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Review

Probiotics in Oral Health and Disease: A Systematic Review

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Abstract: Purpose: Probiotics may exclude or antagonize oral pathogens and be useful to prevent oral dysbiosis and treat oral diseases. The objective of this review was to assess the benefits of probiotics in oral health and disease, and in dental practice; Methods: Primary articles published between January 2012 and 30 December 2020 with full text available were searched in PubMed, ClinicalTrials.gov, ScienceDirect, Google Scholar, B-on, and SciELO; Results: The electronic search identified 361 references of which 91 (25.2%) met all the inclusion criteria. In total, data from 5374 participants with gingivitis, periodontitis, peri-implantitis, caries, orthodontic conditions, halitosis, or oral conditions associated with chemo-radiotherapy were included. Despite major inconsistencies between clinical trials, probiotics have been found to contribute to reduce *S. mutans* counts (*L. paracasei* SD1), reduce probing depth in chronic periodontitis (*B. animalis subsp. lactis* DN-173010 with *L. reuteri*), reduce levels of volatile sulfur compounds and halitosis (*L. salivarius* WB21), treat oral mucositis and improve the quality of life of patients undergoing cancer chemo-radiotherapy (*L. brevis* CD2). Combinations of probiotic bacteria tend to lead to higher clinical efficacy than any individual probiotic agent; Conclusion: Oral probiotics influence favorably the oral microbiota and provide benefits to the oral ecosystem in periodontal diseases, cariology, halitosis, orthodontics and management of oral mucositis resulting from cancer treatment. However, the use of probiotics in dental practice or in self-management preventive strategies requires additional well controlled clinical trials to determine the most effective probiotic combinations, the most appropriate probiotic vehicle, and the frequency of administration.

Keywords: probiotics; oral microbiota; oral health; oral diseases; dental practice

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1. Introduction

The oral cavity is a dynamic ecosystem, with environmental changes and permanent interactions in which commensal bacteria limit the colonization of pathogenic microorganisms. The oral microbiota is heterogeneous and diverse, and its imbalance leads to the onset of major oral diseases such as periodontitis and dental caries [1]. Conventional treatment of these diseases involves removal of the bacterial plaque by mechanical means and antimicrobial drug therapy which may have limited efficacy due to drug resistance [2]. It is necessary to look for alternatives and adjuvants to conventional therapeutic and prevention approaches and probiotics may play an important role in this context.

According to the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO), probiotics are "living microorganisms that, when administered in adequate amounts, confer benefits to host health" [3]. Probiotic-based intervention strategies are widely used for intestinal diseases but not yet for oral diseases due to the limited scientific evidence of usefulness. Probiotics can outcompete pathogenic bacteria and increase the proportion of beneficial bacteria in the mouth thereby contributing for the prevention and therapy of oral diseases [4–6]. In order to be effective in the oral cavity, probiotics must support oral environmental conditions, adhere to and colonize oral surfaces, inhibit oral pathogens [7,8], and/or delay colonization by pathogenic strains [5]. Furthermore, they must not ferment the sugars in order to avoid the pH decrease and

demineralization of the enamel, they should hamper the organization of the extracellular matrix responsible for biofilm formation, limit the production of cytotoxic products by pathogenic bacteria, and beneficially alter the biochemical parameters that influence the dental plaque (e.g., salivary components, buffer capacity) (Figure 1) [9]. In addition, oral probiotics must be safe for the host [10,11].

