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The Effects of Probiotics on the Treatment of Chronic Periodontitis: A Systematic Review

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Background and objectives: Probiotics have recently emerged as adjunctive agents to conventional periodontal treatment, aiming to improve clinical outcomes. This study systematically reviews published literature evaluating the potential clinical benefits of probiotics in treating chronic periodontitis.

Materials and methods: A search of the MEDLINE database (via PubMed) was conducted up to November 2020. Randomized clinical trials (RCTs) in English comparing probiotics to a placebo for treating chronic periodontitis were selected. Clinical outcome variables included probing pocket depth (PPD), clinical attachment level (CAL), plaque index (PI), and bleeding on probing (BOP).

Results: Eight studies met the inclusion criteria. All were double-blind, parallel-arm, placebo-controlled RCTs. Six studies reported a statistically significant reduction in PPD, while four studies showed a beneficial reduction in BOP and PI compared to the control group.

Conclusion: Probiotic consumption appears to moderately improve the treatment of chronic periodontitis. However, heterogeneity among studies may limit the strength of this conclusion.

Keywords: Chronic periodontitis, Periodontal diseases, Probiotics.

1. Introduction

Chronic periodontitis (CP) is a biofilm-associated polymicrobial disease characterized by periodontal attachment loss and alveolar bone destruction.(1) While pathogenic bacteria are recognized as the main etiological factor (2), it is essential to acknowledge that the host response also significantly contributes to disease etiology (3). The primary treatment objective of periodontitis is to reduce bacterial load (4).

The optimal management approach for CP includes non-surgical periodontal therapy in conjunction with a focus on oral hygiene (5). In addition to this gold standard, various adjunctive therapies have been explored to enhance treatment outcomes and address limitations. These adjunctive approaches include antibiotics, antiseptics, and photodynamic therapy (6-8). Probiotic therapy represents another approach toward this goal.

Probiotics are described as "live microorganisms that, when given in sufficient quantities, provide a health advantage to the host."(9) . It is recognized that probiotics can modify existing flora and enhance the function of the host's microbial ecosystems (9). Probiotics have been studied to treat variety of gastrointestinal diseases and urogenital infections (10).

Studies have shown that probiotics may offer potential benefits in the oral cavity, such as preventing and treating halitosis, preventing oral candidiasis, and reducing the development of caries (11-13). Some studies have suggested the potential efficacy of probiotics in CP treatment (14, 15). Therefore, the aim of this systematic review is to evaluate the potential clinical benefits of probiotics in treating CP.

2. Materials and methods

2.1.Protocol

This study followed The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (16). The focused question, in PICO format, was: Does probiotic

consumption (I) lead to clinical improvements (O) in patients with chronic periodontitis (P).

2.2. Selection Criteria

Studies were selected following the PICO format. The population included adult patients with chronic periodontitis. The intervention was the use of probiotics, regardless of administration method. The outcomes of interest were probing pocket depth (PPD), clinical attachment level (CAL), plaque index (PI), and bleeding on probing (BOP). There were no specific restrictions on the control group in the included studies. Only randomized clinical trials evaluating the effect of probiotics on chronic periodontitis treatment were included. We excluded studies involving children, pregnant women, smokers, and patients with systemic conditions that could affect periodontitis or its treatment (e.g., Down syndrome and diabetes). Studies not explicitly stating the periodontal status of participants were also excluded.

2.3. Search Strategy

An electronic search was conducted in Medline (via PubMed) using the query: ("probiotics"[Mesh] OR probiotic*) AND ("periodontitis"[Mesh] OR "chronic periodontitis"[Mesh] OR "periodontal disease"). English-language articles published up to November 2020 were included..

2.4. Study Selection

Three independent reviewers (Z.M, S.O, and S.S) screened titles and abstracts. Studies meeting the inclusion criteria were selected. Subsequently, a thorough review of the selected articles was conducted. Disagreements were resolved through discussion.

2.5. Data Exrtaction

Data extraction was performed and confirmed by three reviewers (Z.M, S.O, and S.S).

2.6. Data Items

The following data were extracted and categorized from the included papers as follows: 1) study design; 2) sample size; 3) definition of chronic periodontitis; 4) probiotic used; 5) follow-up duration; 6) clinical parameters measured; 7) outcomes.

2.7. Risk of Bias Assessment

The Cochrane risk-of-bias tool for randomized trials (RoB 2) was used by two independent reviewers (S.O. and S.S.) to evaluate the risk of bias in studies. The overall risk of bias judgment was categorized as low risk, some concerns, or high risk of bias.

