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Use of Probiotics as Adjuncts in Non-Surgical Periodontal Therapy: A Literature Review

Nicolás Zambrano Pacheco[1], Carolina López Orozco[1] and Rubiel Antonio Marín Jaramillo[2]*

[1]*Periodontist, Department of dentistry, CES University, Colombia.*

[2]*Periodontist. MSc. PhD., Department of dentistry, CES University, Colombia.*

***Correspondence:**
Rubiel Antonio Marín Jaramillo, Periodontist, MSc. PhD., Department of dentistry, CES University, Colombia.

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ABSTRACT

Introduction: *Periodontitis is a chronic inflammatory disease associated with dysbiotic plaque biofilms, characterized by clinical attachment loss (CAL) and alveolar bone loss, which negatively impacts quality of life. There are several treatment approaches, including surgical methods and the use of antibiotics, but limitations and bacterial resistance have led to the search for more effective alternatives. Probiotics may inhibit the recolonization of periodontopathogens through direct and indirect mechanisms. However, evidence regarding their efficacy in the treatment of periodontitis is still inconclusive due to the diversity of methodologies in the studies.*

Objective: *Review the existing literature to evaluate the benefits of probiotics as adjuncts in non-surgical periodontal therapy.*

Materials and Methods: *A search was conducted in electronic databases (PubMed) up to September 2024 for randomized controlled trials (RCTs) comparing scaling and root planing (SRP) combined with probiotics versus SRP alone or with placebo. The outcome variables evaluated included clinical periodontal parameters, immunological and microbiological monitoring.*

Results: *Twelve RCTs were included that evaluated clinical periodontal, microbiological, and immunological parameters. Five demonstrated effectiveness in improving clinical periodontal parameters, four showed a reduction in periodontal pathogens, and three found improvements in the immune response of patients using probiotics as adjuncts to scaling and root planing (SRP).*

Conclusions: *Studies indicate that probiotic supplementation could improve clinical, microbiological, and immunological parameters in patients with periodontal disease. However, the effectiveness of these probiotics varies depending on the formulation, method of administration, duration of treatment, and type of periodontal disease. Long-term randomized controlled trials (RCTs) are needed to confirm the efficacy of probiotics as adjuncts in periodontal treatment and to assess their impact on health over time.*

Keywords
Antibiotics, Chemical agents, Probiotics.

Introduction

Periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms. Its main characteristics include the deterioration of periodontal tissue support, manifested by clinical attachment loss and alveolar bone loss assessed radiographically, the presence of periodontal pockets, and gingival bleeding [1]. According to the *Global Burden of Disease*, severe periodontitis is the eleventh most prevalent chronic disease worldwide [2,3], being an important public health issue as it can lead to tooth loss, negatively affecting function and aesthetics, resulting in significant deterioration in quality of life [4], highlighting the importance of reinforcing its prevention and treatment. Currently, there are several approaches for the treatment

of periodontal disease aimed at the elimination or reduction of bacterial biofilm and subgingival calculus (surgical and non-surgical periodontal therapy), accompanied by adjuncts such as the use of local or systemic antibiotics, chemical agents, and laser [5,6]. The limitations of these treatments and the resistance created by the indiscriminate prescription of antibiotics have led to the need to find more effective alternatives that can enhance periodontal treatment and have fewer side effects [7].

Treated sites can be recolonized by periodontopathogens [7], which can be inhibited if the adhesion receptors bind to other microorganisms with little or no virulence potential [8]. According to the World Health Organization (WHO) and the Food and Agriculture Organization (FAO), probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit to the host" [9,10], they have two main mechanisms of action: first, a direct mechanism, generating interaction with bacteria in the biofilm through competition for binding sites and nutrients, and the production of antimicrobial agents that inhibit their growth; and second, an indirect mechanism, modulating the innate and adaptive immune functions of the host [11,12]. With the available evidence, it is difficult to conclude whether probiotics promote any clinical benefit in the treatment of periodontal disease due to the diversity of methodologies used in the studies [13-15]. The objective of this article is to review the existing literature to understand the benefits of using probiotics as an adjunct to non-surgical periodontal therapy.