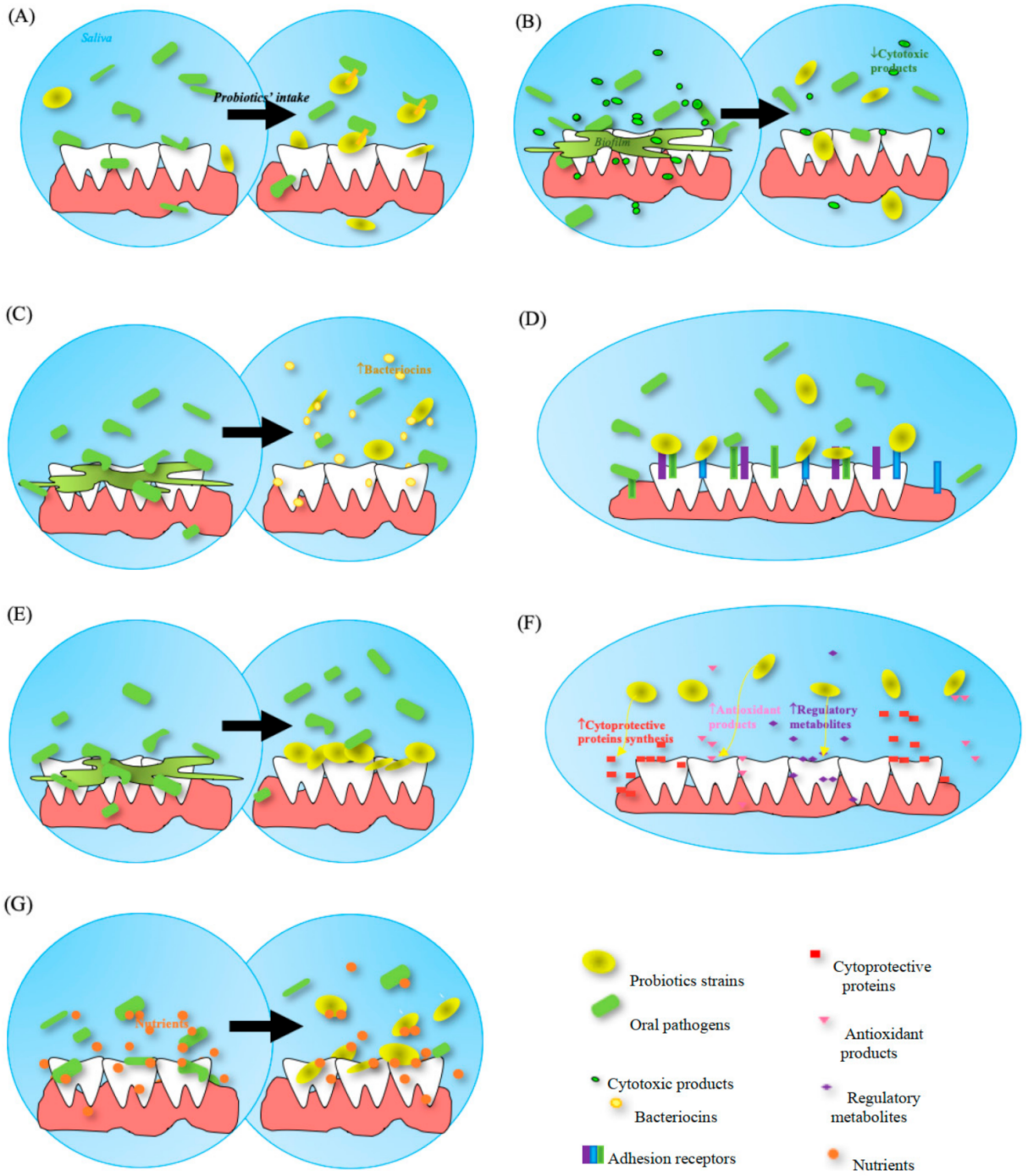

Figure 1. Potential mechanisms of action of probiotics in oral health and disease: (**A**) direct interaction with pathogens to prevent pathogen colonization; (**B**) antagonistic activity on pathogens cytotoxic metabolites, oral biofilm, and extracellular matrix; (**C**) synthesis of antibacterial agents (e.g., bacteriocins) against oral pathogens; (**D**) alter adhesion, aggregation, colonization, and proliferation of pathogens in oral tissues due to mechanisms of exclusion and competition; (**E**) coating oral tissues to protect oral surfaces from pathogens action; (**F**) maintain oral ecosystem balance by synthetizing cytoprotective proteins, antioxidant products, and regulatory metabolites on surface of oral cells; (**G**) competition for nutrients.

The therapeutic and prophylactic potential of probiotics has been explored with promising results in major oral diseases like periodontitis and dental caries [12–15]. However, questions remain regarding the best probiotic species or strains for each oral disease or condition and for each population or individual [16], and regarding the most appropriate probiotic vehicles, dose, and frequency of administration. To determine the usefulness of probiotics in current dental practice we make a critical review of clinical studies assessing the potential benefits of probiotics in oral health and disease.

2. Material and Methods

2.1. Protocol

This systematic review used the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines [17]. The PRISMA checklist is available as a Supplementary file (Table S1).

2.2. Focused Question and Eligibility Criteria

The following question was set: "Is there scientific evidence that the use of probiotics confers benefits to human oral health?" The PICOS criteria that allowed the elaboration of the research question are presented in Table S2.

The eligibility criteria of the studies to be included in the review were:

1. Types of study: randomized clinical trials, without any information of blinding, blind (single, double, or triple), placebo controlled, or non-placebo controlled (compared to another intervention), including cross-over studies.
2. Type of participants: of any age (adults, children, the elderly), without gender restriction, healthy or not.
3. Type of intervention: use of any probiotic (alone or in combination).
4. Considering any dosage regimen, vehicle of delivery or frequency of intervention. Comparators may consist of placebo or other active intervention without probiotics (with or without prebiotic/synbiotic vs. placebo/other intervention). Prebiotics are a group of nutrients that are degraded by gut microbiota. Synbiotic is a mixture of pre- and probiotics. Studies including an auxiliary to the active treatment were analyzed.
5. Primary outcomes: clinical, microbiological, immunological, and biochemical parameters.
6. Secondary outcomes: any adverse effects, rate of adherence, quality of life.

2.3. Search Strategy and Study Selection

The bibliographic search was carried out in the following electronic databases PubMed, ClinicalTrials.gov, ScienceDirect, Google Scholar, B-on, SciELO using the keywords "probiotics", "dental practice", "oral health", "oral diseases" and "oral microbiota" and the conjugation of these keywords. Articles published between January 2012 and 30 December 2020 with full text available were selected. Duplicate references, articles available in 2011 published in 2012, theses, reviews, and articles related to oral probiotics intake with only systemic repercussion were excluded. Further research was done after reading the references of all relevant articles. The full texts of all articles corresponding to the inclusion criteria were obtained and examined for final inclusion. The selection process was included in a PRISMA flow diagram (Figure S1).

3. Results

The electronic search identified 361 references. After removing the duplicates, 308 references were selected for eligibility based on the titles and abstracts, excluding in vitro studies, animal studies, and ongoing and unpublished clinical trials. After searching in the references, 28 additional articles were identified. For the full text review, 129 articles were selected. Of these, 38 clinical trials were excluded because oral health was not the focus of the study, because the study design was unclear, there was no information about allocation, the intake of probiotics was evaluated in animals, and studies were performed in vitro. The 91 randomized controlled trials (RTCs) included in the review involve data from

5374 participants with gingivitis (n = 14), periodontitis (n = 21), peri-implantitis (n = 8), carie (n = 23), orthodontic conditions (n = 6), halitosis (n = 4), oral conditions associated with chemo-radiotherapy (n = 6) and changes in the oral ecosystem (n = 9). Sample sizes range from 10 and 321 participants. The duration of interventions varied between 7 days and up to 2 years. There were 59 studies performed in adults, 24 in children, and 8 in more than one age group. Regarding the probiotic/s administered, 53 studies have implemented a combination of probiotics and 37 have administered a single probiotic. Two studies used symbiotic/prebiotic (1 with a single probiotic and 1 with a combination). The concentrations of the probiotics were not reported in 29 studies and one study did not specify the probiotic that was used. In two studies the duration of administration of probiotic(s) was not given. Adverse effects were reported in 13 trials.

Regarding the study design, there are 11 cross-over trials, 80 placebo-controlled trials and 11 trials compared with another intervention. Regarding the blinding, there are 18 studies without indication of blinding, five single blinding, 61 double-blind, six triple-blind and one with no blinding. The primary results of the studies are mainly focused on clinical, microbiological, and immunological parameters. No data were analyzed regarding financing, for-profit bias, and location of studies.

4. Discussion

4.1. Impact of Probiotics in the Oral Microbiota

The community of microorganisms that colonizes the mouth and forms the dental plaque mainly plays a protective role against pathogens. Dental plaque consists of bacterial cells (mainly streptococci and lactobacilli), bacterial metabolites/products/toxins, salivary polymers/proteins, and food debris [1]. Probiotic lactobacilli may inhibit the adhesion of pathogenic bacteria to the oral tissues, reducing the amount of biofilm formed (Figure 1). On the other hand, lactobacilli probiotics may potentiate dental plaque acidogenicity and increase the load of acid tolerant bacteria such as *S. mutans* and viridans streptococci, making the dental biofilm more pathogenic [18]. The following 9 trials studied the impact of probiotics in the oral ecosystem (Table S3**)**. In Thakkar et al. [19], dental plaque accumulation in children was significantly reduced after 14 days of tablet consumption containing *L. acidophilus, L. rhamnosus, Bifidobacterium longum* and *S. boulardii*, and after three weeks of intervention. In a study by Burton et al. [20], administration of *Streptococcus salivarius* M18 to children for 3 months caused a significant decrease in dental plaque scores. Non-target microorganisms, *S. salivarius, Lactobacillus* spp., hemolytic streptococci and *Candida* spp. levels were not changed during the study. Despite a high adhesion rate (>80%), only 22% of the children were colonized by *S. salivarius* M18 and this lasted until 4 months after discontinuation. *S. mutans* counts were reduced, especially in colonized children, suggesting that *S. salivarius* M18 may have anti-carie activity and that colonization helps the probiotic effect.