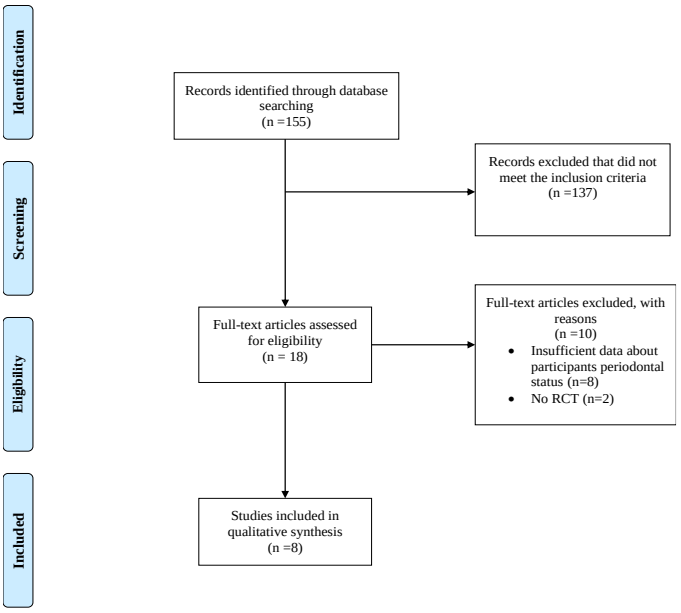

Fig. 1 Flow diagram of study selection

3. Results

3.1. Search Results

A total of 155 studies were identified, 18 studies met the inclusion criteria and underwent full-text analysis. Finally, 8 studies meeting the criteria were selected. The PRISMA flow diagram is shown in Figure 1.

3.2. Study Characteristics

3.2.1. General Characteristics

All selected studies were double-blind, parallel-arm, placebo-controlled randomized clinical trials conducted in English between 2013 and 2020. A total of 275 participants were included, with sample sizes ranging from 20 to 47. Seven out of eight studies reported participant demographics, including mean age and percentage of female individuals (14, 17-22). Mean participant age ranged from 41 to 68 years, with female percentages ranging from 38% to 64%. All selected studies focused on patients with CP, although the definition of CP varied among studies. The criteria for CP definition were ≥4mm PPD in five studies (15, 17, 20, 22), 5-7mm PPD in two studies (14, 18), and ≥5mm PPD in one study (19) . Follow-up periods ranged from 1 month to 1 year in included studies. Three studies

reported 12 months follow up period (14, 18, 19), in one study Clinical examination was recorded in 9 months follow up period (21), in three studies patients received clinical monitoring at 3 months follow up period (15, 20, 22), and one study reported 1 month follow up (17). Table 1 displays the characteristics of the included studies.

3.2.2. Probiotics Characteristics

In various studies, different types of probiotics were utilized. Lactobacillus species were used in six studies including, Lactobacillus reuteri (14, 17, 18), Lactobacillus rhamnosus (19, 21) and Lactobacillus plantarum (20). Two studies assessed the effects of Bifidobacterium animalis subsp. Lactis (15, 22). Additionally, there were various forms of probiotics: lozenges were used in four studies (14, 15, 18, 22), sachets in two studies (19, 21), tablets in one study (17), and hard gelatin capsules in another study (20). The duration of probiotic consumption varied across studies: four studies administered probiotics for three months (18-21), three studies for one month (15, 17, 22), and only one study used probiotics for three weeks (14).

3.3. Risk of Bias Assessment

Using the Cochrane risk-of-bias tool for randomized trials (RoB 2), out of our included studies, six were considered as low risk of bias, and two were classified as having some concerns. The results of the risk of bias assessment are reported in Figure 2.

3.4. Results of Individual Studies

3.4.1. Blending on Probing (BOP)

In all studies using probiotics leads to BOP reduction in comparison with baseline. The range of BOP reduction was 0.7% - 77.85% for the test group and 1.97% - 69.65% for the control group at all time points. There was a greater BOP reduction in one-year follow up ranged 11.7% - 77.85% for the test group and 8.3%-69.65% for the control group (14, 18, 19). The result of 3 months of BOP monitoring in 7 studies (14, 15, 18-22) shows BOP mean difference was from 0.7% to 72.25% and 1.97% to 66.8% in test and control group respectively.

