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Systematic review and meta-analysis of double-blind, placebo-controlled, randomized clinical trials using probiotics in chronic periodontitis

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Abstract

Aim: The aim of the present study was to evaluate the efficacy of probiotics as an adjunct to scaling and root planning (SRP) in the treatment of chronic periodontitis (CP).

Methods: The focused question of the study was: Does adjunctive use of probiotics yield better clinical periodontal outcomes compared to placebo/no treatment group in the treatment of CP? Electronic and manual literature searches were conducted up to December 2017 using the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Oral Health Group Trials Register. Forest plots were computed reporting weighted mean difference (WMD) of outcomes and 95% confidence intervals (CI).

Results: Seven clinical studies were included. Four studies showed additional benefits in reducing periodontal probing depth (PPD) and gaining clinical attachment level (CAL), whereas, three studies showed comparable clinical periodontal outcomes between probiotics and SRP/placebo. Significant heterogeneity was observed for PPD reduction and CAL gain. The overall mean difference for CAL gain between probiotics and placebo/SRP was significant (WMD = 1.41, 95% CI = 0.15-2.67, P = .028) at follow up.

Conclusion: Adjunctive probiotics could result in additional benefits in CAL gain in CP. Nevertheless, further high-quality randomized clinical trials with microbiological outcomes are warranted to obtain strong conclusions in this regard.

KEYWORDS

chronic periodontitis, clinical attachment level gain, dental scaling probiotics, meta-analysis

1 | INTRODUCTION

Chronic periodontitis (CP) is an inflammatory disease of the periodontal tissues that is characterized by periodontal attachment loss and alveolar bone destruction and tooth loss in susceptible patients.[1] It is a multifactorial disease of which the primary factor is periodontopathogenic bacteria that activates inflammatory immune response.[2] The resolution of inflammation through the reduction of bacterial load is the primary goal of periodontal therapy.[3] Scaling and root planing (SRP) is considered the gold standard treatment for CP, as it removes soft and hard microbial deposits and reduces the periodontal pathogenic count.[4] However, in certain cases, such as deep probing depths, inaccessible root furcation, and interproximal areas of malposed teeth, proper access for instrumentation is not possible.[5]

To overcome these deficiencies, there are numerous adjunctive therapies that have been proposed for the successful treatment of CP. The purpose of these adjunctive therapies is to complement SRP in reducing bacterial load and improving clinical periodontal parameters, such as reducing periodontal pocket depth (PPD) and gaining clinical attachment level (CAL). Various adjuncts include local and systemic antibiotics, antiseptic agents, bisphosphonates, laser/photodynamic therapy, and the delivery of statins.[6–14] Of these adjunctive therapies, probiotics have recently gained attention in the treatment of CP.[15,16]

The general clinical benefits observed in therapy with probiotics seem to be greater than expected. These agents regulate tight junctions and enhance mucus secretion from the epithelium, which prevents pathogenic microorganisms from adhesion. Probiotics also compete with pathogens for binding on epithelial cells. Probiotics forms antibacterial compounds, such as bacteriocins and low molecular weight organic acids.[17] In addition to their local effects, probiotics play a significant role in immune modulatory activity; that is, the increased production of anti-inflammatory cytokines and the activation of helper (Th)1, Th2, Th17, or T-regulatory cells.[18,19] These therapeutic effects of probiotics have certainly justified their use in the treatment of CP, and a systematic review to assess the efficacy of adjunctive probiotic in the treatment of periodontitis is warranted. Therefore, the aim of the present study was to evaluate the efficacy of probiotics as an adjunct to SRP in the treatment of CP.

2 | MATERIALS AND METHODS

2.1 | Focused question

Based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines,[20] a specific PICOS (Population: individuals with CP, Intervention: use of probiotics in adjunct to SRP, Comparator: probiotic group compared to placebo/no treatment group with SRP, Outcomes: changes in PPD reduction and CAL gain as primary outcomes, whereas plaque index [PI], bleeding on probing [BOP], and gingival index [GI] were secondary outcomes, Study design: randomized clinical trials [RCT]) question was constructed. The addressed PICOS question of the study was: Does adjunctive use of probiotics yield better clinical periodontal outcomes compared to placebo/no treatment group in the treatment of CP?

