Review

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The Adjunctive Role of Probiotics in Periodontal Therapy: A Narrative Review

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Featured Application

This narrative review provides clinically relevant insights into the use of probiotics as adjunctive agents in periodontal therapy. By summarizing the protocols, strains, dosages, and administration routes investigated in animal and human studies, the findings may help guide clinicians and researchers in the development of more standardized and effective probiotic-based periodontal treatment strategies.

Abstract

Periodontitis is a chronic inflammatory disease driven by microbial dysbiosis and an exacerbated host immune response, leading to progressive periodontal tissue breakdown and contributing to systemic inflammation. Although scaling and root planing remains the standard treatment, its capacity to fully restore immune balance and host–microbiota homeostasis is limited. In this context, probiotics have emerged as promising adjunctive strategies capable of modulating immunological and metabolic pathways involved in disease progression. This narrative review aimed to evaluate current evidence regarding the use of probiotics in periodontal therapy. The review followed the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines. A literature search was conducted in MEDLINE via PubMed for manuscripts indexed up to January 2026 using MeSH-based terms related to periodontitis and probiotics. Evidence from preclinical and clinical studies suggests that probiotics may reduce alveolar bone loss and periodontal inflammation by downregulating proinflammatory mediators, enhancing anti-inflammatory cytokine production, strengthening epithelial barrier function, and modulating innate and adaptive immune responses. Additionally, probiotics may exert systemic effects through interactions with the gut microbiota, potentially improving metabolic regulation and reducing systemic inflammation. Overall, current evidence supports probiotics as biologically plausible adjuncts to periodontal therapy.

Keywords: probiotics; periodontitis; periodontal diseases

1. Introduction

Periodontal disease is a major public health concern, as demonstrated by recent analyses from the Global Burden of Disease Study 2021 [1,2]. Periodontitis is one of the most prevalent oral diseases, consistently ranked among the leading causes tooth loss in adults [1,2].

The etiology of periodontitis involves a dysbiotic biofilm dominated by periodontopathogenic bacteria such as *Porphyromonas gingivalis, Tannerella forsythia*, and *Fusobacterium nucleatum*, which trigger an exaggerated host immune response leading to periodontal tissue breakdown [3]. Beyond its local manifestations, periodontitis has been associated with systemic conditions such as diabetes

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mellitus, cardiovascular disease, and metabolic syndrome, suggesting a bidirectional relationship between oral and systemic health [4,5].

Conventional treatment strategies for periodontitis primarily involve mechanical debridement through scaling and root planning (SRP). While SRP effectively reduces the microbial burden, it does not fully restore microbial homeostasis or modulate the host immune response [6]. Adjunctive use of antimicrobials may provide additional benefits, but concerns about resistance and disruption of beneficial microbiota remain [7]. Consequently, alternative or complementary therapies have been explored to improve treatment outcomes [8].

More recently, probiotics have gained increasing interest as an adjunct to periodontal treatment. Probiotics are defined by the World Health Organization as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [9]. Probiotics have demonstrated therapeutic potential in periodontal therapy. Their mechanisms of action include competitive inhibition of pathogenic bacteria, enhancement of mucosal barrier integrity, modulation of cytokine production, and systemic immunometabolism effects [10–12]. Recent studies have investigated various strains such as *Lactobacillus reuteri, Bifidobacterium animalis* subsp. *lactis, Akkermansia muciniphila, Streptococcus cristatus, Lactobacillus rhamnosus*, and microbial consortia like milk kefir. These microorganisms are thought to exert beneficial effects not only locally within periodontal tissues but also systemically, by influencing gut microbiota, immune regulation, and metabolic pathways [10,13].

Evidence from preclinical studies in rodent and dog models indicates that probiotic administration can attenuate alveolar bone loss, reduce local and systemic inflammation, and modulate epigenetic and immunoregulatory pathways relevant to periodontal and systemic health [14–16]. In addition, clinical investigations have also yielded encouraging results, showing that the incorporation of specific probiotic regimens into non-surgical periodontal therapy or supportive periodontal care can significantly enhance clinical outcomes in individuals with periodontitis [17–19].

This narrative review aimed to evaluate the current evidence on the use of probiotics in periodontitis treatment, with a particular focus on the protocols employed in experimental animal and human studies, including strain selection, dosage, timing, mode of administration (surgical vs. non-surgical), preventive versus therapeutic approaches, and the systemic effects reported to date.

2. Materials and Methods

To ensure methodological rigor and quality, this narrative review was conducted in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) [20]. The SANRA instrument evaluates six key domains: (1) justification of the review's relevance, (2) clarity of the review objectives, (3) description of the literature search methodology, (4) appropriateness of referencing, (5) scientific reasoning, and (6) adequacy of data presentation [20].

To organize and select articles related to probiotics and periodontal disease, three authors (NCK, CJHM and ACPH) independently reviewed manuscripts indexed in the MEDLINE database and accessible through Pubmed. The terms were selected based on the literature and on descriptors indexed in MeSH (Medical Subject Headings), aiming to encompass different approaches to the use of probiotic strains in the context of periodontal diseases.

The search strategy for this narrative review was based on relevant and up-to-date literature related to probiotics and periodontal disease. The authors (NCK, CJHM and ACPH) considered all peer-reviewed studies published in English, including randomized controlled trials, clinical trials, case series, case reports, observational studies (case–control, cross-sectional, and cohort studies), in vitro and in vivo studies, meta-analyses, systematic reviews, narrative reviews, and other review articles. For this review, searches were conducted in PubMed up to January 05, 2026, using the following MeSH terms: Periodontitis AND probiotics; Periodontal diseases AND probiotics; Periodontitis AND Lactobacillus; Periodontal diseases AND Lactobacillus; Periodontitis AND Bifidobacterium; Periodontal diseases AND Bifidobacterium. The reference lists of the selected

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manuscripts were also screened. Relevant titles identified during this process prompted further examination of the corresponding articles. Articles providing additional pertinent information were subsequently included in the review.

3. Literature Review

3.1. Periodontitis

Periodontitis is a chronic multifactorial inflammatory disease that results in the destruction of tooth-supporting tissues [21,22]. Its etiology is understood to involve three essential factors: a susceptible host, the presence of periodontopathogens, and a reduction or absence of beneficial bacteria [23]. Conventional treatment of periodontitis includes biofilm control, subgingival instrumentation, and management of systemic risk factors [5]. Scaling and root planing (SRP) is performed to modify the subgingival microbial profile, reducing periodontopathogens and promoting colonization by health-compatible bacteria, thereby decreasing periodontal inflammation [24]. Clinical parameters have been proposed to indicate remission or disease control following active periodontal therapy. These include the presence of ≤ 4 sites with probing depth (PD) ≥ 5 mm [25] or shallow pockets (≤ 4 mm) without bleeding on probing (BOP) in individuals with less than 30% of periodontal sites exhibiting bleeding [26]. Such parameters are based on the premise that a lower proportion of residual periodontal pockets and reduced inflammation favor disease stability and minimize tooth loss over time [26]. Several factors may influence the outcomes of nonsurgical periodontal therapy, including the initial PD of treated sites, tooth anatomy, the presence of furcation lesions, operator skills, and increased patient susceptibility to disease [27,28]. Furthermore, periodontal sites remain susceptible to recolonization by periodontopathogens, often reestablishing the same microbiota observed prior to treatment [27,28]. Systemic and environmental risk factors, such as diabetes mellitus (DM) and smoking, as well as certain genetically inherited traits, can alter the host's immunoinflammatory response, thereby increasing susceptibility to periodontitis [29]. The host response plays a pivotal role in the pathogenesis of periodontitis [30], an inappropriate immunoinflammatory response may promote biofilm dysbiosis, favoring the proliferation of periodontopathogenic bacterial species and consequently increasing the risk of periodontal tissue destruction [23,30].

