in dentistry, describe their proprieties and identify some knowledge gaps. Nutraceuticals are in small amounts, mainly in foods such as fruit, vegetables, and whole grains, and are classified according to their source of origin into herbal derivatives and dietary supplements<sup>1</sup>. The presence of nutraceuticals on the market has been rapidly growing since 2000. The use of the word “nutraceutical”, judging by the frequency of articles indexed on PubMed, has increased enormously<sup>1</sup>.

The increased consumption and interest in natural products compared to conventional drugs relies on their comprehensive safety and tolerability. Indeed, conventional drugs may have a higher incidence of side effects, allergies, and resistance, particularly to antibiotics<sup>5</sup>. In detail, we will try

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**Table I.** The 15 review articles that found to be eligible were considered for this scoping review.

Authors	Year	Journal	Country	Funding	Type of article	Subject	Clinical Indication	Type of samples	Conclusion	Levels of Evidence
de Sousa Melo <sup>10</sup>	2021	Clinical Nutrition	Brazil	None	Narrative Review	Oral Medicine	Oral mucositis	Humans	This study suggests the effectiveness of vitamin E, zinc and glutamine in preventing and treating oral mucositis. However, the importance of new clinical research to clarify possible doubts is highlighted, as well as the creation of a protocol that includes the dose, route and time of administration, for greater safety in use.	NA
Fageeh et al <sup>17</sup>	2021	BMC Systematic review update	Kingdom of Saudi Arabia	None	Systematic review	Periodontology	Vitamin C	Antioxidants and immunomodulation	Administration of vitamin C as an adjunct to non-surgical periodontal therapy did not result in clinically significant improvements in pocket probing depths at 3 months in periodontitis patients.	Level 1
Nastri et al <sup>12</sup>	2020	Nutrients	Italy	Vanvitelli per la Ricerca (VALERE) program	Scoping Review	Implants	Osseointegration of implants	Humans	This scoping review suggests a limited role of nutraceuticals in promoting osseointegration of dental implants, although, in some cases, such as for vitamin D deficiency, there is a clear link among their deficit, reduced osseointegration, and early implant failure, thus requiring an adequate supplementation.	NA
Hadj-Hamou et al <sup>18</sup>	2020	BMC Oral Health	United Arab Emirates	None	Systematic review	Orthodontics	Probiotic	Prevention and treatment of hard and soft tissues	Probiotic administration does not seem to have an effect on the gingival inflammation and enamel decalcification development in patients under treatment with fixed orthodontic appliances.	Level 1
Pietri et al <sup>20</sup>	2020	Probiotics Antimicrob Proteins	USA	None	Systematic review	Orthodontics	Probiotic	Prevention and treatment of hard and soft tissues	Probiotics exhibit antimicrobial activity against oral pathogenic bacteria; however, due to the limitations of the studies assessed, further well-designed RCTs are needed.	Level 1
Cheng et al <sup>27</sup>	2020	Scientific Reports	China	None	Systematic review and meta-analysis	Oral Medicine	Probiotics	Treatment of recurring aphthous stomatitis	Probiotics are promising for the treatment of recurrent aphthous stomatitis.	Level 1