2.2 | Search strategy

Electronic and manual literature searches were conducted by two independent reviewers (ZA and SI) using the following databases: MEDLINE (1 September 1965 to 1 December 2017), EMBASE (1 February 1967 to 1 December 2017), Cochrane Central Register of Controlled Trials, and Cochrane Oral Health Group Trials Register (1 July 1964 to 1 December, 2017) for articles addressing the focused question. For the PubMed library, combinations of the following controlled terms (MeSH words) were used: Lactobacillus reuteri AND periodontitis AND probiotic AND periodontitis OR chronic periodontitis OR periodontal diseases OR periodontal debridement OR periodontal pockets AND root planing AND dental scaling. We independently screened titles and abstracts for eligible papers. If information relevant to the eligibility criteria was not available in the abstract, or if the title was relevant but the abstract was not available, the paper was selected for full reading of the text. Next, full-text papers that fulfilled the eligibility criteria were identified and included in the review. Reference lists of original studies were hand searched to identify articles that could have been missed during the electronic search. Hand searching of the following journals was performed: *Journal of Clinical Periodontology*, *Journal of Periodontology*, and *Journal of Periodontal Research*. Studies that fulfilled the selection criteria were processed for data extraction.

2.3 | Selection criteria

Articles were included in this systematic review if they met the following inclusion criteria: prospective, RCT; people diagnosed with CP, and ≥10 participants per group allocated to test and control/placebo groups based on having SRP with adjunctive probiotic or placebo with SRP. In order to address the aim of the present study comprehensively, parameters, such as reduction in PPD, CAL gain, PI, BOP, and GI, were further reported. Articles published only in the English language were included in the present review. In vitro studies, case series, case reports, animal studies, letters to the editor, opinion articles, abstracts, review papers, and unpublished articles were excluded.

2.4 | Data extraction

Two reviewers (ZA and SI) performed the data extraction individually. The information from the included studies was tabulated according to the study designs, subject demographics, dropouts, gender distribution, drug administration, follow-up period, main outcomes, and clinical and microbiological parameters. Data collected were based on the focused question outlined for the present systematic review. The reviewers cross-checked all extracted data. Any disagreement was resolved by discussion until consensus was reached.

2.5 | Risk of bias in individual studies

The risk of bias of RCT was assessed based on the revised recommendations of the Consolidated Standards of Reporting Trials statement.[21,22] The risk of bias was estimated for each selected RCT based on the Cochrane Handbook for Systematic Reviews of Interventions. Studies were classified as having high risk of bias (high), low risk of bias (low), or unclear (?) for each of these sections. Overall, studies were considered low risk of bias if all criteria were met (adequate randomization and allocation concealment; "yes" answer to all questions about the completeness of outcome data and blinding, and "no" answer to selective reporting and other sources of bias; unclear risk