In cases where conventional periodontal therapy yields unsatisfactory clinical results, adjunctive therapies have been investigated to enhance disease control. In recent years, growing attention has been directed toward the role of beneficial oral microbiota and its potential application in both the prevention and treatment of periodontitis [31]. Increasing the population of beneficial bacteria through probiotics has been proposed as a promising strategy in the management of periodontal diseases. Probiotics may not only suppress pathogenic colonization but also modulate host immune responses, offering a low-rink and cost-effective adjunctive approach to periodontal therapy [32].

3.2. Probiotics

Probiotics are defined by the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [9]. Increasing evidence indicates that probiotics consumption may enhance the host's immune system and contribute to the prevention or treatment of several diseases [33], including diabetes, intestinal infections, respiratory tract infections, cardiovascular diseases, osteoporosis, urogenital infections, allergic reactions, rheumatoid arthritis, and halitosis, among others [34,35].

The primary goal of probiotics therapy is to suppress the emergence of endogenous pathogens, prevent superinfection by exogenous microorganisms, and protect the host by promoting a favorable immunoinflammatory response [32]. However, the optimal dosage of probiotics microorganisms is not easily determined, as it depends on the specific strain and the type of beneficial effect desired [36]. Evidence from both animal and human studies suggests that probiotics have emerged as either

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a potential monotherapy or an adjunctive therapy, although the underlying mechanisms remain poorly defined [16,37–39]. Their introduction into the oral microbiota may promote microbial balance, attenuate inflammation, and regulate host immune responses, thereby improving host–microbiota interactions [37].

Several mechanisms have been proposed to explain the beneficial effects of probiotics on human health [40–42]. These include immunological modulation, particularly of intestinal immune pathways, mucin production, downregulation of inflammatory responses, secretion of antimicrobial substances, competition with other microbiota through competitive exclusion at epithelial and mucosal adhesion sites, nutrient competition, inhibition of epithelial invasion via regulation of intestinal permeability, and stimulation of immunoglobulin production [43]. Certain probiotics strains may also enhance epithelial barrier function in intestinal cells and regulate genes encoding junctional proteins such as E-cadherin and β-catenin [40,43].

3.3. Probiotic Periodontal and Systemic Mechanisms of Action

In the context of periodontal disease, probiotics can exert direct effects on periodontopathogens by influencing their growth, adhesion, and colonization [44]. They produce bacteriocins and other bacterial metabolites that induce pathogen death or inhibit proliferation [44]. For example, lactobacilli generate organic acids (lactic and acetic acids) that suppress the growth of Gram-negative bacteria [44,45]. Additionally, probiotics compete with pathogens for nutrients and adhesion sites by binding directly to epithelial cells [44].

Another mechanism involves modulation of the host immunoinflammatory response [44]. Probiotics can influence gene expression related to immune pathways, inflammatory signaling, and immunological markers, including nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) in periodontal tissues [42]. Certain probiotics species have been shown to attenuate interleukin (IL)-8 expression induced by periodontopathogens in oral epithelial cells [46] and to reduce levels of pro-inflammatory cytokines (IL-8, IL-17, IL-1β, tumor necrosis factor-α (TNF-α)), neutrophil elastase activity, and concentrations of myeloperoxidase and matrix metalloproteinases (MMP)-3 in gingival crevicular fluid of patients with periodontal disease [47]. Moreover, probiotics can stimulate host cells to produce and release defensins, innate immune proteins that disrupt bacterial activity [41].

Taken together, these antimicrobial and immunomodulatory properties suggest that probiotics may represent a user-friendly, low-risk, and cost-effective adjunctive approach for achieving and maintaining periodontal health [16]. The mechanisms of probiotic action in periodontitis are illustrated in Figure 1.

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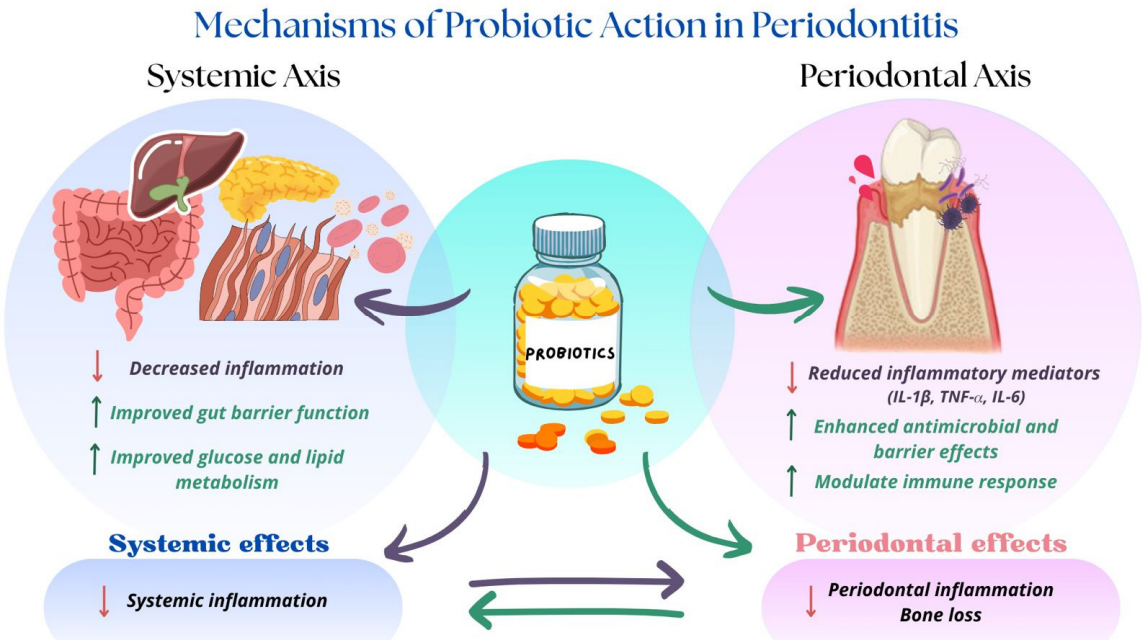

Figure 1. Mechanisms of probiotic action in Periodontitis.

3.4. Clinical Evidence

Several clinical studies have explored the effects of different probiotic regimens on both periodontal tissues and systemic parameters. Probiotic protocols used in clinical studies are summarized in Table 1. Clinical investigations in individuals with periodontitis have evaluated different probiotics regimens as adjuncts and, in several cases, demonstrated added benefits to SRP [17,48–51]. Among *Lactobacillus*-based formulations, the combination of *Limosilactobacillus reuteri* DSM 17938 and ATCC PTA 5289 has been the most extensively studied, consistently demonstrating superior reductions in PD, BOP, plaque index (PI) and gains in clinical attachment level (CAL) when used as adjuncts to non-surgical periodontal therapy [52–55]. This strain combination also delayed recolonization of periodontal pockets by anaerobic pathogens for up to 180 days [52,56], and a meta-analysis supported its use particularly in deep periodontal pockets [57]. It is important to highlight that probiotics effects depend strongly on the specific strain (or strain combinations), dosage, frequency, and route of administration employed [36]. Beyond the systemic or orally delivered formulations most studied, several investigations have also examined the local application of probiotics — using gels, dentifrices, mouthrinses, or subgingival irrigation solutions— in combination with SRP [58–60]. The most ext*ensively studied probiotics genera in Dentistry include Lactobacillus and* Bifidobacterium, which are naturally found in supra- and subgingival biofilms [36].

Table 1. Overview of Probotic Protocols in Clinical Trial Studies.