A significant reduction of salivary *Aggregatibacter actynomycetancomitans, P. gingivalis* and *Streptococcus mutans* counts, and total number of microorganisms was achieved in children after 2-weeks ingestion of Petit-Suisse (cream cheese) with *L. casei* [21]. However, the reduction of total number of microorganisms and *Streptococcus mutans* was attributed to Petit-Suisse alone as it occurred in both the probiotic and control groups.

A significant decrease in *S. mutans* counts and in the total number of microorganisms occurred after once daily consumption of fermented milk containing *L. rhamnosus* SD11 in adults during 4-weeks and after 4-weeks discontinuation [22]. In contrast, *Lactobacillus* spp. counts increased significantly at week 4 in all patients, and the probiotic was detected up to 8 weeks in 80% of the individuals. In a study by Toiviainen et al. [23], a combination of *L. rhamnosus* GG and *B. lactis* BB-12 administered over 4 weeks to adults caused no change in the salivary *S. mutans* or *Lactobacillus* spp. counts. Similarly, *L. reuteri* DSM 17938 and ATCC PTA 5289 administered during 2–12 weeks to adults had no impact on salivary *S. mutans* count and microbial profile and diversity [24–26]. Administration of *L. rhamnosus* GG or *L. reuteri* D2112 and PTA 5289, also did not impact salivary *S. mutans* count [18].

However, there was a significant increase in lactobacilli in volunteers taking *L. reuteri* but not *L. rhamnosus*.

In summary, most probiotic strains analyzed in these trials are safe, as they do not significantly and definitively affect the commensal oral microbiota, and some can transiently colonize the dental surfaces and have the potential to prevent dental caries.

4.2. Probiotics in Periodontology

Periodontitis is caused by periodontopathogenic bacteria (*Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia* and *Aggregatibacter actinomycetancomitans*) that are organized in biofilms at the supragingival and subgingival levels in susceptible hosts [1,27]. Treatment consists of the mechanical removal of pathogenic biofilm and the use of antiseptics or antibiotics [28]. The main objective of the treatments is to avoid recolonization by pathogenic bacteria. Probiotics as adjuvants to mechanical treatment could modify and occupy the subgingival niche susceptible to recolonization by pathogenic bacteria and allow a new equilibrium with the oral environment (Figure 1) [7]. Probiotics could also alter the bacterial profile of the biofilm adjacent to implants [29]. In addition, they could act as immunomodulators in the oral cavity by decreasing pro-inflammatory cytokines IL-1β, TNF-α and matrix metalloproteinases (MMP) levels, and increasing IL-10, TGF-β1 and tissue inhibitor of metalloproteinases (TIMP) levels [30–32].

4.2.1. Probiotics in Gingival Health and Gingivitis

Fourteen randomized clinical trials related to the use of probiotics in gingivitis and gingival health were analyzed (Table S4). In a study by Kuru et al. [33], 4-week use of yogurt supplemented with *Bifidobacterium animalis subsp. lactis* DN-173010 had a positive effect on gingival inflammatory parameters after a 5-day non-brushing period. In a study by Yousuf et al. [9], plaque index (PI) and gingival index (GI) scores were reduced in adolescents after two weeks administration of a probiotic combination containing *Bifidobacterium longum, Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium lactis* and acid lactic *bacillus*. Dhawan and Dhawan [11] showed a significant reduction of PI up to 4 weeks with the probiotic combination *Lactobacillus sporogenes*, *Streptococcus faecalis* PC, *Clostridium butyrium* TO-A, and *Bacillus mesentericus* TO-A in patients with gingivitis. In studies by Desmukh et al. [34] and Nadkerny et al. [7], individuals with gingival health and gingivitis were administered with a probiotic combination for two weeks. Control group used chlorhexidine. The probiotic combination reduced gingival inflammation and plaque accumulation in the same way as chlorhexidine in both studies suggesting it could serve as an adjuvant in plaque control. Alkaya et al. [35] tested three modes of application of *Bacillus subtilis, Bacillus megaterium,* and *Bacillus pumulus* in patients with gingivitis after mechanical therapy and no significant difference was observed between the probiotic and placebo groups.

Similar negative results were obtained by Keller et al. [36] when using *Lactobacillus rhamnosus* and *Lactobacillus curvatus* tablets in patients with gingivitis.

Contrasting results were obtained when using *Lactobacillus reuteri* (DSM17938 and ATCC PTA 5289) probiotic for gingivitis. In a study by Hallstrom et al. [30], there were no clinical, microbiological, and immunological benefits in women with experimental gingivitis. In a study by Iniesta et al. [37], there was a significant reduction in salivary counts of total anaerobes after 4 weeks of intervention, and *Prevotella intermedia* counts after 4 and 8 weeks in patients with gingivitis relative to the placebo group. *Porphyromonas gingivalis* counts also decreased significantly in a subgingival sample up to 4 weeks. However, there was no difference between PI and GI scores in the test and placebo groups. In contrast, Sabatini et al. [4] showed a significant reduction in PI and GI scores in patients with controlled diabetes type II after 30 days on probiotic. Likewise, Schagenhauf et al. [38] showed a significant reduction of clinical parameters and a complete resolution of sites with mild inflammation in pregnant women. The results suggest that *L. reuteri*-based probiotics may help to manage gingivitis in individuals more susceptible to oral infections.

Lee et al. [39] evaluated the effects of *Lactobacillus brevis* CD2 in experimental gingivitis. Significant differences at the bleeding on probing (BOP) level were found on day 10 in favor of the probiotic group but no longer on day 14 suggesting that this strain can delay the onset of gingivitis over a short period of time. Consistent with this, there was a progressive increase in nitric oxide (NO), an inflammatory mediator, in the gingival crevicular fluid (GCF) of the placebo group unlike the probiotic group in which there was no change.