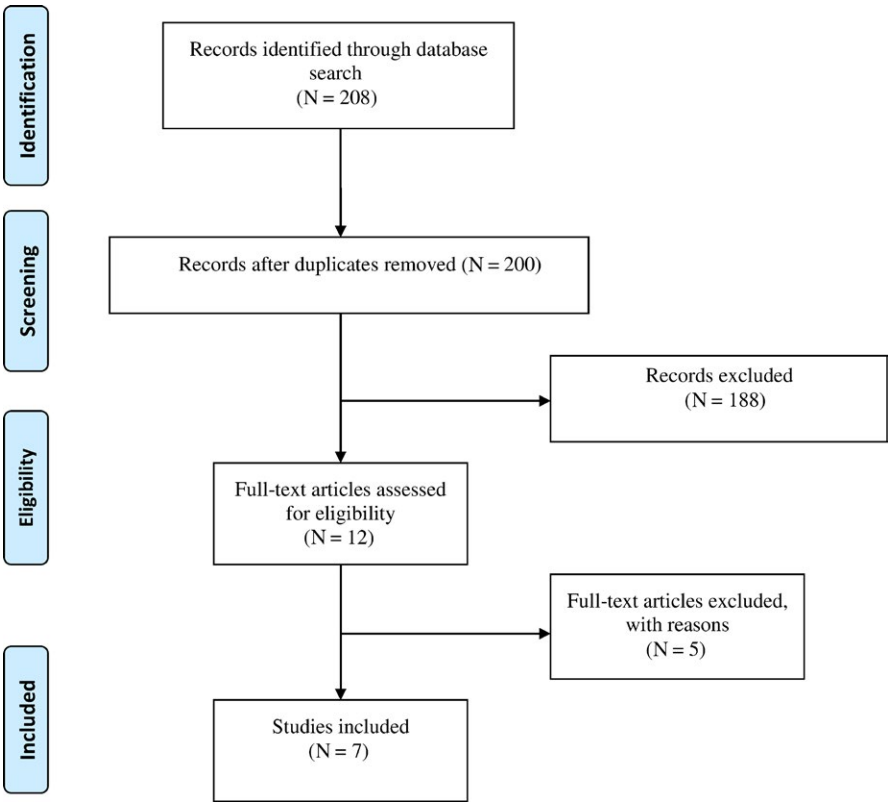

FIGURE 1 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram for studies retrieved through the searching and selection process

of bias if one or more criteria were partly met; or high risk of bias if one or more criteria were not met.

2.6 | Quantitative analysis

Meta-analyses were conducted separately for each of the primary and secondary outcomes. In addition, heterogeneity among the included studies for each outcome was assessed using the χ^2-test and I^2 statistic, and $P < .05$ represented significant heterogeneity. Forest plots were computed reporting weighted mean difference (WMD) of outcomes and 95% confidence intervals (CI). The pooled effect was considered significant if $P < .05$. Data unsuitable for quantitative analysis were assessed descriptively. All of the statistical analyses were carried out using specialized statistical software (MedCalc Statistical Software, version 15.8; MedCalc Software, Ostend, Belgium).

3 | RESULTS

3.1 | Study selection

In total, 208 titles and abstracts were initially identified. After initial screening of the titles and abstracts using the inclusion criteria and removing duplicates, 12 studies were selected for the full-text reading and 188 studies were excluded (κ = .79, 79% agreement). Of these 12 studies, five were further excluded. After the final stage of selection, seven studies were finalized and processed for data abstraction.[16,23–28] The kappa score for inter-reviewer validity at this stage was .96 (96% agreement). All studies included in the present study were performed in registered medical facilities (ie clinical/health-care setups or universities). The study identification flowchart according to PRISMA and the reasons for exclusion of articles are shown in Figure 1.[22]

3.2 | General characteristic of the included studies

General characteristics of the included studies are represented in Table 1. Seven studies were included in the systematic review.[16,23–28] All of the studies were double-blind, placebo-controlled RCT published in the English language between 2010 and 2016.[16,23–28] The number of participants in the included studies ranged between 20 and 40, and their ages ranged between 18 and 60 years. Of seven included studies,[16,23–28] six reported the percentage of female individuals, which ranged between 36% and 55%.[16,23,25–28] All included studies used different criteria of CP as inclusion. Three studies included CP patients with PPD 5-7 mm,[16,23,26] two studies used >4 mm PPD,[25,28] while one study included ≥5 mm as the threshold value of PPD for the inclusion of CP patients.[24] Only one study recruited patients with severe periodontitis; that is, ≥6 mm of bone loss.[27] All of the included studies were designed for comparison between test and control groups. Participants in the test group received probiotics as an adjunct to SRP, while the control group received placebo+SRP. Six studies used oral lozenges containing Lactobacillus reuteri as the probiotic,[16,23,25–28] whereas one study used Lactobacillus reuteri combined with Lactobacillus salivarius as a probiotic in the form of mouth rinse with local subgingival delivery.[24] The follow-up period

