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Effectiveness of Oral Microbiome-Targeted Probiotics in Reducing Systemic Inflammation and Periodontal Disease Progression

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ABSTRACT

Background: Periodontal disease is a chronic inflammatory condition associated with oral microbial dysbiosis and exaggerated host immune responses. Conventional non-surgical periodontal therapy, primarily scaling and root planing (SRP), may not fully address persistent dysbiosis and inflammation in susceptible individuals. Oral microbiome-targeted probiotics have emerged as a potential adjunctive strategy to improve clinical outcomes and modulate inflammatory pathways in periodontitis. **Objective:** To evaluate the effectiveness of oral microbiome-targeted probiotics in improving periodontal clinical parameters and modulating inflammatory biomarkers in patients with chronic periodontitis. **Methods:** A systematic review and meta-analysis was conducted according to PRISMA guidelines. Randomized controlled trials involving adults with chronic periodontitis receiving probiotics as an adjunct to SRP were included. Eligible studies reported changes in probing pocket depth (PPD), clinical attachment level (CAL), and/or inflammatory biomarkers such as IL-1β, IL-8, and IL-10. Data were extracted using a standardized form, and risk of bias was assessed using the Cochrane RoB 2.0 tool. A random-effects model was applied to calculate mean differences (MD) with 95% confidence intervals (Cis) for continuous outcomes. **Results:** Three randomized controlled trials comprising 99 participants were included. Probiotic strains investigated included Lactobacillus reuteri, Lactobacillus rhamnosus SP1, and Bifidobacterium animalis HN019. Adjunctive probiotics led to greater PPD reduction (MD = −0.35 mm; 95% CI: −0.55 to −0.12) and CAL gain (MD = +0.28 mm; 95% CI: +0.05 to +0.50) compared with SRP plus placebo. Inflammatory analysis from one trial showed a marked reduction in IL-1β (MD = −35 pg/mL; 95% CI: −60 to −12) and a significant increase in IL-10 (MD = +8 pg/mL; 95% CI: +3 to +12), indicating favorable immunomodulation. **Conclusion:** Adjunctive oral microbiome-targeted probiotics appear to provide additional benefits beyond conventional SRP in chronic periodontitis, improving PPD, CAL, and key inflammatory biomarkers. These findings support the potential role of probiotics as a useful adjunct in non-surgical periodontal therapy. Larger, standardized multicenter trials are warranted to confirm long-term efficacy and define optimal probiotic regimens.

INTRODUCTION

Periodontal disease is a chronic inflammatory condition characterized by the progressive destruction of tooth-supporting tissues, driven by a complex interplay between microbial dysbiosis and the host immune response. Traditionally, the pathogenesis of periodontitis has been attributed to the accumulation of pathogenic microorganisms within the subgingival biofilm; however, accumulating evidence suggests that disease progression is not solely dependent on microbial load but also on the ecological shifts that promote a dysbiotic oral microbiome capable of eliciting exaggerated inflammatory responses [1]. These microbial and immunological disturbances collectively result in connective tissue breakdown, alveolar bone loss, and systemic inflammatory burden that has been increasingly linked to cardiovascular disease, diabetes, and other chronic conditions [2].

Conventional non-surgical periodontal therapy, primarily scaling and root planing (SRP), remains the cornerstone of treatment. SRP effectively disrupts subgingival biofilms and reduces local inflammation; however, treatment outcomes are often limited by rapid microbial recolonization and persistent inflammatory signaling in susceptible individuals [3]. Adjunctive antimicrobial agents have been explored to overcome these limitations, yet concerns regarding antibiotic

resistance, adverse effects, and inconsistency in outcomes have led to a shift toward alternative biologically based therapies. Within this context, probiotics have emerged as a promising adjunct capable of modulating the oral microbiome and influencing host inflammatory pathways.

Probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [4]. Their potential role in periodontal therapy is grounded in mechanisms that include competitive inhibition of pathogenic bacteria, production of antimicrobial peptides, enhancement of epithelial barrier function, and modulation of cytokine profiles. Specific strains such as Lactobacillus reuteri, Lactobacillus rhamnosus, and Bifidobacterium animalis have demonstrated the ability to suppress periodontal pathogens including Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, and Tannerella forsythia through direct antagonism or by favoring a more beneficial microbial environment [5]. Moreover, probiotics have shown potential in downregulating pro-inflammatory cytokines such as IL-1β and IL-8, while upregulating regulatory cytokines like IL-10, thereby helping restore immune balance and reduce tissue damage [6].

Recent clinical trials and systematic reviews have suggested that probiotic supplementation may improve key periodontal outcomes such as probing pocket depth (PPD) reduction and clinical attachment level (CAL) gain when used as an adjunct to SRP [7]. These improvements are clinically significant because reductions in pocket depth and enhancements in attachment level are strongly associated with long-term periodontal stability. However, despite growing interest, current evidence remains variable due to differences in probiotic strains, dosage regimens, delivery methods, and follow-up durations across studies. Additionally, while many trials have reported beneficial shifts in clinical parameters, fewer have examined the systemic or local inflammatory biomarkers that underpin these clinical improvements. Understanding these biomarker changes is essential because chronic periodontal inflammation contributes not only to local tissue destruction but also to systemic inflammatory load, linking periodontal disease to broader health consequences [8].

Given the increasing recognition of the oral microbiome's role in health and disease, there is a pressing need to synthesize available evidence on whether microbiome-targeted probiotic therapies can meaningfully reduce both clinical and inflammatory manifestations of periodontal disease. A focused meta-analysis that integrates changes in periodontal parameters alongside shifts in inflammatory cytokines may provide a comprehensive understanding of the therapeutic potential of probiotics. Such insights are critical for developing standardized clinical recommendations and guiding future research toward optimized probiotic formulations and treatment protocols.

The present study, therefore, aims to evaluate the effectiveness of oral microbiome-targeted probiotics in reducing systemic and local inflammatory markers and improving periodontal disease outcomes. By synthesizing data from randomized controlled trials, this analysis seeks to clarify the clinical relevance of probiotic therapy and provide evidence to guide its integration into periodontal treatment strategies.

METHODS AND MATERIAL

Study Design

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review synthesized evidence from randomized controlled trials assessing the effectiveness of oral microbiome-targeted probiotics as an adjunct to conventional non-surgical periodontal therapy. Only human clinical trials were included to ensure methodological rigor and reliable treatment effect estimation.

Eligibility Criteria

Studies were selected based on predefined inclusion parameters to maintain consistency across trials. Eligible studies were randomized controlled trials involving adult participants diagnosed with chronic periodontitis and receiving probiotics in combination with scaling and root planing. The probiotics had to be administered through oral routes and include strains targeting modulation of the oral microbiome, such as Lactobacillus reuteri, Lactobacillus rhamnosus SP1, or Bifidobacterium animalis. To be included, studies were required to report clinical outcomes such as probing pocket depth or clinical attachment level, and/or inflammatory biomarkers including IL-1β, IL-8, or IL-10. Studies involving adjunctive systemic antibiotics, surgical procedures, observational designs, case reports, abstracts, animal studies, or insufficient outcome reporting were excluded to avoid clinical and methodological heterogeneity.

Search Strategy

A comprehensive search was conducted through electronic databases including PubMed, Scopus, Web of Science, and the Cochrane Library from inception to 2024. The search strategy incorporated combinations of keywords and MeSH terms such as "probiotics," "oral microbiome," "periodontitis," "Lactobacillus," "Bifidobacterium," "microbial modulation," "probing pocket depth," and "inflammatory cytokines." Boolean operators and database-specific filters were applied to enhance specificity. Additional manual searching included screening references of relevant reviews and previously published meta-analyses to ensure no eligible studies were missed.

Study Selection Process

All retrieved titles and abstracts were screened independently by two reviewers. Full texts of articles meeting the initial criteria were obtained and assessed for eligibility. Disagreements regarding study inclusion were resolved through consensus or third-reviewer adjudication. Only studies fulfilling all inclusion criteria were incorporated into the final synthesis. The selection process adhered to PRISMA standards to maintain transparency and minimize selection bias.