Alanzi et al. [40] evaluated the 4-weeks administration of probiotic tablets containing *Lactobacillus rhamnosus, Bifidobacterium lactis* on adolescents with gingival health. There was a significant reduction in *Aggregatibacter actynomycetancomitans* and *F. nucleatum* counts in saliva and plaque, and *P. gingivalis* count in plaque in the probiotic group. GI scores also improved in the probiotic group. In Montero et al. [41] administration of tablets containing *Lactobacillus plantarum, Lactobacillus brevis,* and *Peiococcus acidilactici* for 6-weeks to patients with gingivitis led to a significant reduction of severe gingival inflammation scores when compared to placebo. In addition, the average number of sites per patient with moderate inflammation was reduced from 56 to 4 after the probiotic intervention period. There was a decrease in *T. forsythia* counts which the authors correlated with the decrease of severe inflammation scores.

Overall, these studies suggest that long term use of some probiotics may aid in oral hygiene, promote gingival health, and help to treat gingivitis. This effect is more significant when there is no mechanical removal of the plaque [4,7,9,11,38,40] than when the plaque is removed [35]. Additional long-term studies are needed in larger population across all age ranges and ethnic groups to obtain more consistent clinical results, and to determine if probiotics need to colonize the oral cavity to cause a beneficial effect.

4.2.2. Probiotics in Periodontitis

The uncontrolled expansion of periodontopathogenic bacteria (*Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia, Filifactor alocis, Parvimonas micra, Aggregatibacter actinomycetemcomitans* and species of *Fusobacterium and Prevotella*) along with dysregulation of the immune barriers and tissue damage leads to periodontitis [1]. Remodeling of the periodontal extracellular matrix depends on the balance between proteolytic enzymes responsible for the degradation and remodeling of extracellular matrix proteins (MMPs), present in saliva, dental plaque and GCF and tissue inhibitors of MMPs, TIMP-1 and TIMP-2 [42,43]. In case of periodontal diseases, an imbalance in the ratio of MMPs/TIMPs (e.g., TIMP-1 reduction and MMP 8–9 increase) leads to periodontal destruction.

The conventional treatment of periodontitis involves the mechanical removal of the subgingival plaque. Scaling and root planing (SRP) is the standard control method and can be complemented by the addition of antibiotics which can lead to development of resistance, modifications of the commensal flora and risk of dysbiosis [28]. On the other hand, bacterial plaque is difficult to remove in low access sites, and remaining bacteria can cause periodontitis relapse and can invade adjacent tissues (i.e., mucosa, tongue, tonsils) and cause new infections [1].

Probiotics were proposed as adjuncts to the mechanical therapy of periodontitis aiming at restoring the commensal microbiota and reduce inflammation and tissue damage [44,45]. For this review, 21 randomized clinical trials related to the implementation of probiotics in periodontal conditions were selected (Table S5). Most trials have used species of *Lactobacillus* because it is a commensal bacterium that antagonizes *P. gingivalis* [10,46].

In Vicario et al. [10], tablets containing *L. reuteri* ATCC 55,730 and *L. reuteri* ATCCPTA 5289 were administered to patients with chronic periodontitis for 30 days. All clinical parameters improved significantly in the test group, suggesting a possible synergy between the strains used. In a study by Imran et al. [47], ingestion of milk with *Lactobacillus casei* for one month provided no clinical benefit to patients with chronic periodontitis in spite of a significant decrease in *P. gingivalis* counts in the first months after the intervention. *Aggregatibacter actynomycetancomitans* and *P. intermedia* counts showed no significant reduction.

Iwasaki et al. [48] evaluated the use for 12 weeks of heat-killed *Lactobacillus plantarum* in patients undergoing supportive periodontal therapy. Mechanical control of plaque was performed and improved clinical parameters in both the test and placebo groups. A significant decrease in favor of the probiotic group was observed at 12 weeks in bleeding on probing (BOP), number of teeth with periodontal pocket depth (PD) >4 mm and number of sites with PD >4 mm, suggesting that this probiotic can prevent a possible recurrence and/or disease progression.

Grusovin et al. [8] evaluated for 12 months the effects of a *Lactibacillus reuteri* DSM 17938 and PTA 5389 probiotic combination in patients treated for a stage III-IV periodontitis, grade C. In the probiotic group, there was a higher reduction of mean PD throughout the study, higher clinical attachment level (CAL) gain at 6 months, and higher reduction of BOP at 6 and 9 months.

In a study by Penala et al. [46], probiotics *L. salivarius* and *L. reuteri* were evaluated as an adjunct to SRP in the treatment of patients with chronic periodontitis. The test group received subgingival delivery of probiotics and probiotic mouthwash for 14 days. A significant difference in favor of the test group was observed after 3 months in the number of moderate periodontal pockets. Moreover, there was a significant reduction in the benzoyl-DL arginine-naphthylamide (BANA) test for detecting digesting peptidase in the test group after 1 month, compared to the placebo group, but the difference was no longer observed at 3 months.

Chandra et al. [49] tested a subgingival combination of probiotics *Saccharomyces boulardii* with a prebiotic (fructo-oligosaccharide) in patients with chronic periodontitis as adjuvant to SRP. Despite a short-term colonization by *Saccharomyces boulardii* (until day 7), there was significant clinical improvement (as measured by the reduction of PI, GI, CAL, and PD) in the test group at 3 and 6 months after the mechanical treatment. The results suggest that *S. boulardii* may be a good auxiliary agent in the treatment of chronic periodontitis.

In a study by Boyeena et al. [50], the effects of a probiotic combination were compared to the application of tetracycline fibers directly in the periodontal pocket after mechanical removal of the plaque. Use of probiotics caused a significant reduction of BOP and PD when compared to the tetracycline fibers. The combination of both approaches showed a significant improvement of BOP and PD when compared to tetracycline fibers alone illustrating the benefits of using tetracycline fibers and probiotics to treat periodontitis.

Shah et al. [51] tested *L. brevis,* with or without doxycycline, for the treatment of patients with aggressive periodontitis after mechanical plaque removal. After 2 weeks, there was a significantly higher reduction of PD in patients on *L. brevis* and doxycycline relative to the other patients. At 2 months *Lactobacillus* spp. count (CFU/mL) increased significantly in patients on *L. brevis* and all patients had significantly improved clinical parameters when compared to baseline.

In a study by Morales et al. [52], the effects of daily administration of *Lactobacillus rhamnosus* SP1 or azithromycin tablets for 3 months were studied as an adjunct to SRP in patients with chronic periodontitis. Clinical and microbiological outcomes (as determined by the presence and levels of *Tannerella forsythia, Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*) improved over the study period but there were no significant differences between groups.

Yuki et al. [53] compared the effects of consumption for 90 days of yogurt containing *L. rhamnosus* L820 with placebo yogurt in individuals with mental deficiency and periodontal disease. The PMA (papillary-marginal-attached) score was significantly reduced in the probiotic group at 90 days suggesting that *L. rhamnosus* L820 may have a beneficial effect on periodontal disease as an adjunct to mechanical oral hygiene.