TABLE 1 General characteristics of the included studies

Author	Study design	Sample size, mean age in years (range), female %	Periodontitis definition	Study groups (N)
İnce et al.[23]	Double-blind, placebo-controlled RCT	30, probiotics: 41 SRP: 42.2 (35-50), 43%	Presence of 2 teeth at least with 1 proximal site PPD of 5-7 mm and a GI of ≥2 in each quadrant	Group 1 SRP+probiotics=15 Group 2 SRP+placebo=15
Penala et al.[24]	Double-blind, placebo-controlled RCT	32, probiotics: 37.2 SRP: 35.3 (25-59), NA	At least 4 teeth showing PPD ≥5 mm, CAL ≥4 mm	Group 1 SRP+probiotics=16 Group 2 SRP+placebo=16
Szkaradkiewicz et al.[25]	Double-blind, placebo-controlled RCT	38, NA (31-46), 52%	Moderate CP with PPD >4 mm and CAL >5 mm on ≥2 non-neighboring teeth	Group 1 SRP+probiotics=24 Group 2 SRP+placebo=18
Tekce et al.[26]	Double-blind, placebo-controlled RCT	40, probiotics: 43.0 SRP: 41.4 (35-50), 55%	CP patients with radiographic evidence of bone loss & presence of 2 teeth with PPD 5-7 mm	Group 1 SRP+probiotics=20 Group 2 SRP+placebo=20
Teughels et al.[27]	Double-blind, placebo-controlled RCT	30, probiotics: 46.6 SRP: 45.7 (15-15), 50%	Moderate-to-severe generalized CP ≥14 teeth affected and bone loss >1/2 of the root length or attachment loss ≥6 mm	Group 1 SRP+probiotics=15 Group 2 SRP+placebo=15
Vicario et al.[28]	Double-blind, placebo-controlled RCT	20, probiotic: 58 SRP: 53.8 (NA), 40%	Moderate CP with PPD >4 mm and CAL >5 mm on ≥2 non-neighboring teeth	Group 1 SRP+probiotics=10 Group 2 SRP+placebo=10
Vivekananda et al.[16]	Double-blind, placebo-controlled RCT	30, probiotics: 41.4 SRP: 41.5 (35-50), 36%	Clinical & radiographic evidence of bone loss & PPD 5-7 mm.	Group 1 SRP+probiotics=15 Group 2 SRP+placebo=15

CAL, clinical attachment level; CP, chronic periodontitis; GI, gingival index; NA, not available; PPD, periodontal pocket depth; RCT, randomized clinical trial; SRP, scaling and root planing.

of these studies ranged between 3 and 52 weeks. None of the participants in the included studies reported adverse effects with the use of probiotics.

3.3 | Clinical periodontal inflammatory parameters of the included studies

The results of the periodontal parameters are reported in Table 2.[16,23–26,28] Six studies evaluated PI, of which five studies reported values in mean and standard deviation that ranged between .35 and 1.65.[16,23–26] Four studies evaluated BOP[23,26–28] and GI[16,23,25,26] that ranged between 11.05% and 29.3% and .73 and 1.21, respectively. All included studies evaluated PPD that ranged between .76 and 4.15.[16,23–28] CAL was reported in six studies,[16,23–27] of which five reported their findings in mean differences that ranged between 0.99 and 1.39.[16,23,24,26,27]

3.4 | Microbiological parameters of the included studies

There were only two studies that measured bacterial load at baseline and follow up, as shown in Table 3.[16,27] The total mean counts for Porphyromonas gingivalis reduction ranged between 1.8 and 85.7, whereas Prevotella intermedia and Aggregatibacter actinomycetemcomitans reduction ranged between 2.12 and 77 and 2.53 and 94.0, respectively.

3.5 | Quality assessment of included studies

All included studies were double-blind, placebo-controlled RCT.[16,23–28] The risk of bias was considered high in four RCT assessed.[16,24,25,28] Five RCT estimated the sample size, reported masking of assessor(s), and methods of allocation concealment.[16,23–26] All studies presented appropriate statistical analysis and description of withdrawals and dropouts.[16,23–28]

3.6 | Main outcome of the included studies

3.6.1 | Qualitative analysis

All studies reporting clinical periodontal parameters showed that probiotics as an adjunct to SRP was effective in the treatment of CP.[16,23–28] When compared with SRP/placebo, four studies showed additional benefits in reducing PPD and gaining CAL.[16,23,25,26]