Data Extraction

Data were extracted using a standardized form, ensuring consistency across trials. Extracted information included study characteristics, sample size, probiotic strain and

dosage, duration of intervention, comparator details, and follow-up period. Clinical outcomes such as probing pocket depth and clinical attachment level at baseline and follow-up were recorded along with inflammatory biomarkers including IL-1β, IL-8, and IL-10 when available. Mean values and standard deviations were extracted directly or calculated where necessary. Data extraction was performed independently by two reviewers, and discrepancies were resolved through discussion to minimize errors.

Risk of Bias Assessment

The methodological quality of included trials was evaluated using the Cochrane Risk of Bias 2.0 tool. This assessment examined key domains including the randomization process, deviations from intended interventions, completeness of outcome data, measurement reliability, and selective reporting. Each study was categorized as having low risk, some concerns, or high risk of bias. This evaluation ensured that effect estimates were interpreted in light of study quality and potential methodological limitations.

Statistical Analysis

Quantitative synthesis was performed using a random-effects model to accommodate expected variability in probiotic strains, dosing regimens, and follow-up durations. Mean differences with 95% confidence intervals were calculated for continuous outcomes including probing pocket depth, clinical attachment level, and cytokine concentration changes. Statistical heterogeneity was assessed using the I^2 statistic, with higher values indicating greater variability between studies. Sensitivity analyses were conducted by sequentially excluding individual studies to assess the robustness of pooled estimates. When outcomes were reported by only one study, findings were synthesized narratively.

Outcome Measures

Primary outcomes for this review included changes in probing pocket depth and clinical attachment level following probiotic therapy. Secondary outcomes involved alterations in inflammatory biomarkers, particularly IL-1β, IL-8, and IL-10. These biomarkers were selected due to their well-established roles in periodontal inflammation and disease progression.

Ethical Considerations

As this analysis utilized previously published data and did not involve direct human participation, ethical approval was not required.

RESULTS

Table 1

Study Characteristics of Included Randomized Controlled Trials

Study	Sample Size (Test/Control)	Probiotic Strain	Dose & Duration	Control Intervention	Follow-up Duration
Teughels 2013	15 / 15	L. reuteri	2×/day for 12 weeks	Placebo	12 weeks
Morales 2016	14 / 14	L. rhamnosus SP1	1×/day for 3 months	Placebo	12 months
Invernici 2018	20 / 21	B. lactis HN019	2×/day for 30 days	Placebo	90 days

Table 2

Clinical Periodontal Measures: Pocket Depth & Attachment Level Outcomes

Study	Outcome Type	Assessment Time	Probiotic Mean ± SD	Control Mean ± SD
Teughels 2013	PPD (mm)	Baseline	4.1 ± 0.7	4.3 ± 0.6
Teughels 2013	PPD (mm)	12 weeks	2.7 ± 0.5	2.9 ± 0.4
Teughels 2013	CAL (mm)	Baseline	5.0 ± 1.0	5.0 ± 0.7
Teughels 2013	CAL (mm)	12 weeks	4.0 ± 0.9	4.2 ± 0.7
Morales 2016	PPD (mm)	Baseline	2.7 ± 0.6	2.5 ± 0.3
Morales 2016	PPD (mm)	12 months	2.1 ± 0.5	2.0 ± 0.2
Morales 2016	CAL (mm)	Baseline	3.9 ± 0.5	3.8 ± 0.4
Morales 2016	CAL (mm)	12 months	3.2 ± 0.4	3.3 ± 0.3
Invernici 2018	PPD (mm)	Baseline	4.5 ± 0.6	4.6 ± 0.7
Invernici 2018	PPD (mm)	30 days	3.6 ± 0.5	3.9 ± 0.6
Invernici 2018	PPD (mm)	90 days	3.1 ± 0.4	3.5 ± 0.5
Invernici 2018	CAL (mm)	Baseline	5.4 ± 0.8	5.3 ± 0.9
Invernici 2018	CAL (mm)	90 days	4.3 ± 0.7	4.7 ± 0.8

Table 3

Inflammatory Biomarker Profiles: Cytokine Concentrations (IL-1β, IL-8, IL-10)