Study	Probiotic strain	Treatment type	Administration	Probiotic protocol
Riccia et al. (2007)[61]	*L. brevis* CD2	Probiotic only	Systemic	4x/day;4 days
Shimauchi et al. (2008)[48]	*L. salivarius*	Probiotic only	Systemic	3x/day, 8 weeks
Mayanagi et al. (2009)[62]	*L. salivarius* WB21	Probiotic only	Systemic	3x/day, 8 weeks
Vicario et al. (2013)[63]	*L. reuteri* ATCC 55730 and ATCCPTA 5289	Probiotic only	Systemic	1x/day, 30 days
Tlaet al. (2013)[37]	*L. reuteri* ATCC PTA 5289 and DSM 17938	SRP + probiotic	Systemic	2x/day, 12 weeks
Szkaradkiewicz et al. (2014)[47]	*L. reuteri* ATCC PTA 5289	SRP + probiotic	Systemic	2x/day, 2 weeks

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Laleman et al. (2015)[49]	*S. oralis* KJ3, S. *uberis* KJ2, *S. rattus* JH145	SRP + probiotic	Systemic	2x/day, 12 weeks
Ínce et al. (2015)[56]	*L. reuteri* ATCC PTA 5289 and DSM-17938	SRP + probiotic	Systemic	2x/day, 3 weeks
Tekce et al. (2015)[52]	*L. reuteri* ATCC PTA 5289 and DSM 17938	SRP + probiotic	Systemic	2x/day, 3 weeks
Morales et al. (2016)[65]	*L. rhamnosus* SP1	SRP + probiotic	Systemic	1x/day, 3 months
Morales et al. (2018)[83]	*L. rhamnosus* SP1	SRP + probiotic	Systemic	1x/day, 3 months
Dhaliwal et al. (2017)[66]	Multi strain	SRP + probiotic	Systemic	2x/day, 21 days
Invernici et al. (2018)[68]	*B. lactis* HN019	SRP + probiotic	Systemic	2x/day, 30 days
Sajedinejad et al. (2018)[69]	*L. salivarius*NK02	SRP + probiotic	Local	2x/day, 28 days
Laleman et al. (2020)[18]	*L. reuteri* ATCC PTA 5289 and DSM-17938	Re-instrumentation + probiotic	Systemic	2x/day, 12 weeks
Theodoro et al. (2019)[70]	*L. reuteri* ATCC PTA 5289 and DSM-17938	SRP + probiotic	Systemic	2x/day, 21 days
Yuki et al. (2019)[17]	*L. rhamnosus* L802	Probiotic only	Systemic	90 days
Vohra et al. (2020)[71]	*L. reuteri* ATCC PTA 5289 and DSM-17938	SRP + probiotic	Systemic	2x/day, 21 days
Kang et al. (2020)[50]	*Weissella cibaria*CMU	SRP + probiotic	Systemic	1x/day, 8 weeks
Invernici et al. (2020)[72]	*B. lactis* HN019	SRP + probiotic	Systemic	2x/day, 30 days
Minić et al. (2022)[60]	Multi strain formulation: *L. acidophilus, B. infantis* and *Enterococcus faecium*	SRP + local probiotic	Local	Daily for 5 days
Elsadek et al. (2020)[73]	*L. reuteri* ATCC PTA 5289 and DSM-17938	SRP + probiotic	Systemic	3x/day, 3 weeks
Nędzi-Góra et al. (2020)[74]	*L. salivarius* SGL03	Supportive therapy	Systemic	1x/day, 30 days
Pelekos et al. (2020)[53]	*L. reuteri* ATCC PTA 5289 and DSM-17938	SRP + probiotic	Systemic	2x/day, 28 days
Morales et al. (2021)[75]	*L. rhamnosus* SP1	SRP + probiotic	Systemic	1x/day, 3 months
Pudgar et al. (2021)[76]	*L. brevis*CECT7480 and *L. plantarum*CECT7481	SRP + probiotic	Local + systemic	1x/day, 3 months
Ramos et al. (2022)[77]	*L. reuteri* ATCC PTA 5289 and DSM-17938	SRP + probiotics	Systemic	2x/day, 21 days
Gullapelli & Koduganti (2023)[85]	Not specified	SRP + local probiotic delivery	Local	Single application post-SRP
Şahin et al. (2024)[79]	Multi strain tablets and Kefir	SRP + probiotic or Kefir	Systemic	1x/day, 14 days
Grusovin et al. (2020)[54]	*L. reuteri* ATCC PTA 5289 and DSM-17938	Supportive therapy	Systemic	2x/day; 3 months x 2 cycle with 3 months of washout

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Jardini et al. (2024)[81]	*L. reuteri* ATCC PTA 5289 and DSM-17938	SRP + probiotic	Systemic	2x/day, 21 days
Poulose et al. (2024)[51]	Multi strain (*S. faecalis, C. butyricum, B. mesentericus, L. sporogenes, S. boulardii*)	SRP + subgingival probiotic placement	Local	Single application
Bujaldón et al. (2026)[84]	*L. reuteri* ATCC PTA 5289 and DSM-17938	SRP + probiotic	Systemic	2x/day, 3 months

Among 38 clinical studies, 31 studies reported improvements in at least one key periodontal clinical parameter, PD, BOP, CAL, or PI, when compared with placebo or SRP alone [17,18,37,48,50–54,56,60–82]. Clinical trials evaluating *B. lactis* HN019 as an adjunct to SRP also demonstrated significant clinical benefits, including reductions in moderate and deep pockets, lower risk of disease progression, and decreased need for periodontal surgery [68,72]. Only 7 studies reported no significant added clinical benefit of probiotics over controls, although all showed improvements over baseline [12,17,73,77,83–85]. A summary of the effects of probiotics on periodontal clinical parameters is presented in Table 2.

Table 2. Influence of Probiotics on Periodontal Clinical Outcomes.

Clinical parameter	Effect vs. control	Clinical outcome (mean difference)	Authors	Follow-up timeframe (months)
PD (mean)	**+**	0.28 – 1.2 mm reduction	18,37,51,52,53,54,56,60,63,68,69,70	1–12
	N/A*	No statistically significant difference	17,48,49,65,66,71,73,74,75,76,77,81,83,84,85	3
CAL (mean)	**+**	0.11 – 0.8 mm gain	37,47,51,52,53,54,56,68	3–12
	N/A*	Comparable outcomes (no significant difference)	49,65,66,73,74,75,76,77,79,81,83,84	3
% BOP (mean)	**+**	Significant reduction in bleeding scores	52,54,56,60,63,68,72	1–12
	N/A*	No statistically significant difference	17,48,49,50,53,65,73,75,77,81,83,84	1–6

*N/A = no statistically significant intergroup difference.

A total of 14 studies assessed inflammatory and immunological biomarkers, among these, 12 studies reported significant reductions in proinflammatory mediators—including IL-1β, IL-6, IL-8, IL-17, TNF-α, MMP-8, and salivary lactoferrin—following probiotic therapy [48,50,52,56,61,64,66,68,69,72,81,85]. Studies with B. lactis HN019 further demonstrated upregulation of β-defensin-3, Toll-Like Receptor 4 (TLR4), and Cluster of Differentiation 4 (CD4), suggesting enhancement of the epithelial immune barrier [72]. Additionally, 6 studies documented increases in protective or regulatory mediators such as IL-10, IL-12, IL-16, β-defensin-3, TLR4, and CD4 [47,61,68,69,72,81].

Microbiological assessments were performed in 20 studies, of which 16 reported reductions in periodontal pathogens such as *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans,*

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Fusobacterium nucleatum, Prevotella intermedia, and red/orange-complex species [37,50–52,56,62,66,68,69,78,80,81]. The oral administration of Ligilactobacillus salivarius TI 2711 also significantly reduced *Porphyromonas gingivalis* levels and improved PD and BOP [86,87]. In 5 studies, probiotic strains were detected in subgingival biofilms for 60–180 days after supplementation, indicating transient colonization [52–54,56,68].

According to preventive vs. therapeutic protocols and delivery methods, 32 evaluated probiotics as adjuncts to SRP, while 6 tested probiotics as stand-alone therapy [17,48,61–63,80]. Adjunctive protocols were more consistently beneficial, with 27 of 32 studies showing superior outcomes compared with SRP alone. Local delivery systems (gels, mouthrinses, subgingival pastes) were tested in 8 studies, with 5 demonstrating significant short-term improvements [51,60,69,80,82].