Probiotic used, route of administration, adverse effects	Follow up (weeks)	Study outcome	Risk of bias
Lactobacillus reuteri oral tablets, none	Up to 52	Significant improvement in test group compared to control group at follow up	Low
Subgingival delivery of probiotics (Lactobacillus reuteri+Lactobacillus salivarius) at baseline 1-, 2-, & 4-week intervals and probiotic mouthwash for 14 days twice daily, none	Up to 12	Both groups showed comparable clinical outcomes at follow up	High
Lactobacillus reuteri oral tablets, none	Up to 3	Significant improvement in test group compared to control group at follow up	High
Lactobacillus reuteri oral tablets, none	Up to 52	Significant improvement in test group as compared to control group at follow up	Low
Lactobacillus reuteri oral tablets, none	Up to 12	Both groups showed comparable clinical outcomes at follow up	Low
Lactobacillus reuteri, oral, none	Up to 4	Both groups showed comparable clinical outcomes at follow up	High
Lactobacillus reuteri oral lozenges, none	Up to 6	Significant improvement in test group compared to control group at follow up	High

However three studies showed comparable clinical periodontal outcomes between probiotics and SRP/placebo.[24,27,28]

3.6.2 | Quantitative analysis

For quantitative data assessment, a meta-analysis was performed. As significant heterogeneity was observed for PPD reduction and CAL gain; therefore, the random model was employed.

Probing depth

Three studies presented data to be included in the meta-analysis considering the effects of adjunctive probiotics on PD reduction.[16,24,27] Considering the effects of adjunctive probiotics as compared to placebo/SRP on PD, a high degree of heterogeneity for PD (Q-value = 11.54, $P = .0031$, $I^2 = 82.69\%$, Figure 2A) was noticed among both groups. No significant statistical differences in PD reduction (WMD = 0.66, 95% CI = −0.36-1.69, $P = .25$) were observed at follow up between the test and control groups.

Clinical attachment level

Four studies were included in the meta-analysis for the effect of adjunctive probiotics on CAL.[16,23,24,27] Considering the effects of probiotics, as compared to placebo/SRP on CAL, a high degree of heterogeneity for CAL (Q-value = 28.88, $P < .0001$, $I^2 = 89.61\%$, Figure 2B) was noticed among both groups. The overall mean difference for CAL gain between both groups was significant (WMD = 1.41, 95% CI = 0.15-2.67, $P = .028$) at follow up.

4 | DISCUSSION

The aim of the present study was to systematically evaluate the efficacy of probiotics as an adjunct to SRP versus SRP combined with placebo in the reduction of PPD and gain in CAL in CP patients. The qualitative findings of the present systematic review showed that approximately 57% of the included studies reported significant improvement in clinical periodontal parameters in CP patients with the adjunctive use of probiotics compared with SRP/placebo.

The role of probiotics is based on the premise that it produces antibacterial compounds, enhances epithelial barrier, and impounds essential nutrients from pathogens, which prevents their adhesion and growth.[29] Probiotics and pathogens compete with each other for the binding sites, which results in the competitive exclusion of pathogenic microorganisms.[30] In addition, through the activation of