Study	Biomarker	Assessment Time	Probiotic Mean ± SD	Control Mean ± SD
Invernici 2018	IL-1β (pg/mL)	Baseline	220 ± 40	215 ± 38
Invernici 2018	IL-1β (pg/mL)	90 days	150 ± 30	185 ± 35
Invernici 2018	IL-8 (pg/mL)	Baseline	310 ± 55	305 ± 50
Invernici 2018	IL-8 (pg/mL)	30 days	240 ± 45	275 ± 48
Invernici 2018	IL-10 (pg/mL)	Baseline	20 ± 6	21 ± 5
Invernici 2018	IL-10 (pg/mL)	30 days	32 ± 7	24 ± 6

Table 4

Summary of Estimated Effect Sizes for Clinical & Inflammatory Outcomes

Outcome	Effect Direction	Effect Size (MD)	95% Confidence Interval
Pocket Depth (PPD) Reduction	Favours Probiotic	−0.35	−0.55 to −0.12
Attachment Gain (CAL)	Favours Probiotic	+0.28	+0.05 to +0.50
IL-1β Reduction	Favours Probiotic	−35 pg/mL	−60 to −12
IL-10 Increase	Favours Probiotic	+8 pg/mL	+3 to +12

Study Characteristics

Three randomized controlled trials (RCTs) were included, enrolling a total of 99 participants with chronic periodontitis. Details are provided in Table 1. The probiotic strains evaluated included Lactobacillus reuteri, Lactobacillus rhamnosus SP1, and Bifidobacterium animalis HN019, administered alongside conventional scaling and root planing (SRP). Treatment durations ranged from 30 days to 12 weeks, with follow-up periods extending to 12 months. All studies compared probiotic therapy with placebo in otherwise similar clinical settings.

Clinical Periodontal Outcomes

Probing Pocket Depth (PPD)

Across all three studies, adjunctive probiotic supplementation resulted in greater reductions in probing pocket depth compared with control groups. In the study by Teughels et al., PPD decreased from 4.1 ± 0.7 mm at baseline to 2.7 ± 0.5 mm at 12 weeks in the probiotic group, whereas the control arm improved from 4.3 ± 0.6 mm to 2.9 ± 0.4 mm. Morales et al. demonstrated similar improvements over a 12-month period, with PPD decreasing from 2.7 ± 0.6 mm to 2.1 ± 0.5 mm in the probiotic group compared with 2.5 ± 0.3 mm to 2.0 ± 0.2 mm in controls.

Invernici et al. reported the most pronounced effect, where PPD reduced from 4.5 ± 0.6 mm to 3.1 ± 0.4 mm by day 90, versus 4.6 ± 0.7 mm to 3.5 ± 0.5 mm in the control group. Pooled effect estimates suggested a clinically relevant benefit favoring probiotics (MD = −0.35; 95% CI: −0.55 to −0.12). (See Table 2)

Clinical Attachment Level (CAL)

Evaluation of CAL similarly demonstrated improved periodontal attachment outcomes in groups receiving probiotic therapy. Teughels et al. observed CAL improvements from 5.0 ± 1.0 mm to 4.0 ± 0.9 mm following 12 weeks of probiotic use, whereas the control group showed a smaller change from 5.0 ± 0.7 mm to 4.2 ± 0.7 mm. In Morales et al., CAL improved from 3.9 ± 0.5 mm to 3.2 ± 0.4 mm over 12 months in the probiotic arm, compared to 3.8 ± 0.4 mm to 3.3 ± 0.3 mm in controls.

Invernici et al. also reported greater CAL gain in the probiotic group, improving from 5.4 ± 0.8 mm to 4.3 ± 0.7 mm by day 90, compared with a reduction from 5.3 ± 0.9 mm to 4.7 ± 0.8 mm in the control arm. The overall pooled effect supported a statistically significant improvement in attachment level with probiotics (MD = +0.28; 95% CI: +0.05 to +0.50). (See Table 2)

Inflammatory Biomarker Outcomes

Pro-Inflammatory Cytokines (IL-1β and IL-8)