Ikram et al. [44] compared *L. reuteri* with metronidazole as adjuvant to SRP in patients with chronic periodontitis. There was a significant improvement in the clinical parameters at all evaluation periods with no difference between groups, indicating that the efficacy of probiotic and antibiotic was similar.

In a study by Laleman et al. [54], the use of *Streptococcus oralis* KJ3, *Streptococcus uberis* KJ2, and *Streptococcus rattus* JH14 was not effective as adjunctive treatment of periodontitis despite lower PI at the end of the monitoring period (24 weeks) and the decrease of salivary *P. intermedia* at 12 weeks.

Murugesan et al. [55] evaluated the efficacy of co-administration of doxycycline and synbiotic tablet (consisting of prebiotic *Streptococcus faecalis* T-110 JPC and probiotics *Clostridium butyricum* TO-A, *Bacillus mesentericus* TO-A and *L. sporogenes*) as adjuvant to SRP in patients with periodontitis. Four weeks after the end of the intervention, a significant reduction of PD, CAL and BOP was observed in the test group indicating that this prebiotic-probiotic mixture can be a complement to the mechanical removal and doxycycline to improve clinical parameters, reduce bacterial load and repopulate the treated niche.

Three different trials studied the impact of *L. reuteri* in patients with chronic periodontitis using comparable study design (administration for 3 weeks of probiotic tablets containing *L. reuteri* compared to placebo) and obtained similar results [5,31,56]. Most clinical and microbiological parameters (as evidenced by a delay of recolonization up to 6 months) were significantly improved during the study period and the probiotic groups had fewer patients at high risk of disease progression and more patients at low risk. In one study the probiotic was found until day 90 in 11 patients and was no longer found on day 180, indicating temporary colonization [31].

Residual periodontal pockets are associated with an increased risk of periodontal disease progression and therefore require additional treatment. The effect of probiotic combination *L. reuteri* ATCC PTA 5289 and DSM 17938 as an adjunct to the SRP treatment of residual pockets was evaluated in patients with chronic periodontitis previously treated [57]. The use of *L. reuteri* after re-instrumentation did not affect colonization by periodontopathogens. While no significant clinical improvement was observed after 12-week consumption of probiotics and after 12 weeks of discontinuation, at 24 weeks after discontinuation PD was significantly reduced in moderate and deep pockets, and more pockets were sealed in the probiotic group. Taken together, these studies suggest that probiotic *L. reuteri* may serve as an effective complement to mechanical therapy in the treatment of chronic and relapsing periodontitis.

In a study by Sajedinejad et al. [45], use of *L. salivarius* NK02 in mouthwash for 28 days significantly improved clinical parameter (reduced PD, GI, and BOP) in patients with chronic periodontitis. In addition, *Aggregatibacter actynomycetancomitans* counts in saliva and gingival crevicular fluid were significantly reduced in the test group which also presented more commensal bacteria than the placebo group.

Bifidobacterium animalis subsp. lactis HN019 was evaluated for 30 days in patients with chronic periodontitis [58]. The probiotic colonized the subgingival flora for 60 days. There was a significant reduction of IL-1β at the end of 30–90 days, and IL-8 at the end of 30 days as compared to the control group. Likewise, there was a higher reduction of periodontopathogens (*P. gingivalis, T. denticola, F. nucleatum sub* spp. *vincentii*) in the test group up to 90 days. Clinical parameters improved significantly in the test group as determined by CAL and PD (in moderate and deep pockets at 90 days), and the risk of disease progression was also lower in the test group relative to the control group.

In a study by Butera et al. [59], the use of probiotics combinations for 6 months as an adjunct to SRP in patients with periodontitis improved clinical parameters in both probiotics groups (group 2: toothpaste with *Bifidobacterium* and *Lactobacillus* and group 3: toothpaste + chewing-gum with *L. reuteri*, *L. salivarius*, and *L. plantarum*), except for adherent gingiva and RG. Hence, BOP, PI, number of bleeding sites, pathological site, and sulcus bleeding index improved significantly at month 3 in both groups (also at month 6 in group 3). PD and CAL also improved significantly at month 3 in both groups. There was a significant reduction of orange complex pathogens *P. intermedia* and *F. nucleatum* between 3 and 6 months in both probiotics groups. Overall, group 3 presented better and more durable effects than group 2 suggesting a synergistic effect between the probiotic strains present in toothpaste and chewing-gum.

4.2.3. Probiotics in Peri-Implant Diseases

Peri-implant mucositis is a reversible soft tissue inflammation around the implants with no bone loss, caused by bacteria biofilm [60]. Its evolution leads to peri-implantitis, characterized by bone resorption and potential implant loss, increased levels of IL-6, IL-1β, and IL-8 and increased GCF volume [61]. The mechanical control of the biofilm and the use of antiseptics and antibiotics may be insufficient for the complete cure. Probiotics may aid in the formation of a new protective biofilm compatible with peri-implant health.

Eight randomized clinical trials investigating the effects of different species of *Lactobacillus* in peri-implant inflammation in otherwise healthy adults were analyzed (Table S6). Laleman et al. [62], studied the use of *L. reuteri* ATCC PTA 5289 and DSM 17938 in initial peri-implantitis. After SRP, probiotics were administered in drops directly to the site of peri-implantitis and afterwards in lozenges consumed for 12 weeks twice a day. There were no clinical and microbiological benefits from the administration of the probiotics. Similar negative results were obtained by Lauritano et al. [63], who evaluated the daily consumption of *L. reuteri* tablets for 28 days in patients with peri-implant mucositis, by Peña et al. [64] who studied the addition for 1 month of *L. reuteri* DSM 17938 and ATCC PTA in patients with peri-implant mucositis who received mechanical therapy and 0.12% chlorhexidine 15 days before the start of probiotic intervention, by Galofré et al. [65] who also evaluated the effects of administration of *L. reuteri* DSM 17938 and ATCC PTA 5289 in patients with peri-implant mucositis and peri-implantitis for 30 days, and by Hallström et al. [29] who administered *L. reuteri* DSM 17938 and ATCC PTA 5289 in patients with peri-implant mucositis for 3 months. Mongardini et al. [66] also found no clinical benefits after 14-days administration of *L. plantarum* and *L. brevis* on patients with experimental peri-implant mucositis.