**Table I (continued).** The 15 review articles that found to be eligible were considered for this scoping review.

Authors	Year	Journal	Country	Funding	Type of article	Subject	Clinical Indication	Type of samples	Conclusion	Levels of Evidence
Wan Mohd Kamaluddi <sup>n24</sup>	2020	Archives of Oral Biology	Malaysia	None	Systematic review	Oral Medicine	Probiotics <i>Lactobacillus plantarum</i> ; <i>Lactobacillus salivarius</i>	Oral cancer prevention	It is known that probiotics have the potential to inhibit oral carcinogenesis, thus supporting the hypothesis of the study.	Level 1
Hu et al <sup>23</sup>	2019	BMC Oral Health	China	None	Systematic review	Oral Medicine	Probiotics	Prophylaxis and treatment of oral candidiasis	Probiotics were superior to the placebo and blank control in preventing and treating oral candidiasis in the elderly and denture wearers.	Level 1
Zauri and Twetman <sup>15</sup>	2019	Caries Research	Neitherlands	None	Critical Appraisal	Conservative Dentistry	Prebiotics and probiotics	Prevention and treatment of caries	The development and evaluation of oral symbiotic products, containing both prebiotics and a probiotic, would be of interest in the future management of dental caries.	NA
Jahanbin et al <sup>11</sup>	2018	Journal of Craniofacial Surgery	Iran	None	Meta-analysis	Oral Surgery	Oral Clefts	Humans	The findings of the present meta-analysis showed the protective effect of periconceptional multivitamin containing folic acid on oral clefts.	Level II-2
Ikram et al <sup>22</sup>	2018	Journal of Investigative and Clinical Dentistry.	Pakistan	None	Systematic review	Periodontology	probiotics	Treatment of chronic periodontitis	Adjunctive probiotics could result in additional benefits in CAL gain in CP.	Level 1
Seminario-Amez et al <sup>16</sup>	2017	Oral Medicine and Pathology	Spain	None	Systematic Review	Oral Medicine	Oral Health	Humans	Probiotics usage could be beneficial for the maintenance of oral health, due to its ability to decrease the colony forming units (CFU) counts of the oral pathogens.	Level 1
JAVED <sup>13</sup>	2016	Implant Dentistry	USA	No	Systematic Review	Implants	Osseointegration of implants	Animals	Efficacy of VD3 supplementation on osseointegration of implants remains controversial and requires further investigations.	Level III
Chee et al <sup>29</sup>	2016	Clinical Oral Investigation	Australia	None	Review	Periodontology	Periodontitis	Humans	Dietary supplementation with fish oil could be a cost-effective adjunctive therapy to the management of periodontal disease.	Level II-3
Inchingolo et al <sup>39</sup>	2022	International Journal of Molecular Sciences	Italy	None	Review	Oral Microbiology	Oral Microbiome	Resveratrol Supplementation	The ability to identify individual microbial families and classify the composition of the MB would allow us to tailor preventive and therapeutic treatment plans with targeted polyphenolic diets when microbial dysbiosis is present.	Level III

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**Table II.** Clinical Study brief characteristics and level of evidence.

<b>Authors</b>	<b>Year</b>	<b>Journal</b>	<b>Country</b>	<b>Funding</b>	<b>Type of article</b>	<b>Subject</b>	<b>Clinical indication</b>	<b>Type of nutraceuticals</b>	<b>Clinical effect/ outcome measure</b>	<b>Level of evidence</b>
Nagao et al <sup>9</sup>	2015	International Journal of Cancer	Japan	Not Mentioned	RCT	Oncology	Oral Leukoplakia	Beta-carotene	Antioxidants and immunomodulation	Level 1
Meghil et al <sup>14</sup>	2019	Oral Diseases	USA	Georgia and NIH-NIDCR (R01 DE014328 [to CWC]).	Randomised Clinical Study	Periodontology	Systemic inflammation in dark-skinned, periodontitis patients	25(OH)D vitamin D supplementation (VDS)	Systemic inflammation	Level 1
Lorenzini et al <sup>33</sup>	2022	International Journal of Translational Medicine	Italy	The Flagship Project InterOmics (MIUR).	Prospective Cohort Study	Oral Ecology	Human Oral Microbiome	Hard Cheese	Oral Microbiome	Level II-2

to analyze the use of nutraceuticals in the various fields of dentistry.

### **Nutraceuticals in the Prevention of Various Disease**

Dental caries is a multifactorial disease. Its pathogenesis involves the microbiota (mainly *S. Mutans*), the host and its immune system, and diet, among other factors<sup>16</sup>. Even if all these factors must occur to develop dental caries, microbiological factors are still the leading cause of this disease<sup>16</sup>. The metabolism of sugars by the oral microbiota leads to the acidification of the ecosystem, a reduction in microbial diversity, and a shift in the microbial proportion towards highly acid-producing and acid-tolerant bacteria<sup>15</sup>. One way to treat or prevent caries-related microbial dysbiosis could be to improve the growth and survival of the oral microbiota associated with health, and for this follows an analysis of the effects produced by prebiotics and probiotics<sup>15</sup>.