Materials and Methods

Search Strategy

An electronic search was conducted in the Medline database (via PubMed) to select randomized clinical trials evaluating the effects of probiotics in periodontal disease, published in the last ten years and with full text available. The search terms were:

Probiotics Probiotical probiotic NOT dental pulp OR pulp OR endodontic OR endodontal OR endodontically

((("probiotics"[All Fields] OR "probiotical"[All Fields] OR "probiotics"[MeSH Terms] OR "probiotics"[All Fields] OR "probiotic"[All Fields] OR ("probiotics"[All Fields] OR "probiotical"[All Fields] OR "probiotics"[MeSH Terms] OR "probiotics"[All Fields] OR "probiotic"[All Fields])) AND "periodont*"[All Fields]) NOT ("dental pulp"[MeSH Terms] OR ("dental"[All Fields] AND "pulp"[All Fields]) OR "dental pulp"[All Fields] OR "pulp"[All Fields] OR ("endodontal"[All Fields] OR "endodontic"[All Fields] OR "endodontical"[All Fields] OR "endodontically"[All Fields] OR "endodontics"[MeSH Terms] OR "endodontics"[All Fields]))) AND ((y_10[Filter]) AND (clinicaltrial[Filter]) AND (fft[Filter])).

Screening and Selection

The titles and abstracts of the selected publications were independently reviewed by two reviewers (L.C and Z.N) and classified as suitable or not suitable for inclusion. Full reports of those studies that appeared to meet the inclusion criteria or for which the information in the title and abstract was insufficient to determine inclusion were obtained and independently reviewed. The manuscripts for full-text review were selected according to the following eligibility criteria:

Inclusion Criteria

1. Randomized clinical trials published in the last 10 years.
2. Studies that evaluated the effect of using probiotics as adjuncts in the non-surgical treatment of periodontal disease.
3. Included a control group where only scaling and root planing were performed.
4. Studies that reported measurements of clinical periodontal parameters.
5. Studies that reported measurements of microbiological and/or immunological parameters.
6. Published in English or Spanish.

Exclusion Criteria

1. Case reports, pilot studies, case series, and literature (or systematic) reviews. Full copies of all potentially relevant studies were evaluated.
2. Patients with systemic compromise.
3. Studies that included other types of adjunctive therapies different from probiotics.

Results

Study Selection

A total of 70 articles were found in the search. After reviewing the titles and abstracts, 48 were excluded as they did not mention the probiotic used or addressed diseases other than periodontitis. Twenty-two articles were evaluated in full text, and four were removed for not meeting the inclusion and exclusion criteria (Figure 1). In total, 12 clinical trials were included in this review.

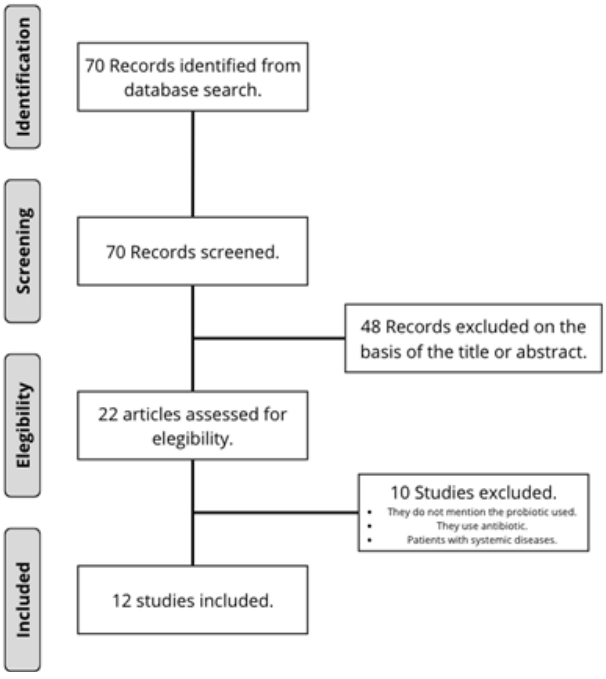

Figure 1: Flowchart of the search and study selection process.

General Characteristics of the Included Studies

The general characteristics are shown in Table 1. Twelve randomized clinical trials (RCTs) were included. The number of patients in the sample varied between 30 and 127. In all studies, the control and test groups were compared. The control group received scaling and root planing (SRP) plus a placebo or SRP alone, while the test group received probiotics as an adjunct to SRP. The most commonly used species was *L. reuteri,* employed in a total of four trials [16-19], in the others, different species of Lactobacillus, Bifidobacterium, or streptococci were used.