3.5. Systemic Effects of Probiotics in Periodontal Therapy

The most consistent evidence supporting probiotics in the management of periodontitis comes from systemic administration, delivered in the form of lozenges, sachets, chewing gums, or functional foods. The systemic route offers the advantage of modulating the intestinal microbiome and restoring host–microorganism homeostasis, thereby preventing or correcting intestinal dysbiosis, which has been linked to multiple systemic conditions [88]. This is particularly relevant because individuals with periodontitis chronically ingest high loads of periodontal pathogens, a process that may contribute to gut dysbiosis [89]. Conversely, an altered intestinal microbiota may exacerbate periodontal tissue destruction, suggesting a bidirectional relationship between oral and gut ecosystems [5,88].

MOREIRA et al. (2023a) showed that *B. lactis* HN019 reduced experimental periodontitis sequelae while modulating intestinal microbiota, downregulating lipogenic genes, and decreasing hepatic steatosis [90]. These findings support the role of the gut-liver axis in the pathogenesis of periodontal disease. Similarly, MOREIRA et al. (2023b) demonstrated that probiotics improved the intestine–adipose tissue axis in rats with metabolic syndrome and periodontitis, reducing systemic inflammation and improving periodontal outcomes [91]. SILVA et al. (2022) confirmed these findings in another metabolic syndrome model, showing that probiotics attenuated systemic cytokines and alveolar bone loss in rats with experimental periodontitis [39]. SONG et al. (2023) provided evidence that *A. muciniphila* can counteract *Fusobacterium nucleatum*-induced periodontitis through immune modulation [92]. VIEIRA et al. (2021) found that kefir supplementation decreased systemic cytokines while attenuating local alveolar bone loss in rats with experimental periodontitis [93]. Collectively, these studies highlight the dual role of probiotics in modulating both periodontal and systemic health parameters, supporting their potential as therapeutic agents in systemic conditions associated with periodontal disease.

Clinical studies have also reported systemic effects of adjuvant use of probiotics in the treatment of periodontitis associated or not with other systemic conditions [68,84,93]. RICCIA et al. (2007) demonstrated that *L. brevis* CD2 lozenges reduced salivary nitrite/nitrate, prostaglandins, MMPs, and interferon-γ, indicating systemic anti-inflammatory activity [61]. INVERNICI et al. (2018) showed that *B. lactis* HN019 increased IL-10 and reduced IL-8 and IL-16 in gingival crevicular fluid, reflecting systemic cytokine modulation [68]. Later, the same authors confirmed that *B. lactis* HN019 strain enhanced β-defensin 3, TLR- 4, and CD4 expression in gingival tissues, suggesting improved epithelial barrier immunocompetence with systemic implications [72].

Animal studies have further reinforced these systemic effects. NIE et al. (2023) showed strain-specific effects in experimental models, with certain probiotics combinations reducing bone loss and enhancing immune responses, though variability across strains raises questions about reproducibility [94]. SILVA et al. (2023) reported that *L. rhamnosus* EM1107 prevented hyperglycemia, reduced systemic inflammation, and preserved alveolar bone in diabetic rats, highlighting the systemic metabolic impact of probiotics in comorbid conditions [95]. PAHUMUNTO et al. (2022), in a translational study combining in vitro and dog models, found that probiotics increased β-defensin expression and reduced IL-6 and IL-8, improving mucosal immunity [96]. These findings collectively

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suggest that probiotics may act through systemic immunomodulation and metabolic regulation, extending their benefits beyond the oral cavity.

In patients with type 2 DM and periodontitis, ELSADEK et al. (2020) observed that adjunctive *L. reuteri* supplementation reduced periodontal pathogens and improved clinical parameters, although glycated hemoglobin (HbA1c) reduction was significant only in the periodontal debridement group [73]. JARDINI et al. (2024) reported that *L. reuteri* (ATCC PTA 5289 and DSM-17938) lozenges increased IL-10, IL-12, and IL-16 levels in gingival crevicular fluid, while also improving lipid metabolism by reducing small low-density lipoprotein (LDL) particles and altering high-density lipoprotein (HDL) subfractions, but no effects were observed in HbA1c levels [81]. BUJALDÓN et al. (2025) further demonstrated that the same combination of *L. reuteri* strains and formulation significantly decreased HbA1c levels at 6 months in diabetic patients, reinforcing the potential of probiotics to improve glycemic control in systemic conditions associated with periodontitis [84].

Although both clinical and experimental studies consistently suggest that probiotics exerts beneficial effects on systemic health through immunomodulation, metabolic regulation, and microbial balance, not all trials have demonstrated uniform outcomes, some reported only transient or limited systemic effects [73,78].

The evaluation of preclinical studies consistently demonstrates that probiotics exert beneficial effects in modulating periodontitis, including reduced alveolar bone loss, attenuation of local inflammation, and improved periodontal healing [36,90,91,93]. These effects have been observed across different experimental models, including ligature-induced periodontitis, immunosuppression, and systemic comorbidities such as diabetes and metabolic syndrome, suggesting that probiotic efficacy involves a combination of local, systemic and immunomodulatory mechanisms [90,91].

Clinical evidence partially supports these findings. Among the most investigated strains, *L. reuteri* has shown consistent benefits, particularly as an adjunct to SRP [37,63,78]. Across clinical studies, adjunctive probiotic therapy was associated with a PD reduction ranging from 0.28 to 1.2 mm when compared with control groups [18,37,51–54,56,60,63,68–70]. These findings are in agreement with systematic reviews indicating that probiotics, particularly *L. reuteri*, may enhance PD reduction, especially in moderate to deep pockets during short- to medium-term follow-up (1–12 months) [57,97,98].

In addition to PD reduction, adjunctive probiotics were associated with modest CAL gain ranging from 0.11 to 0.8 mm [37,47,51–54,56,68]. However, the clinical relevance of these improvements should be interpreted with caution, as mean difference below 1 mm may not necessarily translate into meaningful long-term periodontal stability. Consistently, several randomized clinical trials reported no significant intergroup differences in CAL outcomes [49,65,66,73–77,79,81,83,84], highlighting variability in clinical response.

More recent work extended its impact to systemic pathways, demonstrating beneficial modulation of hepatic lipid metabolism and adipose tissue inflammation through gut–liver and gut–adipose axes [90,91,95]. These systemic improvements are of clinical relevance for patients with metabolic syndrome or diabetes, in whom systemic inflammation exacerbates periodontal breakdown. Importantly, both live and heat-killed strains were effective, as demonstrated by MORAES et al. (2020) [99], suggesting that viability is not always necessary for efficacy and pointing toward the therapeutic promise of postbiotics, which may be particularly relevant in immunocompromised patients.

A more consistent effect was observed for BOP, with several studies reporting significant reductions in gingival bleeding following probiotic use [52,54,56,60,63,68,72]. As BOP reflects gingival inflammation, these findings support the hypothesis that probiotics primarily exert anti-inflammatory and immunomodulatory effects. In contrast, other trials failed to demonstrate significant intergroup differences [17,48–50,65,77,81], suggesting that clinical outcomes may be influenced by baseline disease severity, oral hygiene, and host-related factors. Importantly, reductions in BOP without parallel CAL gain may indicate control of inflammation rather than true periodontal regeneration.

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Mechanistically, probiotics act through multiple pathways, including competition with pathogens for colonization niches and nutrients, production of antimicrobial peptides such as bacteriocins, and reinforcement of epithelial barrier function through mucin and tight-junction protein expression [36]. Immune modulation appears, with reductions in pro-inflammatory cytokines such as IL-1β and TNF-α and increased anti-inflammatory cytokines such as IL-10 and Transforming growth factor beta (TGF-β) [92,99,100]. Additionally, systemic effects have been described, particularly involving modulation of the gut–liver and gut–adipose axes, which may be relevant in patients with metabolic disorders [90,91,95]. These findings support the concept that probiotics may influence both local periodontal and systemic inflammatory pathways.

Despite these promising findings, important limitations must be considered. Clinical studies are highly heterogeneous regarding probiotic strains, dosage, administration routes, and treatment duration, limiting comparisons. Furthermore, several studies reported no additional clinical benefit compared with conventional therapy alone [49,65,66,74,76,81,84]. Studies with follow-up periods shorter than one month were not included in the present quantitative synthesis, as this timeframe is considered insufficient to detect meaningful changes in periodontal clinical parameters such as PD and CAL, which require tissue remodeling and healing over time [101]. Moreover, recent evidence suggests that improvements in inflammatory parameters may occur earlier than periodontal structural changes, reinforcing the notion that the short-term effects of probiotics are primarily anti-inflammatory [102,103].