In contrast, Flichy-Fernández et al. [67] found that administration of *L. reuteri* DSM 17938 and ATCC PTA 5289 for 30 days was useful to treat and prevent peri-implant mucositis. At the end of the study, a single patient developed mucositis and most (17 of 23) of the patients with mucositis were cured. Accordingly, PI, GI, PD and GCF volume were significantly reduced in the probiotic group when compared with placebo. IL-6 and IL-8 levels were also significantly reduced in the mucositis group taking the probiotics. The severity of peri-implant mucositis was also reduced significantly in a more recent trial using a probiotic combination (*L. reuteri* DSM 26866, *L. rhamnosus* DSM 21690, *L. bulgaricus* DSM21690, and *Bifidobacterium animalis* ssp. *lactis* DSM 17741) [68]. Clinical parameters (as determined by PI, GI, BOP, and PD) improved significantly in the test group relative to the control group after 1 month of consumption of probiotics. Salivary flow increased after 1 month in test group, with a significant difference between groups. Immunological parameters (salivary cytokines Il-1β, Il-4, TNF-α) decreased significantly at 1 and 6 months after the start of the intervention. Finally, the pathogenic species *Prevotella intermedia*, *Treponema denticola*, *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Fusobacterium nucleatum*, decreased after 1 month of probiotic consumption. The positive results obtained in these two trials may be related with a better removal of the subgingival plaque prior to the application of probiotics. On the other hand, the lack of results in the remaining trials may be related with small sample sizes and short administration times [69]. Clearly, further standardized clinical trials are indispensable to determine the usefulness of probiotics in prevention, management, and treatment of gingival, periodontal and peri-implant conditions, and to develop practical recommendations and adequate clinical protocols.

4.3. Probiotics in Cariology

Dental caries is a multifactorial disease, related to acidogenic and acid tolerant bacteria such as *S. mutans* and *Lactobacillus* spp. [70]. These bacteria produce acids from fermentation of carbohydrates that demineralize dental tissues. The prevention of dental caries involves the administration of fluoride, the use of sealants and modification of dietary habits (lower consumption of sucrose) [71]. The treatment and control of dental caries

requires mechanical removal of the carious lesions which should be combined with an antimicrobial in the case of high-risk children. Probiotics have been proposed as an adjunct method to dental caries management strategies as they adhere to oral tissues, prevent adhesion/colonization/proliferation of caries pathogens and formation of pathogenic biofilm, produce inhibitors of cell adhesion and antibacterial agents, and consume nutrients before caries pathogens can use them (Figure 1) [33,72–75].

Seventeen clinical trials evaluated the effect of different probiotics on cariology in children and infants (Table S7). Overall, it was easier to modify the immature dental biofilm of children through colonization with probiotics than the established biofilm of adults. Six trials in adults assessed whether permanent integration of probiotics into the mature biofilm can be achieved in a cariogenic environment.

In a study by Rodriguez et al. [76], administration of *L. rhamnosus* SP1 strain in milk to children for 10 months led to a lower prevalence of dental caries relative to the placebo group (54.5% vs. 65.8%), lower incidence of cavitated lesions (9.7% vs. 24.3%), and lower incidence of new lesions. Administration of tablets containing *Streptococcus uberis* KJ2TM, *Streptococcus oralis* KJ3TM and *Streptococcus rattus* JH145TM to children for 3 months, caused a significant reduction in dental caries at the end of one year with prevention of enamel demineralization [77]. In a study by Di Pierro et al. [78], *Streptococcus salivarius* M18 probiotic in tablets was evaluated for 90 days in children with high risk of caries. There was a significant reduction in the overall cariogram result. In the probiotic group, PI and *S. mutans* counts were significantly reduced indicating that the consumption of this probiotic may help to prevent the development of new caries in high-risk children.

The daily and triweekly consumption of probiotic milk containing *L. paracasei* SD1 on *Streptococcus mutans* and lactobacilli counts in saliva and plaque samples was evaluated in preschool children for 6 months [79]. Probiotic administration reduced *S. mutans* counts and increased total lactobacilli counts in the saliva and plaque samples that persisted at least 6 months after discontinuation. Similar results were obtained by Pahumunto et al. [72] after 3-months consumption of milk containing *L. paracasei* SD1, and by Teanpaisan et al. [75] after 6-months consumption. In the latter study, there was colonization by the probiotic strain already at month 3 which decreased progressively with time to undetectable levels at month 12. Overall, the results suggest that in children with high risk of caries, daily consumption of probiotic *L. paracasei* SD1 may be recommended to control the amount of *S. mutans* responsible for the initial process of tooth decay.

Stensson et al. [80] administered *L. reuteri* as drops to pregnant women (from the 9th month of pregnancy) and their infants (up to 1 year old). At 9 years of age, the infants in the test group showed significant improvements in GI and dental caries prevalence relative to placebo (82% children free of carious lesions vs. 58%). *L. reuteri* was detected in only two children from each group. Diet, oral hygiene, fluoride supplementation and socioeconomic factors were similar in both groups at baseline but were not documented at the end of the study preventing the identification of potential contributors for the benefit of probiotics in dental caries development in early age.

In a study by Campus et al. [81], administration of *L. brevis* CD2 lozenges for 6 weeks in children led to significant reduction in salivary *S. mutans* mean counts ($\log_{10}$ CFU/mL), a significant reduction in the dental plaque pH, and a significant reduction in gingival bleeding at week 6. The benefits were also significant 2 weeks after probiotic discontinuation.

Bhalla et al. [82] evaluated *Bifidobacterium animalis subsp. lactis* BB-12 administered in curds to children. A significant reduction in the *S. mutans* count in saliva occurred after 1 h of ingestion and after 7 days of intervention. In a study by Sudhir et al. [83], *L. acidophilus* administered in curds to children for 30 days led to a significant reduction in the *S. mutans* count in saliva in the test group. A probiotic combination of *L. acidophilus* LA5 and *B. lactis* BB12 also caused a significant reduction of salivary *S. mutans* counts in children at days 7 and 30 after ingestion [73]. However, after 6 months of discontinuation, *S. mutans* values returned to the initial values indicating that the colonization was temporary. Tablet consumption of *L. reuteri* DSM 17938 and ATCC PTA 5289 for 28 days also caused

a significant reduction in salivary *S. mutans* and *Lactobacillus* spp. counts in children [84]. In contrast, *L. paracasei* F19 given as a dietary supplement for 9 months had no significant effect at the microbiological and clinical levels at 3, 6 and 9 years of age [74]. Consistent with this, the probiotic did not colonize the oral flora. Likewise, in Taipale et al. [85], *Bifidobacterium animalis subsp. lactis* BB-12, administered by slow release or tablet from the age of 1–2 months to 2 years, had no significant effect in the occurrence of dental caries in children with low caries risk up to 4 years old when compared to xylitol and sorbitol. Administration in children of *L. rhamnosus* and *Bifidobacterium longum* in milk for 9 months [86] or *Bifidobacterium lactis* in yogurt for two weeks [87] also caused no significant impact on *S. mutans* counts, dental caries prevalence, or pH and plaque accumulation. Finally, in Cildir et al. [88], *L. reuteri* administration in drops for 25 days in children with cleft palate (population with higher food retention, and higher levels of dental caries and cariogenic bacteria than healthy children) caused no significant reduction in salivary *S. mutans* and *Lactobacillus* spp. levels.