Changes in Clinical Periodontal Parameters

Probing depth (PD)

Probing depth is the measurement taken from the gingival margin to the base of the gingival sulcus. This measurement serves as a record of the disease history. Accurate identification and precise evaluation are essential for diagnosing periodontitis. Furthermore, recognizing changes is crucial for assessing the severity of the

Table 1: General Characteristics of the Included Studies.

Author and Year	Study Design	Sample Size and Groups	Periodontal Diagnosis	Probiotic Used	Evaluated Parameters	Follow-ups and Presentation
Poulose M et al. 2024 [20]	RCT	n: 62 sites • Test: 31 • Control: 31	Periodontitis stage II or III grade B	*S. faecalis, C. butyricum, B. mesentericus, L. sporogenes and S. boulardii*	• PD, CAL, GI, GR. • Microbiological monitoring	• 12 weeks • 4 and 8 days • Powder
Özener HÖ et al. 2023 [21]	RCT	n: 30 patients • Test: 15 • Control 15	Periodontitis stage III grade B	*Bifidobacterium Animalis subsp. Lactis and DN-173010*	• PD, CAL, PI, BoP, GI. • Microbiological monitoring	• 0, 28 days and 3 months • Yogurt
Ranjith A et al. 2022 [22]	RCT	n: 60 patients • Test: 30 • Control 30	Periodontitis stage II	*L. acidophilus, L. rhamnosus, B. longum, S. boulardii.*	• PD, CAL, PI, GI. • Immunological monitoring	• 0, 1 and 3 months • Rinse
Invernici MM et al. 2018 [23]	RCT	N: 41 patients • Test: 20 • Control 21	Generalized chronic periodontitis	*B. lactis HN019*	• PD, PI, BoP, CAL and GR. • Microbiological and inmunological monitoring	• 0, 30 and 90 days • Lonzenges
Tekce M et al. 2015 [16]	RCT	n: 40 patients • Test: 20 • Control: 20	Chronic periodontitis	*L. reuteri*	• PD, CAL, PI, GI, BoP. • Microbiological monitoring	• 0, 21, 90, 180 and 360 days • Lonzenges
İnce G et al. 2015 [17]	RCT	n: 30 patients • Test: 15 • Control: 15	Chronic periodontitis	*L. reuteri*	• PD, PI, GI, BoP, CAL • Immunological monitoring	• 0, 21, 90, 180 and 360 days • Lonzenges
Alhamoudi N et al. 2023 [24]	RCT	n: 72 patients • SRP: 19 • SRP+PT: 18 • PT+OHI: 17 • PT: 18	Periodontitis stage III and IV grade B and C	*L. rhamnosus*	• PD, CAL, PI, GI • Immunological monitoring	• 0 and 6 weeks • Sachet
De Oliveira A et al. 2022 [25]	RCT	N: 42 patients • Control: 23 • Test: 19	Moderate periodontitis	*5 strains of Lactobacillus and 3 strains of Bifidobacterium*	• PD, CAL, PI, BoP, GB, Sup • Microbiological monitoring	• 0 and 2 months • Capsule
Pudgar et al. 2021 [26]	RCT	40 patients • Test: 20 • Control: 20	Periodontitis stage III or IV	*L. brevis and L. plantarum*	• PD, CAL, GR, GI, PI • Microbiological monitoring	• 0 and 3 months • Gel and lonzenges
Vohra F et al. 2019 [18]	RCT	127 patients • S: SRP: 31 • S: SRP+PB: 32 • NS: SRP: 31 • NS: SRP+PB:33	Chronic periodontitis	*L. reuteri*	• PD, CAL, IP, BoP, MBL.	• 0, 3 and 6 months • Lonzenges
Pelekos G et al. 2020 [19]	RCT	447 sites • Test: 237 • Control: 210	Periodontitis stage III or IV	L. reuteri	• PD, CAL, BoP	• 0, 90 and 180 days • Lonzenges
Morales A et al. 2016 [27]	RCT	28 patients • Test: 14 • Control: 14	Chronic periodontitis	*L. rhamnosus*	• PD, CAL, BoP, PI	• 0, 3, 6, 9, and 12 months • Sachet

RCT: randomized clinical trial; **PT**: probiotic; **S**: shamma users; **NS**: no shamma users; **PD:** probing Depth; **CAL:** clinical attachment level; **BoP:** bleeding on probing; **PI:** Plaque index; **GI:** gingival index; **PISA:** periodontal inflamed surface area; **GR:** gingival recession; **MBL:** medium bone level; **BMI:** body mass index; **GB:** gingival bleeding; **OHI**: oral hygiene index; **SRP:** scaling and rood planning; **Sup:** suppuration.

disease, its progression, and therapeutic efforts [28].