3.4.2. Probing Pocket Depth

Six studies (14, 15, 18-21) reported PPD. Taking probiotics affects this parameter by significant reduction. Mean PPD reduction ranged from 0.09 mm to 1.74 mm in the test group and from 0.02mm to 0.6mm in the control group at all time points. In 1 year follow-up PPD reduction range was 0.6mm-1.74mm in the test group and 0.04 – 0.56mm in the control group (14, 18, 19). Additionally, one study (17) reported the mean percentage of sites with PPD of 4-5mm and sites with PPD of ≥6mm. The mean percentage of sites with PPD of 4-5mm was 40.4% in the test group and 45.3% in the control group at 1-month follow-up, while for sites with PPD of ≥6mm, it was 7.5% in the test group and 13.4% in the control group.

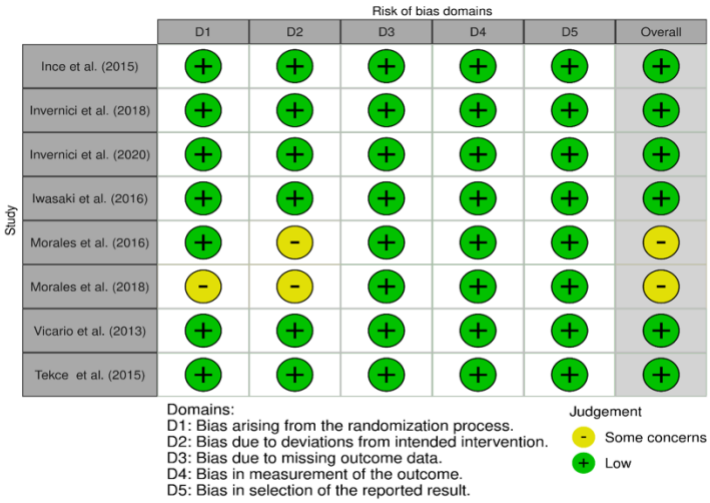

Fig. 2 Risk of bias domains of the included studies.

Table 1 Characteristics of the included studies

Author (y)	Study design	Sample size, No. of dropouts, age(mean), female%	Chronic periodontitis definition	Chronic periodontitis definition	Probiotic frequency	Follow-up (Time-point)	Clinical parameters	Outcomes
Vicario et al. (2013) (17)	Double-blind, Parallel, Placebo-controlled, RCT	20 (T:10; C:9) 1,(T: 58; C: 53.8) 38%	PPD≥ 4mm and CAL> 5mm on ≥ 2 non-neighboring teeth	-PPD≥ 4mm -CAL> 5mm on ≥ 2 non-neighboring teeth	Lactobacillus reuteri, Tablet, At least 2× 10^8 Living cells 1× per day for 1 month	1 month (BL, 1 mo.)	PI, BOP, PPD	The test group exhibited a statistically significant improvement ($p < 0.05$) in all periodontal measures, whereas the control group did not demonstrate any statistically significant changes.
Tekce et al. (2015) (14)	Double-blind, Parallel, Placebo-controlled, RCT	40 (T:20; C:20), 0, (T: 43± 5.01; C: 41.40± 8.86) 55%	Radiographically detected horizontal bone loss and presence of at least 2 teeth with an approximal sites each with a PD of 5-7mm and GI of ≥2 in each quadrant	-Radiographically detected horizontal bone loss -Presence of at least 2 teeth with an approximal sites each with a PD of 5-7mm	Lactobacillus reuteri, Lozenge Above 1× 10^8 CFU 2× per day for 3 weeks	360 days (BL, 21, 90, 180, 360 d)	PI, GI, BOP, PD, CAL	All parameters were significantly ($p<0.05$) lower in test group compared with control group at all time points

				-GI of ≥2 in each quadrant -Chronic periodontitis -Patients with radiographically -Detected horizontal bone loss (Armitage 1999), the presence of at least 2 teeth with one approximal				after treatment.
Ince et al. (2015) (18)	Double-blind, Parallel, Placebo-controlled, RCT	30 (T: 15; C: 15) 0, (T: 41± 3.17; C:42.2± 2.78) 43.3%	radiographically detected horizontal bone loss and the presence of at least 2 teeth with an approximal site each with a PD of 5-7 mm and a GI of ≥2 in each quadrant.	-Radiographically detected horizontal bone loss -Presence of at least 2 teeth with an approximal sites each with a PD of 5-7mm GI of ≥2 in each quadrant	Lactobacillus reuteri, Lozenge, Not reported, 2× per day for 3 months	360 days (BL, 21, 90, 180, 360 d)	PI, GI, BOP, PD, CAL	Inter group comparison of all parameters was found to be significant ($P<0.05$) in favour of test group at all time points. Attachment gain was significantly higher in the test group compared with control group.
Moraes et al.	Double-blind, Parallel,	28 (T:14, C:14) 0,	Presence of ≥5 teeth with periodontal	-Presence of ≥5 teeth with	Lactobacillus Rhamnus SP1,	12 months (BL, 3, 6, 9,	PI, CAL, PPD, BOP	Both test and control groups