Systematic reviews with meta-analyses have reported modest benefits of probiotics as adjuncts to periodontal therapy [98,104]. However, these effects appear to be more pronounced in sites with greater initial disease severity, particularly deep pockets (≥5 mm) [105]. Accordingly, current clinical guidelines do not support the routine use of probiotics as adjunctive therapy, although they acknowledge their safety and lack of significant adverse effects [5].

Taken together, current evidence suggests that probiotics may serve as adjunctive agents in periodontal therapy. The variability in clinical outcomes highlights the importance of strain specificity, dosage, administration, rout, and patient-related factors. Future research should focus on well—designed clinical trials with standardized protocols and longer follow-up periods to determine the optimal therapeutic approach and to clarify the long-term clinical relevance of probiotic use in periodontitis.

Other probiotics also demonstrated promising outcomes, *Akkermansia muciniphila*, for example, reduced bone loss and modulated immune responses in a *Fusobacterium nucleatum*-induced periodontitis model [92]. *S. cristatus* exhibited both preventive and therapeutic potential, reducing TNF-α and IL-1β expression while preserving alveolar bone [106]. *L. rhamnosus* was particularly effective in a diabetic rat model, preventing hyperglycemia, inflammation, and alveolar bone loss, and thus offering promise for patient populations with systemic metabolic dysregulation [95]. Food-based approaches, such as milk kefir, also demonstrated efficacy by reducing local inflammation and improving bone levels [93]. Furthermore, translational studies in gingival epithelial cells and a dog model indicated that probiotics can stimulate β-defensins and suppress IL-6 and IL-8, suggesting both epithelial barrier reinforcement and potential clinical applicability [96].

Emerging evidence also points to possible immunoepigenetic implications. The modulation of inflammatory and lipogenic gene expression observed in *B. animalis* studies suggests that probiotics may induce transcriptional reprogramming. This raises the hypothesis that probiotics or their metabolites might influence the epigenetic landscape of tissue-resident memory T cells, which play a central role in the chronicity of periodontal inflammation [107]. Such interactions could be studied using advanced tools such as ATAC-seq or ChIP-qPCR to evaluate chromatin accessibility and histone modifications, ultimately providing deeper mechanistic insights.

Future Directions

Future studies should prioritize mechanistically oriented and translational approaches to elucidate how probiotics modulate immune and metabolic pathways involved in periodontal disease. Standardized preclinical models integrating immunological, molecular, and metabolic analyses are

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needed to define strain-specific effects on host immunity, osteoimmune regulation, and epithelial barrier function, including the potential role of postbiotics. In parallel, well-designed clinical trials with harmonized probiotic formulations, dosing regimens, and timing relative to periodontal therapy should incorporate immunometabolic biomarkers in addition to clinical parameters. Greater emphasis on systemic interactions, particularly within the gut–metabolic–oral axis, and on the long-term durability of probiotic-induced host modulation will be essential to advance probiotics as evidence-based adjuncts in periodontal therapy.

5. Conclusions

Probiotics show promising potential as adjunctive agents in periodontal therapy, exerting both local and systemic effects through immunomodulation, metabolic regulation, and microbial balance. The heterogeneity in strains, CFU concentrations, administration routes, and treatment durations underscores the need for standardized protocols to ensure reproducibility and maximize clinical efficacy.

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Abbreviations

The following abbreviations are used in this manuscript:

SRP	scaling and root planning
SANRA	scale for the assessment of narrative review articles
Medical Subject Headings	medical subject headings
PD	probing depth
BOP	bleeding on probing
DM	diabetes mellitus
WHO	world health organization
FAO	food and agriculture organization of the united nations
NF-κB	nuclear factor kappa b
MAPK	mitogen-activated protein kinase
IL-	interleukin
TNF-α	tumor necrosis factor-α
MMP-	matrix metalloproteinases
PI	plaque index
CAL	clinical attachment level
TLR4	toll-like receptor 4
CD	cluster of differentiation
HbA1c	glycated hemoglobin
LDL	low-density lipoprotein
HDL	high-density lipoprotein
TGF-β	transforming growth factor beta
CFU	colony-forming units

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References

1. Liang X, Lyu Y, Li J, Li Y, Chi C. Global, regional, and national burden of preterm birth, 1990-2021: a systematic analysis from the global burden of disease study 2021. *EClinicalMedicine* **2024**;76:102840.
2. Wu L, Huang CM, Wang Q, Wei J, Xie L, Hu CY. Burden of severe periodontitis: new insights based on a systematic analysis from the Global Burden of Disease Study 2021. *BMC Oral Health* **2025**;25(1):861.
3. Socransky SS, Haffajee AD. Periodontal microbial ecology. *Periodontol 2000* **2005**;38:135-87.
4. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *J Periodontol* **2018**;89 Suppl 1:S159-s72.
5. Sanz M, Herrera D, Kebschull M, Chapple I, Jepsen S, Beglundh T, et al. Treatment of stage I-III periodontitis-The EFP S3 level clinical practice guideline. *J Clin Periodontol* **2020**;47 Suppl 22(Suppl 22):4-60.
6. Darby I. Risk factors for periodontitis & peri-implantitis. *Periodontol 2000* **2022**;90(1):9-12.
7. Jepsen K, Jepsen S. Antibiotics/antimicrobials: systemic and local administration in the therapy of mild to moderately advanced periodontitis. *Periodontol 2000* **2016**;71(1):82-112.
8. Botelho J, Lyra P, Nascimento GG, Leite FRM, Mendes JJ, Machado V. Antibiotics in periodontal treatment: an umbrella review. *Front Cell Infect Microbiol* **2025**;15:1601464.
9. Food and Agricultural Organization of the United Nations and World Health Organization. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. *World Health Organization*, **2001**. Avalilable online: https://openknowledge.fao.org/server/api/core/bitstreams/382476b3-4d54-4175-803f-2f26f3526256/content (accessed on 10 March, 2026).
10. Tan J, Zhang D, Cheng L, Liu N, Jamali M, Jamloo H, et al. The Impacts of Probiotics Supplementation on the Treatment of Periodontitis: An Umbrella Meta-Analysis. *Nutr Rev* **2026**;84(2):379-94.
11. Sachelarie L, Scrobota I, Romanul I, Iurcov R, Potra Cicalau GI, Todor L. Probiotic Therapy as an Adjuvant in the Treatment of Periodontal Disease: An Innovative Approach. *Medicina (Kaunas)* **2025**;61(1).
12. Laleman I, Teughels W. Probiotics in the dental practice: a review. *Quintessence Int* **2015**;46(3):255-64.
13. Mendonça CD, Mata A, Azevedo LFR, Marques JF, Silveira JML, Marques D. Probiotics in the non-surgical treatment of periodontitis: a systematic review and network meta-analysis. *BMC Oral Health* **2024**;24(1):1224.
14. Alasbily H, Mohamed HH, Asheibi A, Bazina MS, Alkaseh A, Ghaith HM, et al. Probiotics in Periodontal Diseases: Mechanisms, Evidence Mapping, Limitations, and Future Directions. *Cureus* **2025**;17(11):e96042.
15. Zhang M, Liu Y, Afzali H, Graves DT. An update on periodontal inflammation and bone loss. *Front Immunol* **2024**;15:1385436.
16. Gatej SM, Marino V, Bright R, Fitzsimmons TR, Gully N, Zilm P, et al. Probiotic Lactobacillus rhamnosus GG prevents alveolar bone loss in a mouse model of experimental periodontitis. *J Clin Periodontol* **2018**;45(2):204-12.
17. Yuki O, Furutani C, Mizota Y, Wakita A, Mimura S, Kihara T, et al. Effect of bovine milk fermented with Lactobacillus rhamnosus L8020 on periodontal disease in individuals with intellectual disability: a randomized clinical trial. *J Appl Oral Sci* **2019**;27:e20180564.
18. Laleman I, Pauwels M, Quirynen M, Teughels W. A dual-strain Lactobacilli reuteri probiotic improves the treatment of residual pockets: A randomized controlled clinical trial. *J Clin Periodontol* **2020**;47(1):43-53.
19. Mensi M, Sordillo A, Marchetti S, Calza S, Scotti E. Clinical Comparison of Guided Biofilm Therapy and Scaling and Root Planing in the Active Phase of Periodontitis Management. *Eur J Dent* **2025**;19(2):482-92.
20. Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev* **2019**;4:5.
21. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Periodontol* **2018**;89 Suppl 1:S173-s82.
22. Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, et al. A new classification scheme for periodontal and peri-implant diseases and conditions - Introduction and key changes from the 1999 classification. *J Clin Periodontol* **2018**;45 Suppl 20:S1-s8.