In five 5 trials [16,17,20,22,23] it was reported that the test group achieved a significant reduction in probing depth compared to the control group, and 7 studies [18,19,21,24,25,27,29] did not report statistically significant differences between the groups.

Tekce M et al. [16] evaluated 40 patients with chronic periodontitis, divided into 2 groups. The test group received SRP + probiotic (L. reuteri) in lozenges, while the control group received SRP + placebo in lozenges (both lozenges twice a day for 3 weeks). The mean probing depth at 360 days was significantly lower in the test group (1.74 ± 0.62 mm) compared to the control group (0.57 ± 0.24 mm), and the mean difference between both groups was statistically significant (P<0.005). İnce G et al. [17]. In a double-blind clinical trial of 30 patients with chronic periodontitis, the test group received SRP + lozenges (L. reuteri) administered twice a day for 3 weeks, while the control group received only SRP. The mean probing depth at 360 days was significantly lower in the test group (1.70 ± 0.31 mm) compared to the control group (0.55 ± 0.26 mm), and the mean difference between both groups was statistically significant (P<0.05). Poulose M et al. [20] evaluated 62 sites in patients with stage II or III grade B periodontitis. The test group received SRP + probiotic (*S. faecalis, C. butyricum, B. mesentericus, L. sporogenes*, and *S. boulardii*) in powder form applied subgingivally on the day of therapy, while the control group received only SRP. The mean probing depth at 12 weeks for the test group was significantly lower (3.45 ± 0.57) compared to the control group (4.13 ± 0.72), and the intergroup mean difference was statistically significant (P<0.05). Ranjith A et al. [22] evaluated 60 patients with stage II periodontitis. The test group received SRP + probiotic (L. acidophilus, L. rhamnosus, B. longum, S. boulardii), while the control group received SRP + placebo, both as a rinse twice a day for 30 days. The mean probing depth at 90 days for the test group was significantly lower (2.65 ± 0.11 mm) compared to the control group (2.74 ± 0.15 mm), and the intergroup mean difference was statistically significant (P<0.05). Invernici MM et al. [23] evaluated 41 patients with chronic periodontitis. The test group received scaling and root planing (SRP) plus probiotics (B. lactis HN019), while the control group received SRP plus a placebo, both in lozenges twice a day for 30 days. Regarding moderate periodontal pockets (4-6 mm), the control group showed a lesser reduction (3.50 ± 0.45 mm) compared to the test group (3.19 ± 0.52 mm). In deep pockets (≥7 mm), the control group also had a lower reduction (4.64 ± 1.00 mm) compared to the test group (3.75 ± 1.32 mm) at 90 days, with a statistically significant intergroup difference (P<0.05).

Clinical Attachment Level (CAL)/Attachment Gain

Clinical attachment level (CAL) is the distance from the cementoenamel junction (CEJ) to the most apical point of probing depth [30]. It is an indicator of past periodontal destruction and can be used to monitor the progression of periodontitis. It has been utilized in clinical trials to assess the efficacy of various therapeutic modalities that may slow the progression of periodontal disease or allow for the regeneration of lost supportive tissues and attachment [31].