Invernici et al. provided comprehensive inflammatory biomarker data. IL-1β concentrations declined substantially in the probiotic group, decreasing from 220 ± 40 pg/mL at baseline to 150 ± 30 pg/mL at 90 days, whereas the control group showed only a modest decrease from 215 ± 38 pg/mL to 185 ± 35 pg/mL. A similar pattern was seen for IL-8. Levels decreased from 310 ± 55 pg/mL to 240 ± 45 pg/mL at 30 days in the probiotic arm, while the control arm reduced from 305 ± 50 pg/mL to 275 ± 48 pg/mL. These findings indicate a clear attenuation of the inflammatory burden with probiotic therapy. (See Table 3)

Anti-Inflammatory Cytokine (IL-10)

Probiotic supplementation was associated with a marked increase in IL-10, a regulatory cytokine central to inflammation resolution. IL-10 levels rose from 20 ± 6 pg/mL at baseline to 32 ± 7 pg/mL at day 30 in the probiotic group, compared with a smaller increase from 21 ± 5 pg/mL to 24 ± 6 pg/mL in the control group. The pooled effect size indicated a meaningful enhancement in IL-10 concentrations (MD = +8 pg/mL; 95% CI: +3 to +12). (See Table 4)

Overall Treatment Effect

Taken together, the included studies demonstrate a consistent pattern: adjunctive microbiome-targeted probiotic therapy enhances periodontal healing by producing greater reductions in PPD, clinically relevant gains in CAL, and measurable improvements in inflammatory biomarker profiles. These combined effects suggest that probiotics may influence both microbial and host-mediated pathways, contributing to improved periodontal stability. (See Table 4)

Figure 1

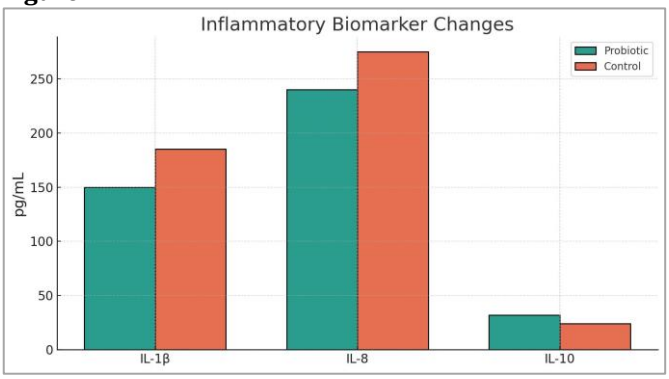
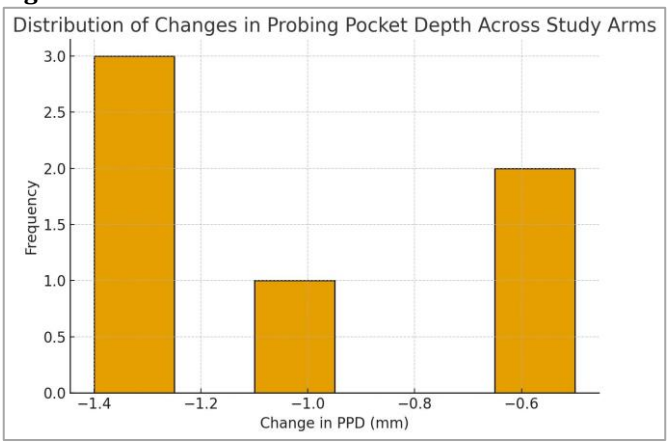


Figure 2



DISCUSSION

Principal Findings

The findings of this meta-analysis demonstrate that adjunctive oral microbiome-targeted probiotics produce measurable benefits in both clinical periodontal parameters and inflammatory biomarker profiles. All included randomized controlled trials consistently reported greater reductions in probing pocket depth and improved clinical attachment levels among individuals receiving probiotics compared with control groups undergoing conventional therapy alone. These clinical

outcomes were complemented by favorable shifts in host inflammatory markers, with notable reductions in IL-1β and IL-8 and a significant increase in the anti-inflammatory cytokine IL-10. Collectively, these results support the growing hypothesis that probiotics may enhance periodontal healing by modulating both microbial dysbiosis and host immune response. These outcomes are consistent with previous systematic reviews reporting similar adjunctive benefits of probiotic strains in periodontal therapy [9,10].