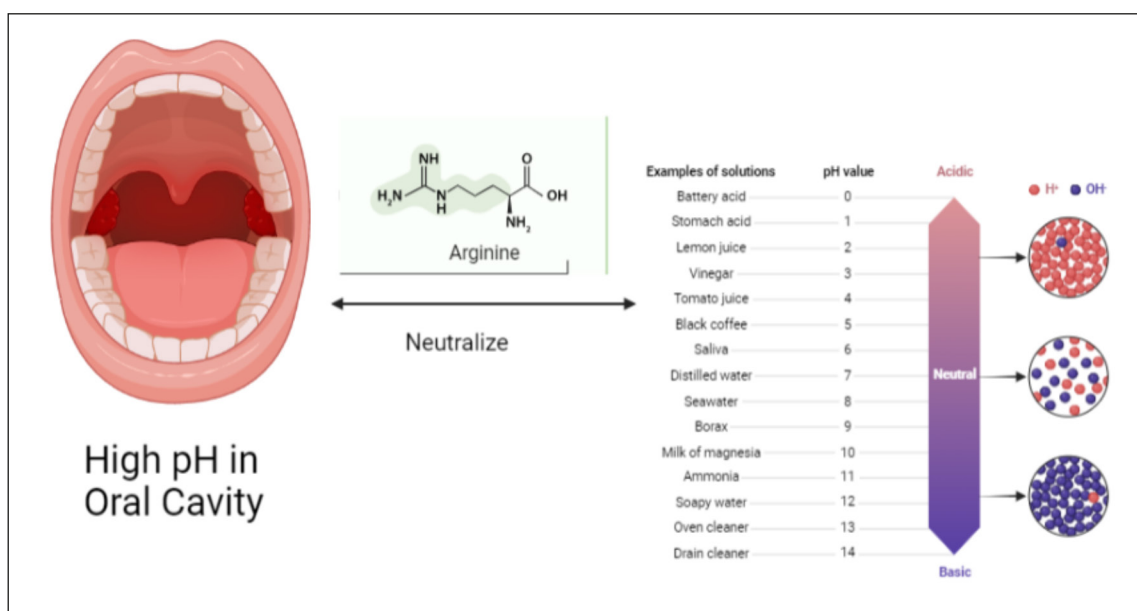
Of the selected articles, Zaura and Twetman<sup>15</sup> the relationship between prebiotic and probiotic nutraceuticals and the prevention of caries disease. Both confirmed that probiotics are a type of bacteriotherapy that leads to a decrease in the CFU count of cariogenic pathogens (mainly *S. Mutans*), resulting in a reduction in the incidence of caries. The second, led by Zaura and Twetman<sup>34</sup>, added that prebiotics (particularly

arginine) could inhibit caries development by acting on acidogenic and aciduric microbes, thus improving pH recovery through the generation of alkalis (Figure 2).

### **Nutraceuticals in Periodontology**

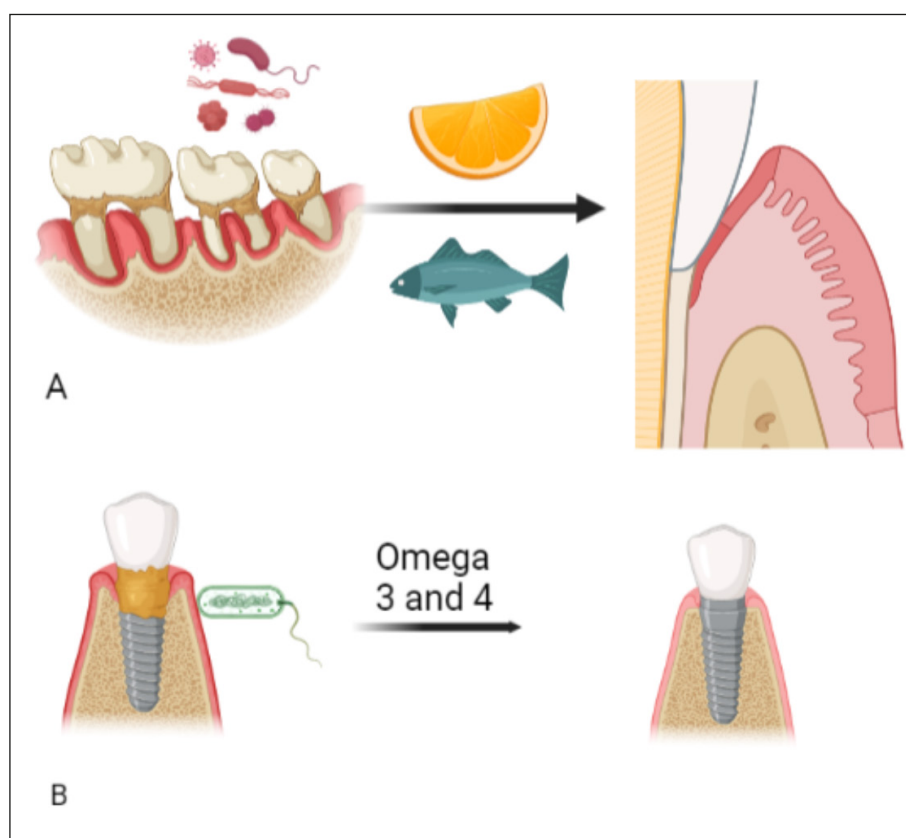
Among the articles considered, five<sup>7,16,22,29,31</sup> suggested an active role of nutraceuticals in the prevention and treatment of periodontal diseases. In particular, the review on the efficacy of probiotics in oral health was conducted by Amez et al<sup>16</sup>. They concluded that there is a compelling clinical improvement in bleeding on probing, probing depth, and gingival index following the intake of probiotics with supplements or fortified foods (Figure 3). The same conclusions on the use of probiotics in the periodontal field were reached by Ikram et al<sup>22</sup>, who additionally suggested their use in chronic periodontitis in combination with causal therapy.