In five studies [16,17,20,22,23] a greater increase in clinical attachment level was reported when probiotics were used, along with findings from seven studies [18,19,21,24,25,27,29] did not report statistically significant differences between groups in the gain in clinical attachment level. Tekce M et al. [16] demonstrated that the mean gain in CAL at 360 days was significantly higher in the test group (1.39 ± 0.26 mm) compared to the control group (0.53 ± 0.24 mm), and the difference in means between the two groups was statistically significant (P<0.005). İnce G et al. [17] found that the mean gain in CAL at 360 days was significantly higher in the test group (1.39 ± 0.26 mm) compared to the control group (0.43 ± 0.24 mm), and the difference in means between the two groups was statistically significant (P<0.05). Poulose M et al. [20] found that the CAL at 12 weeks for the test group was significantly lower (5.81 ± 0.79 mm) compared to the control group (6.68 ± 1.01 mm), and the intergroup difference in means was statistically significant (P < 0.05). Ranjith A et al. [22] demonstrated that the CAL at 90 days for the test group was significantly lower (2.25 ± 0.11 mm) compared to the control group (2.72 ± 0.10 mm), and the intergroup difference in means was statistically significant (P<0.05). Invernici MM et al. [23] reported that concerning moderate periodontal pockets (4-6 mm), the control group had a higher clinical attachment level (3.94 ± 0.63 mm) compared to the test group (3.48 ± 0.59 mm). In deep pockets (≥7 mm), the control group also had a higher clinical attachment level (5.55 ± 1.37 mm) compared to the test group (4.03 ± 1.44 mm) at 90 days, with a statistically significant intergroup difference (P<0.05).

Gingival Recession (GR)

It is the distance between the cementoenamel junction (CEJ) and the gingival margin that indicates the degree of recession. This can lead to increased sensitivity due to the exposure of dentin and can be identified by the appearance of a clinically longer tooth and the variation in the proportion of the teeth compared to the adjacent ones [32].

In two studies [20,23], they reported a reduction in gingival recession and findings from one study there were no statistically significant differences [29]. Poulose M et al. [20] found that the mean GR at 12 weeks for the test group was significantly lower (2.32 ± 0.48 mm) compared to the control group (2.65 ± 0.55 mm), and the intergroup difference in means was statistically significant (P<0.05). Invernici MM et al. [23] reported differences only in deep periodontal pockets (≥7 mm) with a statistically significant difference (P<0.05), finding that the test group had lower GR (0.28 ± 0.66 mm) compared to the control group (0.40 ± 0.47 mm) at 90 days. Pudgar P et al. [29] evaluated 40 patients with stage III and IV periodontitis, divided into 2 groups. The test group received SRP + probiotics (L. brevis and L. plantarum) in lonzenges once a day for 30 days and in gel administered in periodontal pockets ≥ 5 mm at the end of SRP, while the control group received SRP + placebo in lonzenges. The mean reduction in GR at 3 months of follow-up did not show statistically significant differences (P < 0.05).

Bleeding on Probing (BoP)

The evaluation of the presence or absence of bleeding on probing (BoP) is a widely used clinical parameter [21]. To determine the progression of periodontal disease, serving as an indicator of active disease or periodontal stability [33,34]. Four studies [17,18,23,25] demonstrated a reduction in BoP, while five studies [18,19,25,27,29] did not show statistically significant differences. Tekce M et al. [16] reported a higher reduction in BoP at 360 days in the test group (11.05 ± 3.99) compared to the control group (19.95 ± 4.88), and the difference in means between the two groups was statistically significant ($P < 0.05$). İnce G et al. [17] reported a higher reduction in BoP at 360 days in the test group (11.60 ± 4.35) compared to the control group (19.00 ± 5.42), and the difference in means between the two groups was statistically significant ($P < 0.05$). Invernici MM et al. [23] reported that regarding BoP in moderate pockets (4-6 mm), the test group had a higher reduction (15.95 ± 10.58) compared to the control group (10.23 ± 8.82). In deep pockets (≥7 mm), the test group also had a higher reduction (4.35 ± 3.95) compared to the control group (3.10 ± 2.40) at 90 days, with a statistically significant intergroup difference ($P < 0.05$). Özener HÖ et al. [21] demonstrated a higher reduction in BoP at 3 months in the test group (42.12 ± 22.30) compared to the control group (26.82 ± 11.63), and the difference in means between the two groups was statistically significant ($P < 0.05$).

Gingival Index (GI)

It was designed to assess gingival condition, clearly distinguishing between the quality of the gum (the severity of the lesion) and the location (quantity) in relation to the four areas (buccal, mesial, distal, lingual) that make up the total circumference of the marginal gum [35]. This index does not consider the depth of periodontal pockets, degrees of bone loss, or any other quantitative changes in the periodontium. The criteria are limited exclusively to qualitative changes in the gingival soft tissue [36]. Five studies [16,17,20-22] found reduction in the GI y en 2 estudios [24,29] it is not the case.