TABLE 2 Clinical periodontal outcomes of the included studies

Author	Pocket probing depth	Clinical attachment level	Plaque index	Bleeding on probing	Gingival index
İnce et al.[23]	Group 1 Baseline: 5.85 ± 0.54 Follow up: 4.15 ± 0.44 Group 2 Baseline: 5.57 ± 0.39 Follow up: 5.01 ± 0.40	Group 1 Baseline: 8.97 ±0.96 Follow up: 1.39 ± 0.26* Group 2 Baseline: 8.91 ± 1.02 Follow up: 0.43 ± 0.24*	Group 1 Baseline: 2.28 ± 0.29 Follow up: 0.76 ± 0.24 Group 2 Baseline: 2.23 ± 0.24 Follow up: 1.43 ± 0.26	Group 1 Baseline: 88.90 ± 7.66 Follow up:11.60 ± 4.35 Group 2 Baseline: 88.65 ± 4.11 Follow up:19.00 ± 5.42	Group 1 Baseline: 2.15 ±0.11 Follow up: 0.73 ± 0.28 Group 2 Baseline: 2.11 ± 0.28 Follow up:1.73 ± 0.31
Penala et al.[24]	Group 1 Baseline: 3.12 ± 0.71 Follow up: 0.76 ± 0.43* Group 2 Baseline: 3.19 ± 0.44 Follow up: .69 ± .38*	Group 1 Baseline: 2.98 ± 0.78 Follow up: 0.42 ± 0.18* Group 2 Baseline: 2.88 ± 0.40 Follow up: 0.40 ± 0.19*	Group 1 Baseline: 1.81 ± 0.47 Follow up: 0.35 ± 0.18* Group 2 Baseline: 2.16 ± 0.35 Follow up: 0.72 ± 0.39*	NA	NA
Szkaradkiewicz et al.[25]	Group 1 Baseline: 3.35 ± 0.32 Follow up: 3.06 ± 0.35 Group 2 Baseline: 3.39 ± 0.36 Follow up: 3.34 ± 0.38	Group 1 Baseline: 3.47 ± 0.38 Follow up: 3.16 ± 0.27 Group 2 Baseline: 3.49 ± 0.35 Follow up: 3.56 ± 0.41	Group 1 Baseline: 1.61 ± 0.31 Follow up: 1.65 ± 0.26 Group 2 Baseline:1.64 ± 0.29 Follow up: 1.72 ± 0.34	NA	Group 1 Baseline: 1.33 ± 0.29 Follow up: 1.21 ± 0.36 Group 2 Baseline: 1.36 ± 0.31 Follow up: 1.31 ± 0.27
Tekce et al.[26]	Group 1 Baseline: 5.23 ± 0.68 Follow up: 3.49 ± 0.87 Group 2 Baseline: 5.36 ± 0.72 Follow up: 4.80 0.70	Group 1 Baseline: NA Follow up: 1.39 ± 0.26 Group 2 Baseline: NA Follow up: 0.53 ± 0.24	Group 1 Baseline: 2.29 ± 0.28 Follow up: 0.73 ±0.24 Group 2 Baseline: 2.31 ± 0.41 Follow up: 1.39 ± 0.28	Group 1 Baseline:.88 ± 0.07 Follow up: 11.05 ± 3.99 Group 2 Baseline: 0.87 ± 0.04 Follow up: 19.05 ± 4.84	Group 1 Baseline: 2.12 ± 0.15 Follow up: 0.80 ± 0.38 Group 2 Baseline: 2.11 ± 0.21 Follow up:1.66 ± 0.36
Teughels et al.[27]	Group 1 Baseline: 4.15 ± 0.71 Follow up: 2.73 ± 0.57 Difference: 1.41 ± 0.25* Group 2 Baseline: 4.32 ± 0.50 Follow up: 2.93 ± 0.40 Difference: 1.39 ± 0.15*	Group 1 Baseline: 4.97 ± 1.01 Follow up: 3.97 ± 0.97 Difference: 0.99 ± 0.22* Group 2 Baseline: 4.97 ± 0.61 Follow up: 4.21 ± 0.67 Difference: 0.76 ± 0.36*	NA	Group 1 Baseline: 70.70% ± 14.53 Follow up: 15.51% ± 11.92 Group 2 Baseline: 67.53% ± 11.37 Follow up: 16.58% ± 10.54	NA
Vicario et al.[28]	Group 1 Baseline: 50.1 ± 17.92 Follow up: 40.4 ± 17.76 Group 2 Baseline: 38.1 ± 16.37 Follow up: 45.3 ± 10.38	NA	Group 1 Baseline: 69.5 ± 16.95 Follow up: 52.5 ± 14.25 Group 2 Baseline: 62.9 ± 24.21 Follow up: 67.4 ± 16.57	Group 1 Baseline: 55.3 ± 16.39 Follow up: 29.3 ± 15.04 Group 2 Baseline: 40.0 ± 23.36 Follow up:47.0 ± 17.43	NA
Vivekananda et al.[16]	Group 1 Baseline: 5.08 ± 0.75 Follow up: 1.31 ± 0.49* Group 2 Baseline: 5.26 ± 0.53 Follow up: 0.49 ± 0.39*	Group 1 Baseline: 3.93 ± 0.93 Follow up: 1.09 ± 0.62* Group 2 Baseline: 4.46 ± 1.94 Follow up: 0.29 ± 0.51*	Group 1 Baseline: 1.79 ± 0.36 Follow up: 0.76 ± 0.29 Group 2 Baseline: 1.77 ± 0.20 Follow up: 0.27 ± 0.13	NA	Group 1 Baseline: 1.85 ± 0.22 Follow up: 0.84 ± 0.23 Group 2 Baseline: 1.88 ± 0.12 Follow up: 0.38 ± 0.23

*Significantly different from baseline values. NA, not available.