Chee<sup>29</sup> instead focused on the effects of integrating long-chain n3 PUFAs at the periodontal level. Thanks to their anti-inflammatory and antimicrobial action, they act on three levels: firstly, they reduce inflammation by limiting the production of pro-inflammatory cytokines and eicosanoids. Secondly, they diminish bone resorption by inhibiting osteoclasts, and thirdly they produce an antibacterial effect on various oral pathogens, including *S. Mutans*, *C. Albicans*, and *P. Gingivalis*.



**Figure 2.** Arginine, in particular, may reduce caries development by acting on acidogenic and aciduric bacteria, enhancing pH recovery through the production of alkalis (Source: Biorender).





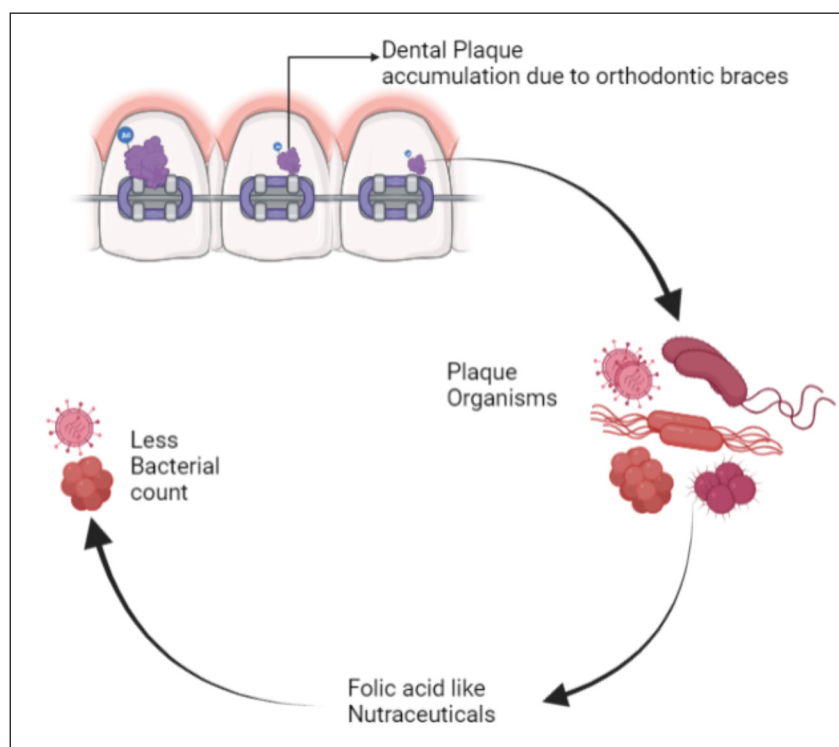
**Figure 3.** Illustration of nutraceuticals in reduction of periodontal problems (A) and the peri-implantitis (B). (Source: Biorender).

Fageeh HN<sup>7</sup> and Meghil et al<sup>31</sup> investigated the beneficial effect of vitamin supplementation in the management of periodontitis. The first one conducted a systematic review on the efficacy of vitamin C in addition to non-surgical periodontal therapy, which showed no clinically significant improvements in pocket probing depths after three months in patients with periodontitis. Conversely, they showed promising results in preventing periodontal health<sup>7</sup>. The second one investigated vitamin D supplementation during periodontal therapy, demonstrating a benefit to the immune system in fighting periodontal pathogens without disrupting immune homeostatic function and a vitamin D-mediated immunoregulation that could prove a beneficial local effect in a larger clinical trial in vitamin D deficient patients<sup>31</sup>. Cassiano et al<sup>34</sup> revealed the role of lifestyle in periodontitis incidence. According to the findings of the review, moderate/severe periodontitis appears to be linked to the intake of processed and ultra-processed foods (Figure 3).