(2016) (19)	Placebo - controlled, RCT	(T: 52.7± 7.3; C: 46.9± 10.3) 50%	sites with PPD≥4mm and CAL≥1mm and presence of 20% BOP and extensive radiographically determined bone loss.	periodontal sites with PPD≥4mm CAL≥1mm -Presence of 20% BOP extensive radiographically determined bone loss	Sachet, 2×10^7 CFU 1× per day for 3 months	12 mo.)		showed reduction in clinical parameters at all time points. ($p<0.05$)
Iwasaki et al. (2016) (20)	Double-blind, Placebo - controlled, RCT	39 (T: 19; C: 17), 3, (T: 68.2± 9.7; C: 67± 8.1) 64%	Having one or more initial periodontal pocket ≥ 4mm and having completed active treatment for chronic periodontitis.	-Having completed active treatment for chronic periodontitis having one or more initial periodontal pocket ≥ 4mm	Lactobacillus plantarum L-137, hard gelatin capsule, 50 mg of Lp20, 1× per day for 12 weeks	12 weeks (BL, 1, 2, 3 mo.)	PI, GI, BOP, PPD	BOP and PD were significantly reduced in both groups while there was significantly greater PD reduction ($P< 0.05$) in the experimental group than in the control group.
Moraleset al. (2018) (21)	Double-blind, Parallel, Placebo - controlled, RCT	47 (T:16; C:15; antibiotics :16) 0, (T: 46.5± 9.3; C: 52.8± 7.5; antibiotics : 49.0± 7.9) 45%	Presence of at least five teeth with periodontal sites with PPD ≥ 4mm and CAL ≥1 mm, 20% BOP and extensive radiographically determined bone loss.	-Presence of ≥5 teeth with periodontal sites with PPD≥4mm CAL≥1mm -Presence of 20% BOP extensive radiographically determined bone loss	Lactobacillus Rhamnosus SP1, Sachet, 2×10^7 CFU 1× per day for 3 months	9 months (BL,3, 6,9 mo.)	PI, CAL, PPD, BOP	All groups demonstrated improvements in clinical parameters at all time points ($p<0.05$), with no significant differences observed between

								the groups.
Invernici et al. (2018) (15)	Double-blind, Placebo-controlled, RCT	41 (T: 20; C:21), 0, Not reported	Having 30% or more of the sites with PPD≥4mm and CAl≥ 4mm or presence of BOP and minimum of 5 teeth with at least 1 site with CAL and PPD≥ 5mm	-Having 30% or more of the sites with: PPD≥4mm CAP≥ 4mm -Presence of BOP minimum of 5 teeth with at least 1 site with CAL and PPD≥ 5mm	Bifidobacterium animalis subsp. lactis HN019, Lozenges, CFU 10^9 2× per day for 30 days	90 days (BL, 30, 90 d)	PI, BOP, PPD, CAL, GR	The test group presented a decrease in PPD and a CAL significantly higher than those of the control group. ($p<0.05$)
Invernici et al. (2020) (22)	Double-blind, Parallel, Placebo-controlled, RCT	30 (T: 15; C: 15) 0, (T: 47.6± 9.97; C: 47.6± 9.49) 57%	Having 30% or more of the sites with PPD≥4mm and CAl≥ 4mm or presence of BOP and minimum of 5 teeth with at least 1 site with CAL and PPD≥ 5mm.	-Having 30% or more of the sites with: PPD≥4mm CAP≥ 4mm -Presence of BOP -Minimum of 5 teeth with at least 1 site with CAL and PPD≥ 5mm	Bifidobacterium animalis subsp. lactis HN019, Lozenge, CFU 10^9 2× per day for 1 month	90 days (BL, 30, 90 d)	PI, BOP	Test group presented lower PI and lower BOP when compared with control group. ($p<0.05$)

BL=baseline; BOP=bleeding on probing; C=control group; CAL=clinical attachment level; CFU=colony forming unit; GI=gingival index; GR=gingival recession; PD=probing depth; PI=plaque index; PPD=pocket probing depth; RCT=randomized clinical trial; T=test group

3.4.3. Plaque Index (PI)

All studies reported PI reduction followed by probiotic usage. Three studies utilized Löe and Silness' index, with mean PI reduction ranging from 0.04 to 1.56 in the test group and from 0.05 to 0.91 in the control group (14, 18, 20). Five studies measured PI dichotomously, with mean percentages ranging from 28.1% to 52.5% in the test group and from 27.4% to 67.4% in the control group (15, 17, 19, 21, 22). A noticeable PI (%) reduction was reported : 17% for the test group and 4.5% for the control group at 1-month follow-up (17).