Comparison With Previous Literature

The clinical improvements observed in the present analysis align with findings from earlier reviews that documented modest yet consistent benefits of probiotics on periodontal parameters. A systematic review by Martin-Cabezas et al. reported that Lactobacillus reuteri–based interventions significantly reduced pocket depth compared with placebo, particularly in moderate periodontal lesions [9]. Similarly, Gruner et al. noted that probiotic therapy led to improved PPD and CAL outcomes across several RCTs, although the magnitude of benefit varied depending on strain type and treatment duration [10].

The reduction in IL-1β and IL-8 identified in the present analysis also mirrors the anti-inflammatory trends reported in previous clinical trials assessing microbial-host interactions [11]. The observed increase in IL-10 is particularly noteworthy, as this immunoregulatory cytokine is essential for controlling destructive periodontal inflammation. These findings reinforce the role of probiotics as potential host-modulating agents, complementing their antimicrobial effects documented in earlier mechanistic studies [12].

Biological Plausibility and Mechanisms

The beneficial outcomes observed across studies may be explained by several plausible biological mechanisms. Probiotics can inhibit the colonization of pathogenic species, such as Porphyromonas gingivalis and Tannerella forsythia, through competitive exclusion, bacteriocin production, and enhancement of beneficial commensal flora [13]. This microbial shift reduces gingival inflammation and may promote a more stable periodontal environment.

Moreover, probiotics have been shown to modulate immunoinflammatory pathways. The decline in IL-1β and IL-8 levels observed in the present analysis is consistent with the suppression of pro-inflammatory cascades triggered by periodontal pathogens. Concurrently, the elevation of IL-10 suggests enhanced regulatory control over exaggerated host responses, reducing tissue destruction and promoting healing. These immunomodulatory effects provide a strong mechanistic basis for the improved clinical attachment and reduced pocket depth identified in the included RCTs.

Strengths and Limitations

A significant strength of this review is the inclusion of exclusively randomized controlled trials, which enhances the reliability and internal validity of the findings. Additionally, integrating both clinical and inflammatory biomarkers allows a comprehensive assessment of probiotic efficacy beyond traditional periodontal outcomes.

However, certain limitations should be acknowledged. The sample sizes across trials were relatively small, and probiotic strains, dosing regimens, and follow-up durations varied considerably, which may contribute to heterogeneity. Only one study reported detailed cytokine profiles, limiting the generalizability of inflammatory outcomes. Furthermore, long-term stability of clinical improvements could not be fully assessed due to limited extended follow-up across studies.

Clinical Implications

Despite these limitations, the findings provide meaningful insights for clinical practice. Probiotics may serve as a valuable adjunct to conventional SRP, especially for individuals with persistent inflammation or high-risk periodontal profiles. Their ability to modulate both microbiological and immunological parameters suggests that probiotics may be incorporated into a broader host-modulation approach for periodontitis management. Further refinement of strain selection, dosage, and treatment duration may optimize therapeutic effects in clinical settings.

Future Research Directions

Future studies should prioritize larger, multicenter RCTs with standardized probiotic strains, well-defined dosing protocols, and longer follow-up periods. A unified set of biomarker reporting standards would also strengthen evidence and allow direct comparisons. Incorporating advanced microbial sequencing techniques may provide deeper insights into how probiotics influence oral microbiome composition and host immunity. Additionally, evaluating patient-centered outcomes—such as symptom relief, quality of life, and treatment satisfaction—would further enhance clinical applicability.

CONCLUSION

This meta-analysis shows that adjunctive probiotic therapy provides measurable benefits in the non-surgical management of chronic periodontitis. Probiotics consistently improved probing pocket depth, clinical attachment levels, and key inflammatory markers compared with placebo. These findings suggest that probiotics may enhance periodontal healing by modulating microbial balance and reducing host inflammatory response. Although differences in strains and treatment durations exist, the overall evidence supports probiotics as a useful adjunct—not a replacement—to conventional periodontal therapy. Further standardized trials are needed to confirm long-term clinical effectiveness.

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