### ***Nutraceuticals in Orthodontics***

Orthodontic therapy is performed to correct dental malocclusions and craniofacial skeletal discrepancies<sup>35,36</sup>. To induce tooth movement, appliances such as brackets, orthodontic bands, and wires are attached to the tooth surfaces for a prolonged period<sup>37</sup>. However, fixed orthodontic appliances can facilitate plaque accumulation on teeth and appliance surfaces, and the microbes it contains can become pathogens under opportunistic conditions such as poor oral hygiene maintenance<sup>17,20</sup>. As these changes in the oral environment may be detectable even two years after removal of the brackets, meticulous oral hygiene and care of oral health are considered essential for a favorable outcome of orthodontic treatment<sup>17-19</sup> (Figure 4).

In this systematic review, Hadj-Hamou et al<sup>18</sup> and Pietri et al<sup>20</sup> investigated the use of nutraceuticals in the orthodontic field. They studied the hypothesis of using probiotics during fixed orthodontic treatment to reduce the microbial activity



**Figure 4.** Illustration of nutraceuticals in reduction of plaque microbiome that accumulated due to orthodontic braces.

of oral pathogens responsible for plaque accumulation and the appearance of white spots (Figure 4). However, the results are conflicting according to the systematic review conducted by Hadj-Hamou et al<sup>18</sup> who demonstrated that there is no natural effect on gingival inflammation and the development of enamel decalcification in patients treated with fixed orthodontic appliances. Conversely, the systematic review of RCTs by Pietri et al<sup>20</sup> on probiotics showed antimicrobial activity against oral pathogenic bacteria.

The third study, by Jahanbin et al<sup>11</sup>, reported that multivitamin supplementation, including folic acid in the periconceptional period, reduces the risk of forming specific types of oral clefts.

### **Nutraceuticals in Oral Surgery and Implantology**

Osseointegration is “a process by which a clinically asymptomatic rigid fixation of alloplastic materials is achieved and maintained in the bone during functional loading<sup>12</sup>”. In other words, the formation of direct bone-to-implant contact (BIC) is one of the fundamental criteria for the overall success of implant therapy<sup>13</sup>.

Osseointegration thus leads to a functional unit that can rehabilitate one or more missing teeth, supporting the dental prosthesis<sup>12</sup>. In addition to

critical factors influencing osseointegration, such as surgical technique, bone quality and quantity, post-operative inflammation or infection, smoking habits, and implant material and surface area, several micronutrients affecting bone metabolism have been shown to influence the skeletal system<sup>12</sup>.

In particular, in this systematic review, the analysis of the effects of vitamin D supplementation was carried out by Javed et al<sup>13</sup> and Nastri et al<sup>12</sup>. Both of them agreed that vitamin D deficiency is often associated with reduced osseointegration and an increased incidence of early implant failure in both animal and human studies.

A third study, Hallström et al<sup>38</sup>, investigated the beneficial effect of probiotics in reversible inflammation of the soft tissue around implants. These reversible inflammations of the mucosa are called peri-implant mucositis, and effective early treatment is supposed to prevent the development of more severe and irreversible peri-implantitis. The results of this RCT showed that the reduction in bleeding on probing (BOP) was clear and statistically significant compared to the baseline in both groups. At the same time, the overall improvement in periodontal pocket depth (PPD) of ~ 0.5 mm did not reach statistical significance. However, the probing depth in the deepest pocket of each implant was significantly improved.

Therefore, probiotic therapy did not increase the effectiveness of treatment with mechanical debridement combined with adequate oral hygiene instructions.

### **Nutraceuticals in Oral Medicine**

The importance of diet is even more apparent when it comes to oral diseases such as candidiasis, aphthous stomatitis, leukoplakia, and oral cancer.