 doi:10.20944/preprints202603.1076.v1

23. Bartold PM, Van Dyke TE. Host modulation: controlling the inflammation to control the infection. *Periodontol 2000* **2017**;75(1):317-29.
24. Mombelli A. Microbial colonization of the periodontal pocket and its significance for periodontal therapy. *Periodontol 2000* **2018**;76(1):85-96.
25. Feres M, Retamal-Valdes B, Faveri M, Duarte P, Shibli J, Soares GMS, et al. Proposal of a Clinical Endpoint for Periodontal Trials: The Treat-to-Target Approach. *J Int Acad Periodontol* **2020**;22(2):41-53.
26. Loos BG, Needleman I. Endpoints of active periodontal therapy. *J Clin Periodontol* **2020**;47 Suppl 22(Suppl 22):61-71.
27. Gellin RG, Miller MC, Javed T, Engler WO, Mishkin DJ. The effectiveness of the Titan-S sonic scaler versus curettes in the removal of subgingival calculus. A human surgical evaluation. *J Periodontol* **1986**;57(11):672-80.
28. Adriaens PA, Adriaens LM. Effects of nonsurgical periodontal therapy on hard and soft tissues. *Periodontol 2000* **2004**;36:121-45.
29. Salvi GE, Lang NP. Host response modulation in the management of periodontal diseases. *J Clin Periodontol* **2005**;32 Suppl 6:108-29.
30. Marsh PD, Devine DA. How is the development of dental biofilms influenced by the host? *J Clin Periodontol* **2011**;38 Suppl 11:28-35.
31. Furlaneto F, Ishikawa KH, Messora MR, Mayer MPA. Probiotics During the Therapeutic Management of Periodontitis. *Adv Exp Med Biol* **2022**;1373:353-75.
32. Messora MR, Pereira LJ, Foureaux R, Oliveira LF, Sordi CG, Alves AJ, et al. Favourable effects of Bacillus subtilis and Bacillus licheniformis on experimental periodontitis in rats. *Arch Oral Biol* **2016**;66:108-19.
33. Markowiak P, Śliżewska K. Effects of Probiotics, Prebiotics, and Synbiotics on Human Health. *Nutrients* **2017**;9(9).
34. Martinez RC, Bedani R, Saad SM. Scientific evidence for health effects attributed to the consumption of probiotics and prebiotics: an update for current perspectives and future challenges. *Br J Nutr* **2015**;114(12):1993-2015.
35. Cuthill S, Muroke V, Dubois A, Dubé MP, Guertin MC, Millette M, et al. Effect of probiotic supplementation on glycemic control in patients with type 2 diabetes: A randomized controlled trial. *Clin Nutr ESPEN* **2025**;68:148-52.
36. Ricoldi MST, Furlaneto FAC, Oliveira LFF, Teixeira GC, Pischiotini JP, Moreira ALG, et al. Effects of the probiotic Bifidobacterium animalis subsp. lactis on the non-surgical treatment of periodontitis. A histomorphometric, microtomographic and immunohistochemical study in rats. *PLoS One* **2017**;12(6):e0179946.
37. Teughels W, Durukan A, Ozcelik O, Pauwels M, Quirynen M, Haytac MC. Clinical and microbiological effects of Lactobacillus reuteri probiotics in the treatment of chronic periodontitis: a randomized placebo-controlled study. *J Clin Periodontol* **2013**;40(11):1025-35.
38. Foureaux Rde C, Messora MR, de Oliveira LF, Napimoga MH, Pereira AN, Ferreira MS, et al. Effects of probiotic therapy on metabolic and inflammatory parameters of rats with ligature-induced periodontitis associated with restraint stress. *J Periodontol* **2014**;85(7):975-83.
39. Silva GA, Moreira ALG, Silva PHF, Salvador SL, Casarin RCV, Vicente RM, et al. The use of probiotics can reduce the severity of experimental periodontitis in rats with metabolic syndrome: An immunoenzymatic and microtomographic study. *J Periodontol* **2022**;93(2):e1-e12.
40. Meurman JH. Probiotics: do they have a role in oral medicine and dentistry? *Eur J Oral Sci* **2005**;113(3):188-96.
41. Homayouni Rad A, Torab R, Ghalibaf M, Norouzi S, Mehrabany EV. Might patients with immune-related diseases benefit from probiotics? *Nutrition* **2013**;29(3):583-6.
42. Bedaiwi MK, Inman RD. Microbiome and probiotics: link to arthritis. *Curr Opin Rheumatol* **2014**;26(4):410-5.
43. Saavedra JM, Abi-Hanna A, Moore N, Yolken RH. Long-term consumption of infant formulas containing live probiotic bacteria: tolerance and safety. *Am J Clin Nutr* **2004**;79(2):261-7.
44. Stamatova I, Meurman JH. Probiotics: health benefits in the mouth. *Am J Dent* **2009**;22(6):329-38.