Tekce M et al. [16] reported a lower GI at 360 days in the test group (0.80 ± 0.38) compared to the control group (1.66 ± 0.36), and the difference in means between the two groups was statistically significant ($P < 0.05$). İnce G et al. [17] reported a lower GI at 360 days in the test group (0.73 ± 0.28) compared to the control group (1.73 ± 0.31), and the difference in means between the two groups was statistically significant ($P < 0.05$). Poulose M et al. [20] found that the mean GI at 12 weeks for the test group was significantly lower (0.95 ± 0.39 mm) compared to the control group (1.31 ± 0.52 mm), and the intergroup difference in means was statistically significant ($P < 0.001$). Özener HÖ et al. [21]. They demonstrated a higher reduction in GI at 3 months in the test group (1.34 ± 0.35) compared to the control group (1.08 ± 0.27), and the difference in means between the two groups was statistically significant ($P < 0.05$). Ranjith A et al. [22]. They found that the mean GI at 90 days for the test group was lower (0.89 ± 0.07) compared to the control group (1.0 ± 0.07), and the intergroup difference in means was statistically significant ($P < 0.05$).

Plaque Index (PI)

The Plaque Index (PI) is based on the same principle as the Gingival Index, namely the need to clearly distinguish between the severity and location of soft debris accumulations [37]. The aim of introducing this system was also to create a plaque index that would completely correspond with the Gingival Index [36]. Inflammation at the site is initiated by the accumulation of dental biofilm, which plays an essential role in the onset of periodontal disease. Therefore, plaque control is crucial for periodontal health [38,39]. Three studies [16,17,21] demonstrated a lower amount of plaque, while six studies [18,22,24,25,27,29] showed no statistical differences in the reduction of the plaque index.

Tekce M et al. [16] reported a lower PI at 360 days in the test group (0.73 ± 0.24) compared to the control group (1.39 ± 0.28), and the difference in means between the two groups was statistically significant ($P < 0.05$). İnce G et al. [17] reported a lower PI at 360 days in the test group (0.76 ± 0.24) compared to the control group (1.43 ± 0.26), and the difference in means between the two groups was statistically significant ($P < 0.05$). Özener HÖ et al. [21] demonstrated a higher reduction in PI at 3 months in the test group (1.63 ± 0.23) compared to the control group (1.43 ± 0.16), and the difference in means between the two groups was statistically significant ($P < 0.05$).

Microbiological Monitoring

In the study by Poulose M et al. [20] the difference in the mean colony-forming units (CFU) in the test group at baseline showed a statistically significant reduction on days 4 and 8 when probiotics were used as an adjunct to non-surgical periodontal therapy. Invernici MM et al. [23] reported a higher count of *A. naeslundii* and *S. mitis* in the test group, along with a more pronounced reduction in the counts of *P. gingivalis, T. denticola, F. nucleatum vincentii, C. showae,* and *E. nodatum* compared to the control group for deep periodontal pockets. Additionally, the test group showed significantly lower mean proportions of orange complexes (at 30 days), and red and blue complexes (at 90 days) than the control group. De Oliveira AM et al. [25] found a significant decrease in the microbial species count in subgingival plaque with no differences between the groups assessed from baseline to 2 months post-therapy. Tekce M et al. [16] demonstrated a lower quantity of obligate anaerobes and CFUs up to day 180 with the administration of probiotics, but at 360 days, there were no statistically significant differences. Pudgar P et al. [29] found a suppression below the detection threshold of *F. nucleatum* in a greater number of subjects in the test group who received probiotics compared to subjects in the control group. Özener HÖ et al. [21] did not demonstrate statistically significant differences at 3 months with the use of probiotics in microbiological monitoring.