Oral candidiasis is a fungal infection considered the most common infectious disease of the oral mucosa and is mainly caused by *Candida albicans*<sup>23</sup>. The accepted treatment for oral candidiasis uses antifungal agents, such as nystatin, fluconazole, or miconazole<sup>23</sup>. Due to adverse effects and side effects, such as subsequent candida resistance to antifungal agents, dysgeusia, and gastrointestinal complaints, including nausea, vomiting and diarrhea, the clinical application of antifungal drugs may be limited<sup>23</sup>. Therefore, Hu et al<sup>23</sup> proposed the exploration of new prophylaxis and therapeutic strategies for oral candidiasis. Specifically, their systematic review concluded that probiotics have a higher performance in the prevention and treatment of oral candidiasis compared to the placebo and control group in both clinical trials, in the elderly and prosthesis wearers and animal experiments, including inhibition of *Candida* colonization on the surface of the oral mucosa and reduction of clinical signs and symptoms due to fungal infections.

Recurrent aphthous stomatitis (RAS) is the most common self-limiting oral mucosal disease in the world, with a prevalence ranging from 5 to 66% in different countries<sup>24</sup>. RAS is characterized by recurrent round or elliptical ulcers that can occur anywhere in the oral cavity and are common in the non-keratinized epithelium, such as the lingual margin and the buccal and labial mucosa<sup>24</sup>. Lesions are often single but sometimes multiple. The symptoms can cause severe oral pain and affect swallowing and chewing, negatively affecting the quality of life<sup>24</sup>. In their study, Cheng et al<sup>27</sup> suggest using probiotics as an adjuvant in treating RAS. They concluded that probiotics relieve oral pain but do not reduce ulcer severity. The combination of probiotics and steroids or anesthetic, antiseptic gel proved to be more effective than steroids or anesthetic, antiseptic gel alone in reducing ulcer severity and oral pain for patients with RAS. Probiotics are therefore promising for the treatment of recurrent aphthous stomatitis.

Kamaluddin et al<sup>24</sup> proposed the third use of probiotics in oral medicine, through their me-

ta-analysis, and investigated possible beneficial effects of probiotics in inhibiting oral carcinogenesis. Oral cancer, also known as squamous cell carcinoma of the head and neck (HNC), is the sixth most deadly cancer in the world<sup>25</sup>. It occurs mainly in the buccal mucosa, tongue, floor of the mouth and lips, and the main etiological agents are excessive alcohol consumption and tobacco smoking. This systematic review<sup>24</sup> highlighted the ability of probiotics to inhibit oral cancer cell proliferation through the antiproliferative effects and apoptosis-inducing characteristics of probiotics in cancer cells.

A frequent side effect of cancer treatment in the head and neck region is oral mucositis<sup>10</sup>. Oral mucositis (OM) has a debilitating potential for the health of those affected, interfering negatively with nutritional status and quality of life<sup>10</sup>. Due to the incredible complexity of its pathogenicity, different forms of prevention and treatment interventions are being investigated. In particular, according to de Sousa Melo et al<sup>42</sup> the use of dietary supplements such as vitamin E, glutamine, and zinc is an essential tool for the treatment and prevention of OM, as well as for the recovery of the health of patients with HNC and the consequent improvement of quality of life.

Other nutraceuticals active in oral medicine are vitamins A and C<sup>9</sup>. Nagao et al<sup>9</sup> studied the effects of vitamins A and C, through a multicenter randomized, double-blind controlled trial and evaluated the use of low-dose beta-carotene in combination with vitamin C supplements for the treatment and prevention of malignant transformation of oral leukoplakia. Oral leukoplakia is a potentially malignant disease of the oral cavity associated with an increased risk of oral cancer<sup>9</sup>. A multitude of options is currently available for the treatment of oral leukoplakia. Still, there is no consensus on the most appropriate management method, ways to minimize malignant transformation and surgical procedures. Although laser treatment reduces the risk of malignant transformation, it is sometimes associated with recurrence<sup>9</sup>. However, this study concluded that beta-carotene and vitamin C are neither effective for clinical remission nor for protection against cancer development. Therefore, the data from this RCT do not support the hypothesis that chemoprevention with this treatment is effective for oral leukoplakia. Based on the reviews (Table I) and experimental/observation studies (Table II), nutraceuticals have a promising effect on all the specialties of dentistry (Figure 5).