 doi:10.20944/preprints202603.1076.v1

45. de Melo Pereira GV, de Oliveira Coelho B, Magalhães Júnior AI, Thomaz-Soccol V, Soccol CR. How to select a probiotic? A review and update of methods and criteria. *Biotechnol Adv* **2018**;36(8):2060-76.
46. Sliepen I, Van Essche M, Loozen G, Van Eldere J, Quirynen M, Teughels W. Interference with Aggregatibacter actinomycetemcomitans: colonization of epithelial cells under hydrodynamic conditions. *Oral Microbiol Immunol* **2009**;24(5):390-5.
47. Szkaradkiewicz AK, Stopa J, Karpiński TM. Effect of oral administration involving a probiotic strain of Lactobacillus reuteri on pro-inflammatory cytokine response in patients with chronic periodontitis. *Arch Immunol Ther Exp (Warsz)* **2014**;62(6):495-500.
48. Shimauchi H, Mayanagi G, Nakaya S, Minamibuchi M, Ito Y, Yamaki K, et al. Improvement of periodontal condition by probiotics with Lactobacillus salivarius WB21: a randomized, double-blind, placebo-controlled study. *J Clin Periodontol* **2008**;35(10):897-905.
49. Laleman I, Yilmaz E, Ozcelik O, Haytac C, Pauwels M, Herrero ER, et al. The effect of a streptococci containing probiotic in periodontal therapy: a randomized controlled trial. *J Clin Periodontol* **2015**;42(11):1032-41.
50. Kang MS, Lee DS, Lee SA, Kim MS, Nam SH. Effects of probiotic bacterium Weissella cibaria CMU on periodontal health and microbiota: a randomised, double-blind, placebo-controlled trial. *BMC Oral Health* **2020**;20(1):243.
51. Poulose M, Gujar D, Panicker S, Rokade S, Guruprasad M, Gopalakrishnan D. Efficacy and Viability of Subgingival Application of Probiotics as an Adjunct to Scaling and Root Planing in Periodontitis. *Indian J Dent Res* **2024**;35(1):59-64.
52. Tekce M, Ince G, Gursoy H, Dirikan Ipci S, Cakar G, Kadir T, et al. Clinical and microbiological effects of probiotic lozenges in the treatment of chronic periodontitis: a 1-year follow-up study. *J Clin Periodontol* **2015**;42(4):363-72.
53. Pelekos G, Acharya A, Eiji N, Hong G, Leung WK, McGrath C. Effects of adjunctive probiotic L. reuteri lozenges on S/RSD outcomes at molar sites with deep pockets. *J Clin Periodontol* **2020**;47(9):1098-107.
54. Grusovin MG, Bossini S, Calza S, Cappa V, Garzetti G, Scotti E, et al. Clinical efficacy of Lactobacillus reuteri-containing lozenges in the supportive therapy of generalized periodontitis stage III and IV, grade C: 1-year results of a double-blind randomized placebo-controlled pilot study. *Clin Oral Investig* **2020**;24(6):2015-24.
55. El-Bagoory GKM, El-Guindy HM, Shoukheba MYM, El-Zamarany EA. The adjunctive effect of probiotics to nonsurgical treatment of chronic periodontitis: A randomized controlled clinical trial. *J Indian Soc Periodontol* **2021**;25(6):525-31.
56. İnce G, Gürsoy H, İpçi Ş D, Cakar G, Emekli-Alturfan E, Yılmaz S. Clinical and Biochemical Evaluation of Lozenges Containing Lactobacillus reuteri as an Adjunct to Non-Surgical Periodontal Therapy in Chronic Periodontitis. *J Periodontol* **2015**;86(6):746-54.
57. Martin-Cabezas R, Davideau JL, Tenenbaum H, Huck O. Clinical efficacy of probiotics as an adjunctive therapy to non-surgical periodontal treatment of chronic periodontitis: a systematic review and meta-analysis. *J Clin Periodontol* **2016**;43(6):520-30.
58. Dassi E, Ferretti P, Covello G, Bertorelli R, Denti MA, De Sanctis V, et al. The short-term impact of probiotic consumption on the oral cavity microbiome. *Sci Rep* **2018**;8(1):10476.
59. Ranjith A, Nazimudeen NB, Baiju KV. Probiotic mouthwash as an adjunct to mechanical therapy in the treatment of stage II periodontitis: A randomized controlled clinical trial. *Int J Dent Hyg* **2022**;20(2):415-21.
60. Minić I, Pejčić A, Bradić-Vasić M. Effect of the local probiotics in the therapy of periodontitis A randomized prospective study. *Int J Dent Hyg* **2022**;20(2):401-7.
61. Riccia DN, Bizzini F, Perilli MG, Polimeni A, Trinchieri V, Amicosante G, et al. Anti-inflammatory effects of Lactobacillus brevis (CD2) on periodontal disease. *Oral Dis* **2007**;13(4):376-85.
62. Mayanagi G, Kimura M, Nakaya S, Hirata H, Sakamoto M, Benno Y, et al. Probiotic effects of orally administered Lactobacillus salivarius WB21-containing tablets on periodontopathic bacteria: a double-blinded, placebo-controlled, randomized clinical trial. *J Clin Periodontol* **2009**;36(6):506-13.

 doi:10.20944/preprints202603.1076.v1

63. Vicario M, Santos A, Violant D, Nart J, Giner L. Clinical changes in periodontal subjects with the probiotic Lactobacillus reuteri Prodentis: a preliminary randomized clinical trial. *Acta Odontol Scand* **2013**;71(3-4):813-9.
64. Szkaradkiewicz AK, Stopa J, Karpiński TM. Effect of oral administration involving a probiotic strain of Lactobacillus reuteri on pro-inflammatory cytokine response in patients with chronic periodontitis. *Arch Immunol Ther Exp (Warsz)* **2014**;62(6):495-500.
65. Morales A, Carvajal P, Silva N, Hernandez M, Godoy C, Rodriguez G, et al. Clinical Effects of Lactobacillus rhamnosus in Non-Surgical Treatment of Chronic Periodontitis: A Randomized Placebo-Controlled Trial With 1-Year Follow-Up. *J Periodontol* **2016**;87(8):944-52.
66. Dhaliwal PK, Grover V, Malhotra R, Kapoor A. Clinical and Microbiological Investigation of the Effects of Probiotics Combined with Scaling and Root Planing in the Management of Chronic Periodontitis: A Randomized, Controlled Study. *J Int Acad Periodontol* **2017**;19(3):101-8.
67. Galofré M, Palao D, Vicario M, Nart J, Violant D. Clinical and microbiological evaluation of the effect of Lactobacillus reuteri in the treatment of mucositis and peri-implantitis: A triple-blind randomized clinical trial. *J Periodontal Res* **2018**;53(3):378-90.
68. Invernici MM, Salvador SL, Silva PHF, Soares MSM, Casarin R, Palioto DB, et al. Effects of Bifidobacterium probiotic on the treatment of chronic periodontitis: A randomized clinical trial. *J Clin Periodontol* **2018**;45(10):1198-210.
69. Sajedinejad N, Paknejad M, Houshmand B, Sharafi H, Jelodar R, Shahbani Zahiri H, et al. Lactobacillus salivarius NK02: a Potent Probiotic for Clinical Application in Mouthwash. *Probiotics Antimicrob Proteins* **2018**;10(3):485-95.
70. Theodoro LH, Cláudio MM, Nuernberg MAA, Miessi DMJ, Batista JA, Duque C, et al. Effects of Lactobacillus reuteri as an adjunct to the treatment of periodontitis in smokers: randomised clinical trial. *Benef Microbes* **2019**;10(4):375-84.
71. Vohra F, Bukhari IA, Sheikh SA, Albaijan R, Naseem M, Hussain M. Effectiveness of scaling and root planing with and without adjunct probiotic therapy in the treatment of chronic periodontitis among shamma users and non-users: A randomized controlled trial. *J Periodontol* **2020**;91(9):1177-85.
72. Invernici MM, Furlaneto FAC, Salvador SL, Ouwehand AC, Salminen S, Mantziari A, et al. Bifidobacterium animalis subsp lactis HN019 presents antimicrobial potential against periodontopathogens and modulates the immunological response of oral mucosa in periodontitis patients. *PLoS One* **2020**;15(9):e0238425.
73. Elsadek MF, Ahmed BM, Alkhawtani DM, Zia Siddiqui A. A comparative clinical, microbiological and glycemic analysis of photodynamic therapy and Lactobacillus reuteri in the treatment of chronic periodontitis in type-2 diabetes mellitus patients. *Photodiagnosis Photodyn Ther* **2020**;29:101629.
74. NĘdzi-GÓra M, WrÓblewska M, GÓrska R. The Effect of Lactobacillus salivarius SGL03 on Clinical and Microbiological Parameters in Periodontal Patients. *Pol J Microbiol* **2020**;69(4):441-51.
75. Morales A, Contador R, Bravo J, Carvajal P, Silva N, Strauss FJ, et al. Clinical effects of probiotic or azithromycin as an adjunct to scaling and root planning in the treatment of stage III periodontitis: a pilot randomized controlled clinical trial. *BMC Oral Health* **2021**;21(1):12.
76. Pudgar P, Povšič K, Čuk K, Seme K, Petelin M, Gašperšič R. Probiotic strains of Lactobacillus brevis and Lactobacillus plantarum as adjunct to non-surgical periodontal therapy: 3-month results of a randomized controlled clinical trial. *Clin Oral Investig.* **2021**;25(3):1411-22.
77. Ramos TCS, Boas MLV, Nunes CMM, Ferreira CL, Pannuti CM, Santamaria MP, et al. Effect of systemic antibiotic and probiotic therapies as adjuvant treatments of subgingival instrumentation for periodontitis: a randomized controlled clinical study. *J Appl Oral Sci* **2022**;30:e20210583.
78. Salinas-Azuceno C, Martínez-Hernández M, Maldonado-Noriega JI, Rodríguez-Hernández AP, Ximenez-Fyvie LA. Probiotic Monotherapy with Lactobacillus reuteri (Prodentis) as a Coadjutant to Reduce Subgingival Dysbiosis in a Patient with Periodontitis. *Int J Environ Res Public Health* **2022**;19(13).
79. Şahin T, Akca G, Özmeriç N. The role of probiotics for preventing dysbiosis in periodontal disease: a randomized controlled trial. *Turk J Med Sci* **2024**;54(1):357-65.