TABLE 3 Microbiological parameters of the included studies

Author	Porphyromonas gingivalis	Prevotella intermedia	Aggregatibacter actinomycetemcomitans
İnce et al.[23]	NA	NA	NA
Penala et al.[24]	NA	NA	NA
Szkaradkiewicz et al.[25]	NA	NA	NA
Tekce et al.[26]	NA	NA	NA
Teughels et al.[27]	Group 1 Baseline: 6.67 ± 1.5 Follow up: 4.87 ± 1.21 Difference: 1.8 ± 1.17* Group 2 Baseline: 6.37 ± 1.7 Follow up: 5.43 ± 1.73 Difference: 0.94 ± 0.61*	Group 1 Baseline: 6.34 ± 2.14 Follow up: 4.22 ± 2.07 Difference: 2.12 ± 1.7* Group 2 Baseline: 6.17 ± 2.73 Follow up: 4.81 ± 2.44 Difference: 1.57 ± 1.21*	Group 1 Baseline: 3.84 ± 2.7 Follow up:1.98 ± 2.38 Difference: 2.53 ± 1.98* Group 2 Baseline: 3.57 ± 1.97 Follow up: 1.86 ± 2.12 Difference: 1.98 ± 1.23*
Vicario et al.[28]	NA	NA	NA
Vivekananda et al.[16]	Group 1 Baseline: 89.7 ± 70.4 Follow up: 85.7 ± 73.5* Group 2 Baseline: 98.7 ± 60.4 Follow up: 0.49 ± 0.39*	Group 1 Baseline: 81.0 ± 67.0 Follow up: 77.0 ± 65.1* Group 2 Baseline: 80.3 ± 73.1 Follow up: 6.4 ± 67.9*	Group 1 Baseline: 105.3 ± 66.8 Follow up: 94.0 ± 62.8* Group 2 Baseline: 103.0 ± 66.4 Follow up: 6.4 ± 75.7*

*Significantly different from baseline values. NA, not available.