Immunological Monitoring

Ranjith A et al. [22] evaluated salivary IgA using the Enzyme Immunoassay Kit (XEMA Co. Ltd., catalogue no: K276), showing an increase in the probiotic group at 30 days, returning to baseline levels by 90 days. Additionally, the use of probiotics significantly

increased salivary pH at both 30 and 90 days. Invernici MM et al. [23] found that the test group had higher levels of Interleukin-10 (IL-10) at 30 days. In contrast, the control group exhibited a higher ratio of Interleukin-1β (IL-1β) at both 30 and 90 days, and Interleukin-8 (IL-8) at 30 days when compared to the test group. İnce G et al. [17] using the ELISA test, demonstrated a lower amount of matrix metalloproteinase-8 (MMP-8) and a higher amount of tissue metalloproteinase inhibitor (TIMP-1), with these changes being statistically significant ($P < 0.05$) up to 180 days; however, at 360 days, there were no differences. Alhamoudi N et al. [24] found no statistical differences ($P < 0.05$) in cortisol levels at any follow-up period between the two groups.

Discussion

Summary of the evidence

In this literature review, the results demonstrate a significant efficacy of using probiotics as an adjunct to SRP compared to those treated with placebo plus SRP, improving periodontal clinical parameters in five trials [16,17,20,22,23], in the other seven trials, no significant improvement was observed [18,19,21,24,25,27,29]. These results are comparable to the systematic review by Jayaram P et al. [13] which evaluated 14 randomized clinical trials. Of the trials included in this systematic review, 6 demonstrated benefits from the use of probiotics as an adjunct to SRP, while 8 did not report such benefits. The probiotics used in the included trials were *L. reuteri [16-19], L. rhamnosus [24,27], B. lactis HN019 [23],* combinations of 5 strains of *Lactobacillus and 3 de Bifidobacterium [25], L. brevis* and *L. plantarum [29], Bifidobacterium Animalis subsp. Lactis and DN-173010 [21], Spp. faecalis, C. butyricum, B. mesentericus, L. sporogenes and S. boulardii [20] and L. acidophilus, L. rhamnosus, B. longum, S. boulardii [22]*.

It has been suggested that probiotics as adjuncts to non-surgical periodontal therapy could influence periodontal clinical parameters through both direct and indirect mechanisms of action. The direct interaction of probiotics occurs through their ability to resist colonization, which includes competition for binding sites, nutrients, and the production of antibacterial agents that inhibit the growth of pathogens [7,12]. It is suggested that probiotics can induce modifications in the structure of the microbial community, which may lead to changes in interactions between bacteria (cooperation and competition), reduce the presence of more virulent pathogens, and restore the balance of the oral ecosystem [40,41]. This action of probiotics is enhanced by the release of antimicrobial peptides such as lactic acid, hydrogen peroxide, bacteriocins, bacteriocin-like substances, and reuterin. They exhibit anti-inflammatory, immunomodulatory, and antipathogenic effects in the human body, including the oral cavity. These properties have been observed in most species of lactobacilli, such as *L. reuteri*, *L. brevis*, and *L. salivarius* [42,43].

In the microbiological results found in this literature review, the use of adjunctive probiotics was associated with a reduction in colony-forming units (CFU) [16,20]. Reduction of *P. gingivalis, T. denticola, C. showae, E. nodatum* [23] and *F. nucleatum* [23,29]. Additionally, Tekce M et al. [16] demonstrated a lower quantity of obligate anaerobes at 180 days. These results are supported by other studies showing a significant reduction of *P. gingivalis* [12,44]*, T. forsythia* [12,44,45]*, T. denticola* [44,45], *P. intermedia* [44] y *Aggregatibacter actinomycetemcomitans* [44,46].