3.4.4. Clinical Attachment Level (CAL)

Five studies (14, 15, 18, 19, 21) reported CAL. All these studies demonstrated attachment gain ranged from 0.07mm to1.39mm in the test group and 0.09mm to 0.53mm in the control group at all time points. Only two studies showed a statistically significant reduction in CAL :1.39mm for the test group and 0.43mm - 0.53mm for the control group in 1 year follow-up (14, 18). 3 months of monitoring of this parameter resulted in CAL reduction ranging from 0.05mm-1.18mm and 0.18mm to 0.79mm in the test and the control group respectively (14, 15, 18, 19, 21).

4. Discussion

The aim of his article was to assess the clinical benefits of probiotic consumption in improving chronic periodontitis. In summary, Six out of eight studies reviewed reported clinical benefits from probiotics, with probiotics used as adjunctive therapy in seven studies (14, 15, 17, 18, 20, 22).

While scaling and root planning stand as the gold standard treatment, adjunctive therapies are often necessary, especially in cases where SRP alone may be insufficient due to difficult access for instrumentation (1). Probiotics have emerged as a potential adjunct therapy for periodontal inflammation, offering benefits such as the production of antibacterial compounds, improvement of the epithelial barrier, prevention of pathogenic bacterial adhesion by forming biofilms on hard and soft tissues, and limiting pathogen access to essential nutrients required for adhesion and growth (23). Additionally, probiotics have shown promise in managing peri-implant mucositis, as reported by Hallström et al. (24).

In the analysis of 8 randomized clinical trials, all studies demonstrated a reduction in bleeding on probing (BOP), although only five studies showed statistically significant reductions compared to the control group. Probing pocket depth (PPD) reduction was statistically significant in favor of the probiotic group in six studies. Subgroup analysis indicated a statistically significant reduction in plaque index (PI) in four studies. Five studies reported a reduction in clinical attachment level (CAL), but only two were statistically significant (14, 18)

Previous reviews have yielded differing results regarding the effectiveness of probiotics on clinical parameters of periodontal diseases. While some randomized controlled trials have shown improvements across parameters, most reviews have found it challenging to draw definitive conclusions due to the limited number of available studies (14, 18, 25-27).

Future studies employing standardized protocols for probiotic application and follow-up may yield more comparable results. Despite the variability in concentrations and frequency of probiotics, an optimal amount for these factors remains unclear. The other sources of probiotics in the patients' daily meals were unclear, and they may have affected the results. Additionally, the studies did not use local delivery of probiotics, which may have resulted in better periodontal outcomes compared to oral probiotics. Therefore, more standardized clinical trials are recommended to obtain precise results for routine clinical management. Furthermore, adjunctive methods such as photodynamic therapy, as reported by Sgolastra et al., may enhance the effectiveness of SRP (30).

5. Limitations

It's important to note that the search process for this systematic review was conducted in only one database, and only English-language studies were included. This may have led to the omission of studies in other languages and databases, potentially introducing publication bias (28).

All studies included in this review demonstrated a variety of benefits in periodontal factors, but heterogeneity was observed among them (29). Several factors, such as varying types of probiotics, probiotic concentration, treatment duration, frequency of administration, and follow-up, should be considered for interpretation. Additionally, differences in the definition of chronic periodontitis among the included studies may have influenced treatment outcomes.

6. Conclusion

In conclusion, the findings of this review suggest that probiotics are safe and beneficial in managing chronic periodontitis, resulting in moderate improvements in treatment outcomes. However, the significant heterogeneity observed between studies may limit the generalizability of these conclusions. Further standardized research efforts are warranted to better understand the optimal protocols for probiotic use in chronic periodontitis management and to enhance the reliability of findings for routine clinical practice.

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Authors' contribution

Farshid Bastami: conceptualization, methodology, investigation, resources, data curation, writing-original draft, writing-review and editing, visualization, supervision, project administration
Saba Olyaie: conceptualization, methodology, investigation, resources, data curation, writing-original draft, writing-review and editing, visualization, project administration
Zahra Mansouri: conceptualization, methodology, investigation, resources, data curation, writing-original draft, writing-review and editing, visualization, project administration
Samin Soleymani Ghazijahani: conceptualization, methodology, investigation, resources, data curation, writing-original draft, writing-review and editing, visualization, project administration

Conflict of Interest

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