In adults, consumption of yogurt with *L. acidophilus* LA5 and/or *Bifidobacterium lactis* BB12 for 2 weeks caused a significant temporary reduction of *S. mutans* count in saliva after 2 weeks [89,90]. This effect was lost 2 weeks after discontinuation. Similar results were obtained in adults who consumed white cheese with *L. casei* LAFTI L26 for 2 weeks [91]. Administration for 4 weeks of *L. paracasei* SD1 in milk allowed a significant reduction of *S. mutans* quantities at all monitoring times [92]. *Lactobacillus* spp. count increased significantly in most (75%) of the patients up to week 4 suggestive of probiotic colonization. Ingestion of ice cream containing *B. infantis* for 28 days, caused a significant reduction in *S. mutans* counts when compared to baseline and to the control group [93]. There was no effect in *Lactobacillus* spp. levels.

The topical application of *Streptococcus dentisani* in an adhesive gel on dental surfaces in single and multiple doses was evaluated in healthy adults [94]. There was a significant increase of the number of *S. dentisani* in dental plaque at day 14 after the first application which was no longer observed on day 28. In dental plaque samples, *S. mutans* count decreased significantly in the single dose group on day 28.

In summary, *L. acidophilus, L. reuteri, S. dentisani, S. salivarius, B. lactis* and *L. paracasei* may be effective as an adjunct method to restorative treatment in children at any risk of caries especially when used in conjunction with changes in dietary habits. Dairy products (yogurt, milk) appear to be the favorite vehicles for oral probiotics in children. Besides being easy to ingest, they contain essential nutrients: calcium, phosphorus, vitamin, protein, casein phosphopeptides that promote enamel remineralization, neutralize acids, participate in buffering, and interfere with the acidity of the probiotics *Lactobacillus* spp. or *Bifidobacterium* spp. The mixture of probiotic(s) with dairy products induces a synergistic effect. The heterogeneity of the trials (variability in study design, range of administration, strains used, dosage, vehicle) likely explains variations in results and prevents significant comparisons. Overall, however, these studies suggest that short term consumption of probiotics may reduce cariogenic bacteria counts, prevent dental plaque formation, and thus control the progression of dental caries. These effects seem to require the temporary colonization of the oral ecosystem which may lead to the exclusion of bacterial pathogens (Figure 1). However, probiotics are unable to definitively eliminate pathogenic bacteria and a reduction in salivary counts does not imply a reduction of bacterial plaque virulence [24]. Future trials should not only evaluate the cariogenic bacteria counts but also the dental caries progression/incidence because, as already mentioned, virulence and counting are not synonymous [72,75,81].

4.4. Probiotics in Orthodontics

The orthodontic treatment causes dysbiosis of the oral microbiome due to difficulty in hygienizing the orthodontic appliance [95]. Probiotics may be useful as supplements to hinder bacterial colonization and render the dental biofilm less virulent in patients with

fixed or removable orthodontic appliances. Six studies related to the effect of probiotics on orthodontics were analyzed (Table S8).

Jose et al. [96] found a significant reduction of *S. mutans* levels in dental plaque around the bracket evaluated after probiotic (undisclosed composition) administration with curd or toothpaste. In a study by Ritthagol et al. [97], four weeks ingestion of milk containing *L. paracasei* SD1 in adolescents with non-syndromic lip-palatine cleft led to a significant increase of salivary *Lactobacillus* spp. count and decrease of *S. mutans* count at all times of evaluation when compared with baseline data. *L. paracasei* SD1 temporarily colonized the oral microbiota, being detected in saliva up to 4 weeks after cessation. The results suggest that this probiotic may help to prevent caries after orthodontic treatment in this population.

The effectiveness of 14-days milk consumption of *L. casei* or *L. reuteri* lozenges was investigated in young adults undergoing orthodontic treatment [98]. Periodontal condition was improved in both probiotic groups, better results being observed in the *L. reuteri* group. Alp and Baka [99] assessed the effect of a systemic probiotic (*Lactococcus lactis* subsp, *Leuconostoc* spp., *Lactobacillus* spp. and *S. thermophilus* and yeasts isolated from cereal grains) or local intervention (bacteriocin extracted from lactic acid bacteria), for 6 weeks on salivary microbial colonization in orthodontic patients. There was a significant reduction in *S. mutans* count at weeks 3 and 6 in both intervention groups. *Lactobacillus* spp. counts decreased significantly at week 3 in the probiotic group and at week 6 in the local intervention group. In contrast, in a study by Pinto et al. [100] there were no oral benefits after two-weeks consumption of yogurt containing *B. animalis subsp. lactis* DN-173010, and in Gizani et al. [101] there were no clinical and microbiological advantages to the use of *L. reuteri* lozenges in patients with maxillary orthodontic appliance. In summary, daily consumption of some but not all probiotics may help to prevent caries and improve periodontal condition in patients on orthodontic treatment.

4.5. Probiotics in Halitosis

Halitosis has multiple etiologies, and may be caused by ingestion of certain foods, poor oral hygiene, periodontitis, respiratory infections, tobacco consumption, genetic predisposition, dry mouth and oral microbiome dysbiosis [102]. Volatile sulfur compounds (VCS) responsible for halitosis include hydrogen sulfide, methyl mercaptan and dimethyl sulfide. In the oral cavity, these substances essentially result from the metabolic activity of oral microorganisms [102]. Several factors contribute to the production of these compounds, such as higher prevalence of gram-negative anaerobic bacteria, alkaline salivary pH, low redox potential, and the presence of sulfuric substrates (cysteine and methionine) [103,104]. Four studies have looked at the impact of probiotics in reducing halitosis by decreasing the density of the bacteria responsible by VCS production (Table S9).

Lee et al. [105] assessed the effect of consumption of *Weissella cibaria* tablets for 8 weeks on halitosis in healthy adults. *W. cibaria* counts were higher in the probiotic group at 4 and 8 weeks, and there was a significant reduction in VCS levels at week 4, and a significant reduction in bad breath improvement (BBI) score at week 8. The results suggest that *W. cibaria* tablets can be a useful oral hygiene product to control bad breath.