The indirect interaction of probiotics occurs through immune modulation, both innate and adaptive. It has been observed that lactic acid-producing bacteria can interact with immune system cells, such as macrophages and T cells, modifying cytokine production and, consequently, the overall functioning of immunity. In addition to influencing immune responses, certain probiotic species can increase mucin production and enhance barrier function, regulate antimicrobial peptides, and stimulate angiogenesis and wound healing [41]. Although immunomodulatory properties of probiotics are suggested, few studies have evaluated the impact of probiotic administration in this literature review. Ranjith A et al. [22] reported an increase in IgA; this increase in salivary IgA enhances the anti-inflammatory properties of L. rhamnosus by conditioning mucosal dendritic cells and improving their tolerogenic profiles, essential for maintaining homeostasis [47]. In contrast, a meta-analysis by Ebrahimpour-Koujan S et al. [48] found no significant increase in salivary IgA levels after oral probiotic treatments compared to placebo. Invernici et al. [23] reported an increase in IL-10, which has been shown to delay bone loss, favor anti-inflammatory properties, and maintain periodontal health [49-51]; A meta-analysis by Milajerdi A et al. [52] reported an increase in IL-10 when probiotics were used (SMD 0.21; 95% CI, 0.04, 0.38); İnce G et al. [17] reported an increase in TIMP-1 and a reduction in MMP-8, an enzyme involved in the destruction of periodontal tissue. The production of these biomarkers is regulated by various cytokines and growth factors. TIMPs act as inhibitors that bind to the active site of MMPs, resulting in reduced MMP activity. An imbalance between MMP activity and regulation by TIMPs leads to the degradation of matrix proteins, contributing to the destruction of periodontal tissue [53,54]. A meta-analysis by Gheisary Z et al. [12] reported a statistically significant reduction in MMP-8 (SMD = 0.819, 95% CI: 0.417, 1.221, $I^2 < 0.001$, p-value ≤ 0.05). Alshareef A et al. [55] demonstrated lower levels of MMP-8 at 30 days with the use of probiotics as an adjunct to SRP, but this difference was not statistically significant when compared to SRP alone. Invernici MM et al. [23] reported a reduction in IL-1β and IL-8, both pro-inflammatory cytokines related to adaptive and innate immune responses, associated with inflammation, autoimmunity, cardiovascular disorders, and cancer [56]. Contradictory results were found in a meta-analysis by Ebrahimpour-Koujan S et al. [48] which demonstrated an increase in IL-1β and IL-8 after oral probiotic treatments compared to placebo. Other pro-inflammatory cytokines that have been evaluated include tumor necrosis factor-alpha (TNF-α), an inflammatory cytokine produced by macrophages and monocytes during acute inflammation. When elevated, it activates mechanisms that lead to the destruction of periodontal tissues, affecting the formation and maturation of osteoclasts as well as bone remodeling [57,58]. Additionally, IL-17 is another pro-inflammatory cytokine that stimulates neutrophil activation

[59] and mediates pro-inflammatory reactions by cooperating with other pro-inflammatory cytokines, primarily TNF-α and IL-1β [60]; A positive correlation has been reported between IL-17 and the severity of periodontitis [61]. In a RCT de Szkaradkiewicz AK et al. [62] a reduction in these pro-inflammatory cytokines (TNF-α, IL-1β, and IL-17) was found with the administration of probiotics as an adjunct to SRP compared to SRP alone.

The use of antibiotics as a complementary therapy to non-surgical periodontal therapy has been documented, and their effectiveness has been evaluated against probiotics. In a systematic review by Puzhankara L et al. [63] probiotics showed a significant reduction in probing depth (PD) and clinical attachment level (CAL) compared to antibiotics. Antibiotics were more effective in reducing plaque index (PI) and gingival index (GI). A combination of probiotics and antibiotics was superior compared to the use of either alone. However, antibiotics have reported side effects such as headaches, metallic taste, nausea, vomiting, abdominal pain, microbial resistance, and allergies [64,65]. Additionally, Tekce M et al. [16] and Invernici MM et al. [23] reported excellent compliance and adherence to treatment with probiotics.

The limitations of this literature review stem from the variety of case definitions for periodontal disease and the follow-up periods (ranging from 4 to 360 days). Additionally, the diversity of protocols used in the studies, which includes variations in strains, doses, formulations, and treatment durations, contributes to heterogeneity in the results. This variability not only complicates comparisons between different studies but also restricts the ability to draw firm conclusions about the effectiveness of probiotics. The inclusion of smoking and diabetic patients in literature reviews on the use of probiotics for periodontal disease treatment presents challenges for analysis, primarily due to the lack of studies with long-term follow-up, which limits the understanding of the sustained effects of probiotics in these populations.

Conclusion

Currently, few studies have investigated the effect of adjunctive probiotics in SRP for the management of periodontitis, although this emerging therapy shows potential. The results suggest a possible improvement in clinical, microbiological, and immunological parameters with the supplementation of adjunctive probiotics to SRP in patients with periodontal disease. However, the effectiveness of this supplementation depends on several factors, such as the formulation of the probiotic, the method of administration, the duration of treatment, and the type of periodontal disease present. Long-term randomized controlled trials (RCTs) are needed to confirm the efficacy of probiotics as adjuncts in the treatment of periodontal disease and to assess their impact on periodontal health over time.

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