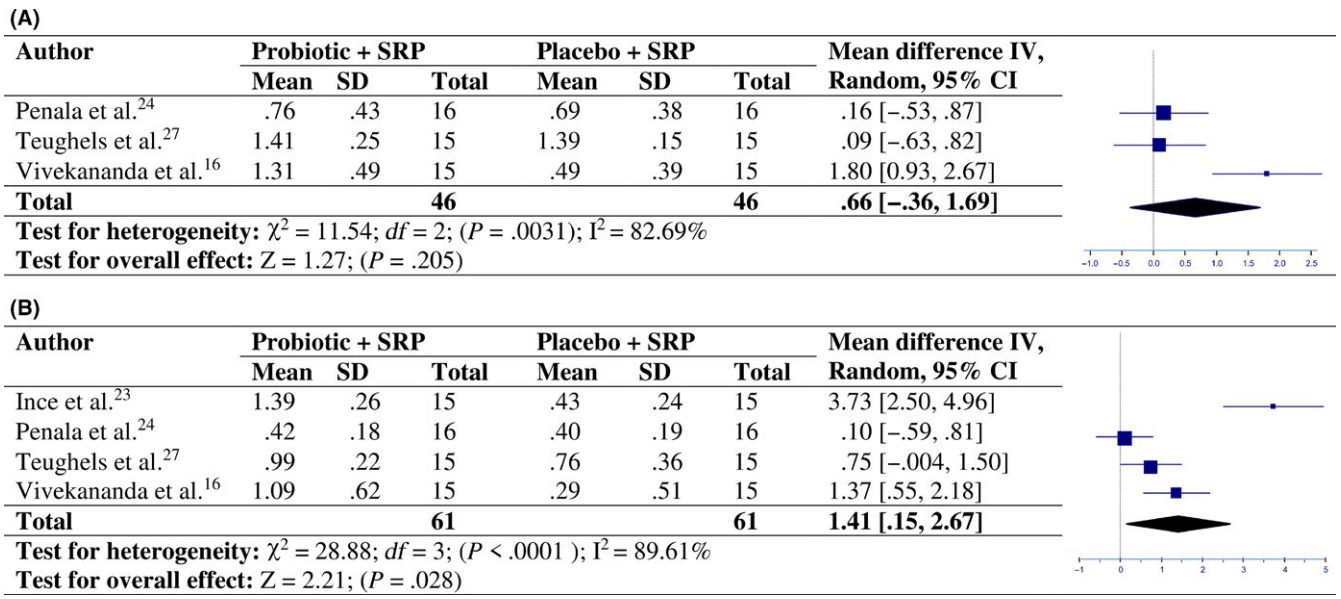

FIGURE 2 Forest plot presenting post-therapy (A) probing depth reduction and (B) clinical attachment level gain by comparing adjunctive probiotics versus scaling and root planing (SRP). CI, confidence interval; SD, standard deviation

dendritic cells, probiotics modulate the immune system to overcome infections.[29] In a recent systematic review by Matsubara et al., it was reported that oral probiotics are as safe and effective as adjunct to SRP in CP.[31]

The majority of the included studies showed additional benefits of probiotics in periodontal inflammation; however, these results should be interpreted with caution due to several factors. Factors, such as dosage of probiotics, route of administration, frequency of applications, and follow up, should be taken into consideration. It is important to note that none of the studies reported a threshold dosage regarding the efficacy of probiotics in the treatment of CP. In addition, none of the included studies used the local drug delivery of probiotics, which could have resulted in superior periodontal outcomes compared to those with oral probiotics. Furthermore,

the frequency of probiotics use varied among the included studies. Using probiotics at each follow up and standardizing the applications might have given enhanced results in the studies showing comparable outcomes. Although these clinical studies reported oral and systemic probiotic use to gain attachment level, a precise dosage and frequency of the drug that would yield the most favorable clinical outcome remains unclear. As seen in the studies that favored the use of adjunctive probiotics compared to placebo/SRP, their follow up was long compared to studies that showed comparable outcomes (follow up ranging from 6 to 12 weeks only).[16,23,25,26]

Another noteworthy fact was that only two clinical studies assessed bacterial counts. We were unable to perform the meta-analysis, as the two clinical studies reported microbiological outcomes in different units.[16,27] It is well established that the eradication of periopathogenic bacteria that are implicated in the pathogenesis of CP from deep periodontal pockets determine successful treatment outcomes.[32] In addition, only two studies assessed the levels of cytokines.[23,25] It is well recognized that the outcomes of CP also rely on the assessment of biomarker levels that could be used as a surrogate measure.[33] Further studies are warranted with regard to the levels of bacteria and cytokines so that future systematic reviews could quantitatively assess the total overall effects of probiotics in the successful treatment of CP.

The following limitations should be taken into account when considering the conclusions of the present review. The present systematic review only considered studies published in the English language. This could have resulted in publication bias, with potentially relevant studies published in other language being missed.[34] The follow-up period seemed inadequate, and longer follow-up periods could have yielded different outcomes. Therefore, to determine the clinical outcomes in the management of CP with the use of probiotics, further studies with long follow-up periods are recommended in order to witness changes in the clinical severity and microbiological changes in CP. In addition, a high risk of bias was found in more than half of the included studies for sample-size calculation, masking of assessors, and internal validity (selection bias).[16,24,25,28] These methodological shortcomings should be cautiously considered when interpreting the findings of the present systematic review. A significant heterogeneity was observed in the included studies in terms of probing depth reduction ($P = .0031$) and CAL gain ($P < .0001$). This could be due to the inclusion of a low number of studies and variations in the differences of clinical periodontal outcomes.

In light of other methodological aspects in the included studies,[16,23–28] such as short follow-up period and low-quality studies, it is suggested that the role of probiotics in improving clinical signs and symptoms of CP compared to placebo/SRP results in CAL gain, but is still debatable with regard to PPD reduction. Therefore, studies with long-term follow up and high-quality, controlled clinical trials are recommended to reliably assess the efficacy of probiotics in the reduction of signs and symptoms of CP.

4.1 | Conclusion

The data from this systematic review suggest that adjunctive probiotics could result in additional benefits in CAL gain in CP. Nevertheless, further high-quality RCT with microbiological outcomes are warranted to obtain strong conclusions in this regard.

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