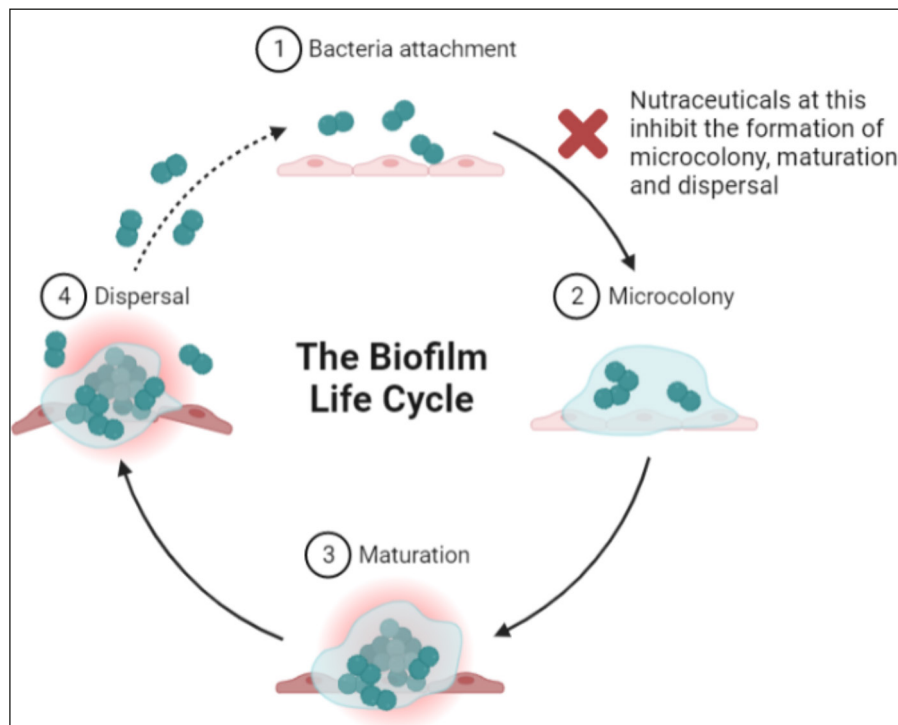


Figure 5. Illustration of biofilm cycle and inhibition of biofilm formation by nutraceuticals. (Source: Biorender).

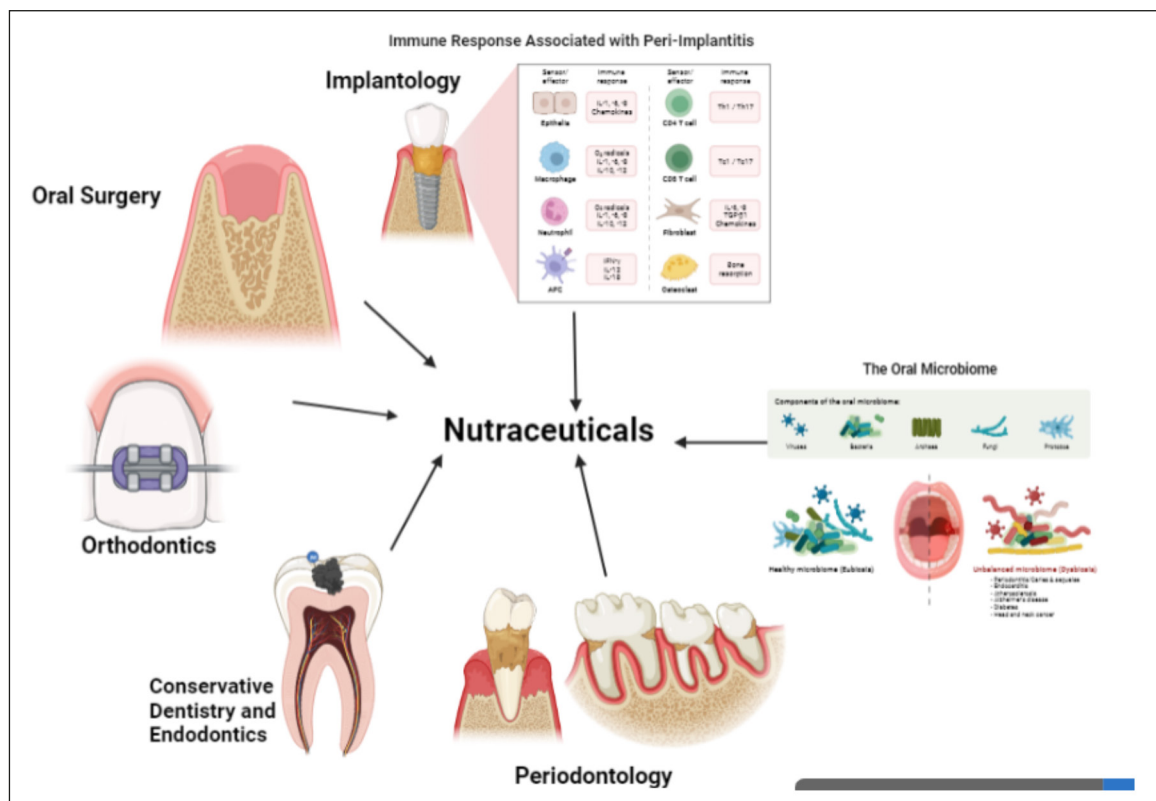


Figure 6. Dental Specialities and nutraceuticals application (Source: Biorender).