 doi:10.20944/preprints202603.1076.v1

80. Boyapati R, Peeta J, Dhulipalla R, Kolaparthy L, Adurty C, Cheruvu RNS. Comparative evaluation of the efficacy of probiotic, Aloe vera, povidine-iodine, and chlorhexidine mouthwashes in the treatment of gingival inflammation: A randomized controlled trial. *Dent Med Probl* **2024**;61(2):181-90.
81. Jardini MAN, Pedroso JF, Ferreira CL, Nunes CMM, Reichert CO, Aldin MN, et al. Effect of adjuvant probiotic therapy (Lactobacillus reuteri) in the treatment of periodontitis associated with diabetes mellitus: clinical, controlled, and randomized study. *Clin Oral Investig* **2024**;28(1):80.
82. Manas A, Swain JR, Kantale SA, R N, S JP, Seshadri PR, et al. Probiotics, tetracycline fibres and chlorhexidine gel's effectiveness in treating chronic periodontitis as a supplement to scaling and root planning. *Bioinformation* **2024**;20(8):933-7.
83. Morales A, Gandolfo A, Bravo J, Carvajal P, Silva N, Godoy C, et al. Microbiological and clinical effects of probiotics and antibiotics on nonsurgical treatment of chronic periodontitis: a randomized placebo-controlled trial with 9-month follow-up. *J Appl Oral Sci* **2018**;26:e20170075.
84. Bujaldón R, Montero E, Gamonal JD, Abuelo A, Marín MJ, Iniesta M, et al. Use of the Probiotic Limosilactobacillus reuteri as an Adjunct to Subgingival Instrumentation in the Treatment of Periodontitis Patients With Diabetes: A Randomised Clinical Trial. *J Clin Periodontol* **2026**;53(1):26-36.
85. Gullapelli P, Koduganti RR. Efficacy of Probiotics Versus Tetracycline Fibers as Adjuvants to Scaling and Root Planing on Interleukin 1β Levels in Type 2 Diabetic Patients With Periodontitis: A Clinical and Biochemical Study. *Cureus* **2023**;15(12):e50968.
86. Kobayashi R, Kobayashi T, Sakai F, Hosoya T, Yamamoto M, Kurita-Ochiai T. Oral administration of Lactobacillus gasseri SBT2055 is effective in preventing Porphyromonas gingivalis-accelerated periodontal disease. *Sci Rep* **2017**;7(1):545.
87. Myneni SR, Brocavich K, H HW. Biological strategies for the prevention of periodontal disease: Probiotics and vaccines. *Periodontol 2000* **2020**;84(1):161-75.
88. Wade WG. The oral microbiome in health and disease. *Pharmacol Res* **2013**;69(1):137-43.
89. Lourenço TGB, Spencer SJ, Alm EJ, Colombo APV. Defining the gut microbiota in individuals with periodontal diseases: an exploratory study. *J Oral Microbiol* **2018**;10(1):1487741.
90. Moreira ALG, Silva GA, Silva PHF, Salvador SL, Vicente RM, Ferreira GC, et al. Bifidobacterium animalis subspecies lactis HN019 can reduce the sequelae of experimental periodontitis in rats modulating intestinal parameters, expression of lipogenic genes, and levels of hepatic steatosis. *J Periodontal Res* **2023A**;58(5):1006-19.
91. Moreira ALG, Silva PHF, Salvador SL, Ishikawa KH, Ferreira GC, Tanus-Santos JE, et al. Effects of probiotics in rats with experimental metabolic syndrome and periodontitis: An investigation of the intestine-adipose tissue axis. *J Periodontol* **2023B**;94(11):1363-75.
92. Song B, Xian W, Sun Y, Gou L, Guo Q, Zhou X, et al. Akkermansia muciniphila inhibited the periodontitis caused by Fusobacterium nucleatum. *NPJ Biofilms Microbiomes* **2023**;9(1):49.
93. Vieira LV, de Sousa LM, Maia TAC, Gusmão J, Goes P, Pereira KMA, et al. Milk Kefir therapy reduces inflammation and alveolar bone loss on periodontitis in rats. *Biomed Pharmacother* **2021**;139:111677.
94. Nie Q, Wan X, Tao H, Yang Q, Zhao X, Liu H, et al. Multi-function screening of probiotics to improve oral health and evaluating their efficacy in a rat periodontitis model. *Front Cell Infect Microbiol* **2023**;13:1261189.
95. Silva DNA, Cruz NTS, Martins AA, Silva RCM, Almeida HC, Costa HES, et al. Probiotic Lactobacillus rhamnosus EM1107 prevents hyperglycemia, alveolar bone loss, and inflammation in a rat model of diabetes and periodontitis. *J Periodontol* **2023**;94(3):37688.
96. Pahumunto N, Duangnumsawang Y, Teanpaisan R. Effects of potential probiotics on the expression of cytokines and human β-defensins in human gingival epithelial cells and in vivo efficacy in a dog model. *Arch Oral Biol* **2022**;142:105513.
97. Inchingolo F, Inchingolo AM, Malcangi G, De Leonardis N, Sardano R, Pezzolla C, et al. The Benefits of Probiotics on Oral Health: Systematic Review of the Literature. *Pharmaceuticals (Basel)* **2023**;16(9).
98. Ikram S, Hassan N, Raffat MA, Mirza S, Akram Z. Systematic review and meta-analysis of double-blind, placebo-controlled, randomized clinical trials using probiotics in chronic periodontitis. *J Investig Clin Dent* **2018**;9(3):e12338.

 doi:10.20944/preprints202603.1076.v1

99. Moraes RM, Lescura CM, Milhan NVM, Ribeiro JL, Silva FA, Anbinder AL. Live and heat-killed Lactobacillus reuteri reduce alveolar bone loss on induced periodontitis in rats. *Arch Oral Biol* **2020**;119:104894.
100. Oliveira LF, Salvador SL, Silva PH, Furlaneto FA, Figueiredo L, Casarin R, et al. Benefits of Bifidobacterium animalis subsp. lactis Probiotic in Experimental Periodontitis. *J Periodontol* **2017**;88(2):197-208.
101. Lang NP, Bartold PM. Periodontal health. *J Periodontol* **2018**;89 Suppl 1:S9-s16.
102. Liu S, Song T, Zhao J, Yao J. Effect of probiotics combined with periodontal basic therapy on inflammatory factors in gingival crevicular fluid in patients with moderate periodontitis. *Medicine (Baltimore)* **2025**;104(52):e46471
103. Hromcik F, Holochova P, Bohm J, Kuzelova Kostakova E, Pokorny Z, Ruzicka F, et al. Probiotic-Containing Nanofiber-Based Dental Floss Suppresses Subgingival Red Complex Periopathogens: A Randomized Double-Blind Crossover Trial. *Probiotics Antimicrob Proteins* **2026**.
104. Gheisary Z, Mahmood R, Harri Shivanantham A, Liu J, Lieffers JRL, Papagerakis P, et al. The Clinical, Microbiological, and Immunological Effects of Probiotic Supplementation on Prevention and Treatment of Periodontal Diseases: A Systematic Review and Meta-Analysis. *Nutrients* **2022**;14(5).
105. Ho SN, Acharya A, Sidharthan S, Li KY, Leung WK, McGrath C, et al. A Systematic Review and Meta-analysis of Clinical, Immunological, and Microbiological Shift in Periodontitis After Nonsurgical Periodontal Therapy With Adjunctive Use of Probiotics. *J Evid Based Dent Pract* **2020**;20(1):101397.
106. Zhao D, Li MH, Pan T, Guo J, Li J, Shi C, et al. Preventive and Therapeutic Potential of Streptococcus cristatus CA119 in Experimental Periodontitis in Rats. *Probiotics Antimicrob Proteins* **2024**.
107. Graves DT, Oates T, Garlet GP. Review of osteoimmunology and the host response in endodontic and periodontal lesions. *J Oral Microbiol* **2011**;3.