Streptococcus salivarius M18 has also been shown to reduce halitosis in patients with orthodontic treatment [106]. This required a month of consumption of two probiotic lozenges per day. Only *Rothia* spp. levels were significantly reduced in the probiotic group. The VCS score decreased significantly throughout the study in the probiotic group and placebo groups after 1 month but, after 3 months of follow-up, the VCS levels returned to the baseline value in the placebo group whereas in the probiotic group the VCS levels decreased significantly. A reduction in halitosis levels was also observed 1 and 3 months after ingestion of *L. salivarius* and *L. reuteri* for 14 days in patients with chronic periodontitis and halitosis [46]. In a similar study performed with *L. salivarius* WB21 only, VCS levels were significantly reduced and there was a significant reduction of PD [107]. Also, bacteria known to produce malodourous compounds like *F. nucleatum* were reduced in the probiotic

group. Finally, in Keller et al. [108] *L. reuteri* reduced the organoleptic scores in patients who had a subjective feeling of bad breath.

In summary, regular consumption of probiotics *L. salivarius, S. salivarius, W. cibaria* or *L. reuteri* may complement mechanical oral care in controlling halitosis.

4.6. Probiotics in Oral Wound Healing and Oral Mucositis Related with Cancer Therapy

Wound healing in the oral mucosa involves several inflammatory mediators/molecules and is impacted by several factors such as age, dietary habits, and the oral microbiome [109,110]. Cancer therapy affects salivary quality and reduce salivary glycoproteins that cover and protect oral mucosa against microorganism's adherence and irritation. In addition, it induces oral mucositis that may favor the emergence of opportunistic infections, fever, anorexia, hemorrhage, severe pain, dysphagia and dysgeusia [111]. Oral glutamine has been recommended to mitigate radiotherapy-induced oral mucositis in head and neck cancer patients but other effective interventions are needed [112]. As mentioned previously, probiotics may participate indirectly in re-epithelization and tissue regeneration due to their potential to: (1) influence immune-regulating factors (e.g., kB nuclear factor, toll-like receptors in dendritic cells), (2) modulate inflammatory mediator levels (e.g., cytokines such as IL-1β, TNF-α, IL-6 and IL-15 and chemokines such as IL-8); and (3) induce the production of proteolytic enzymes involved in tissue remodeling (MMPs).

A few clinical trials have investigated the role of topical administration of probiotics in oral wound healing and in the treatment of oral mucositis in patients undergoing chemo-radiotherapy (Table S10). In a study by Twetman et al. [113], the application of *L. reuteri* in adults with healthy mucosa one week before standardized biopsy of the oral mucosa and one week later showed no improvement in healing. However, patients in the probiotic group had lower pain, less erythema/edema and the fibrin more rapidly covered the wound. There was no change in the levels of MMP1-3 and IFN-α2, IFN-β and IFN-γ in the wound exudate during the first healing week [114].

Walivaara et al. [115] evaluated the effects of *L. reuteri* supplements administered 3 times a day for 2 weeks on the healing of wounds after surgical extraction of lower third molars. Probiotic had no effect on the healing process as determined by extra-oral swelling, level of salivary oxytocin, and presence of bacteria. However, in patients on probiotic the subjective perception of pain, discomfort and swelling was significantly reduced and leading to improved quality of life during the healing process.

Limaye et al. [116] assessed the safety and tolerability of a 1, 3 or 6 mouthwash/day containing *Lactococcus lactis* (AG013, a strain that produces human trefoil factor 1) in patients newly diagnosed with advanced squamous cell head and neck cancer who were to start chemotherapy. The mean number of days with oral mucositis was reduced by 35% in the probiotic group, and there were fewer emergency visits (36% vs. 60%). The placebo patients had at least 2 days with oral mucositis while 29% of those taking AG013 had oral mucositis for 0 or 1 day. *Lactococcus lactis* AG013 was detected in mucosa and saliva shortly after the mouthwash, and up to 14 days after the mouthwash in equivalent number in the test groups. The probiotic was safe as there was no infection in neutropenic patients.

In a study by Jiang et al. [117], a significant improvement in oral mucositis was observed in patients with nasopharyngeal carcinoma undergoing chemoradiotherapy taking a probiotic combination of *Bifidobacterium longum, Lactobacillus lactis,* and *Enterococcus faecium*. Finally, Sharma et al. [118] evaluated the effect of *L. brevis* CD2 taken in lozenges in patients with squamous cell carcinoma of head and neck submitted to chemo-radiotherapy. The incidence and severity of oral mucositis was reduced in the probiotic group. In the probiotic group, more patients completed the cancer treatment, and fewer patients needed adjuvant medications to control the pain associated with mucositis. In summary, while probiotics seem to have no direct effect on oral wound healing, they can contribute to attenuate oral mucositis and improve quality of life in patients undergoing cancer therapy.

5. Conclusions

The use of probiotic bacteria is an expanding area of research in dentistry. Oral probiotics are safe, influence favorably the oral microbiota and provide benefits to the oral ecosystem in periodontal diseases, cariology, halitosis, orthodontics and management of oral mucositis resulting from cancer treatment. The areas in which probiotics should be further developed are endodontics, dental traumatology, and healing of chronic oral wounds.

Probiotics likely act without colonization or by transient colonization of the oral cavity, so a daily intake is advised. In addition, synergistic combinations of probiotic bacteria should lead to higher clinical efficacy than any individual probiotic agent.

Before recommending probiotic use in daily dental practice and considering probiotics as a self-management preventive strategy or adjuvant/alternative therapy, additional large-scale, long-term, randomized, placebo-controlled clinical trials studies are needed to determine the most effective probiotic strain combinations, the most suitable probiotic vehicles, and the most appropriate dosage and frequency of administration. Further research is also needed on product compliance and acceptance by different age groups. Finally, a better understanding of the mechanisms of action of probiotics and of the host response to probiotics is needed. Algorithms matching person-specific data and known factors interfering with probiotic efficacy will allow the identification of the optimal probiotic modality for stratified populations or individuals [16].

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/app11178070/s1, Figure S1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram, Table S1: PRISMA checklist, Table S2: PICOS criteria, Table S3: Characteristics of clinical trials of probiotics in the oral ecosystem, Table S4: Characteristics of clinical trials of probiotics in gingivitis and gingival health, Table S5: Characteristics of clinical trials of probiotics in periodontal diseases, Table S6: Characteristics of clinical trials of probiotics in peri-implantitis, Table S7: Characteristics of clinical trials of probiotics in cariology, Table S8: Characteristics of clinical trials of probiotics in orthodontics, Table S9: Characteristics of clinical trials of probiotics in halitosis, Table S10: Characteristics of clinical trials of probiotics in oral wound healing and treatment of oral mucositis related to cancer treatment.

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