### **Nutraceuticals in Oral Microbiome**

Lorenzini et al<sup>33</sup> and Inchingolo et al<sup>39</sup> conducted recent cohort studies that revealed the role of nutraceuticals such as hard cheese and resveratrol supplementation in balancing the oral microbiota for the benefit of oral and general health. When microbial dysbiosis is present, Inchingolo et al<sup>43</sup> stated that the capacity to identify distinct bacteria families and define the composition of the MB would allow us to customize preventive and therapeutic treatment strategies with targeted polyphenolic diets. Furthermore, Lorenzini et al<sup>33</sup> discovered that eating Italian Grana Padano (GP) cheese after dinner delivers key micronutrients (calcium, vitamins, and certain amino acids like arginine) and shifts mouth pH toward basic conditions, leading to a modest adjustment of the oral microbiome toward a more basic state and hence reduction in the overall number of acidophilic bacteria.

In Table I we highlighted various conclusions regarding the use of vitamins, minerals, and probiotics in oral health. Amanda de Sousa Melo et al<sup>10</sup>; suggest the use of vitamin E, zinc, and glutamine in managing oral mucositis, while others conclude that the addition of vitamin C to non-surgical periodontal treatment is not effective. Nastri et al<sup>30</sup> suggested a limited impact of nutraceuticals on promoting osseointegration of dental implants, although vitamin D supplementation may be necessary for early implant failure. The use of probiotics has shown to be more effective than placebo in managing oral candidiasis, but further high-quality clinical trials are needed to confirm its effectiveness against oral pathogens. Periconceptional multivitamins containing folic acid have been found to be protective against oral clefts, and dietary supplementation with fish oil has been suggested as a cost-effective adjunctive therapy for periodontal disease. The study suggests that identifying and classifying the composition of the oral microbiome can help tailor preventive and therapeutic treatments in cases of microbial dysbiosis. Further clinical research is needed to confirm the effectiveness of these interventions and establish proper dosing guidelines for safe usage<sup>40,41</sup>.

In summary, nutraceuticals have become popular in different healthcare fields, including dentistry, where they are used in various specialties. Orthodontics utilizes supplements like vitamin D and calcium to maintain healthy teeth and enhance orthodontic appliances. Periodontics uses antioxidants such as vitamin C and E, and ome-

ga-3 fatty acids to prevent or manage periodontal disease. Endodontics uses probiotics and prebiotics to promote beneficial oral microbiome growth to prevent endodontic infections. Nutraceuticals with anti-inflammatory properties, such as arnica, bromelain, and quercetin, are used in oral surgery to reduce post-operative swelling and discomfort. Additionally, nutraceuticals like xylitol, green tea extract, and cranberry extract are used in dental products to prevent cavities (Figure 6). However, it is important to consider scientific evidence and carefully evaluate their use to ensure safe and effective outcomes.

### **Conclusions**

According to the literature reviewed, nutraceuticals are micronutrients that may be useful in dentistry. This scoping review has revealed that nutraceuticals perform various actions in the human body and are therefore considered promising agents in the prevention and treatment of various systemic and oral disorders. In particular, the literature reviewed highlights their anti-inflammatory, antimicrobial, immune-boosting, and antioxidant properties in fighting against oxidative stress and protecting and preserving oral health. However, further randomized studies with homogeneous methodologies are needed to confirm the actual effectiveness and possibly expand the use of nutraceuticals in dentistry.

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### **Conflict of Interest**

The Authors declare that they have no conflict of interests.

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### **Authors' Contributions**

The authors confirm contribution to the paper as follows: study conception and protocol design for scoping review: NC, SK, and PC; data collection: NC, SK, and PC; analysis and interpretation of results: NC, SK, PC, PD, MM, MDF and GMT; draft manuscript preparation: NC, SK, PC, MDF, and GMT. All authors reviewed the results and approved the final version of the manuscript. NC, SK, PC, PD, MM, MDF, and GMT confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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