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Clinical effects of probiotics on the treatment of gingivitis and periodontitis: a systematic review and meta-analysis

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Abstract

Aims This study aimed to evaluate the impact of probiotics as an adjunct to periodontal therapy on clinical outcomes in patients with gingivitis and periodontitis through a meta-analysis of available evidence.

Materials and methods A detailed bibliographic search on four databases (PubMed, Scopus, Cochrane and EMBASE) was conducted with a language restriction. The collected data were assessed according to the predefined eligibility criteria and randomized clinical trials reporting the effects of probiotics on plaque index (PI), bleeding on probing (BOP) and pocket probing depth (PPD) compared to control or placebo groups were selected and analysed. The risk of bias assessment was conducted using SYRCLE's RoB- 2 tool. The GRADEpro tool was used to determine the overall quality of evidence.

Results Twenty-four studies (10 about gingivitis and 14 about periodontitis) were included in the meta-analysis. In the gingivitis studies, lower but non-significant PI and BOP were found in the probiotic group. In periodontitis, lower PI (95%-CI [- 0.54; - 0.15], $p = 0.001$) were reported in the probiotic group, and this difference was greater in studies with longer follow-up. Lower BOP (95%-CI [- 0.58; - 0.05], $p = 0.021$) was also reported, but this difference was only significant in studies with a shorter follow-up (95%-CI [- 0.86; - 0.11], $p = 0.012$). Meta-analysis for PPD showed lower, but non-significant, values (95%-CI [- 0.53; + 0.03], $p = 0.077$). However, this difference became significant when assessing studies with shorter follow-up (95% CI [- 0.77; - 0.07], $p = 0.019$).

Conclusions The meta-analysis provides evidence suggested that probiotics can serve as a beneficial adjunct to periodontal treatment in patients with periodontitis, particularly in improving clinical outcomes such as plaque index and bleeding on probing. The results from gingivitis studies highlight the need for further investigation to better understand the impact of probiotics in the early stages of periodontal disease. These findings emphasize the importance of future research with standardized protocols and longer follow-up periods to confirm and expand on the clinical utility of probiotics in periodontal therapy.

Keywords Gingivitis, Periodontitis, Probiotics, Meta-analysis, Systematic review

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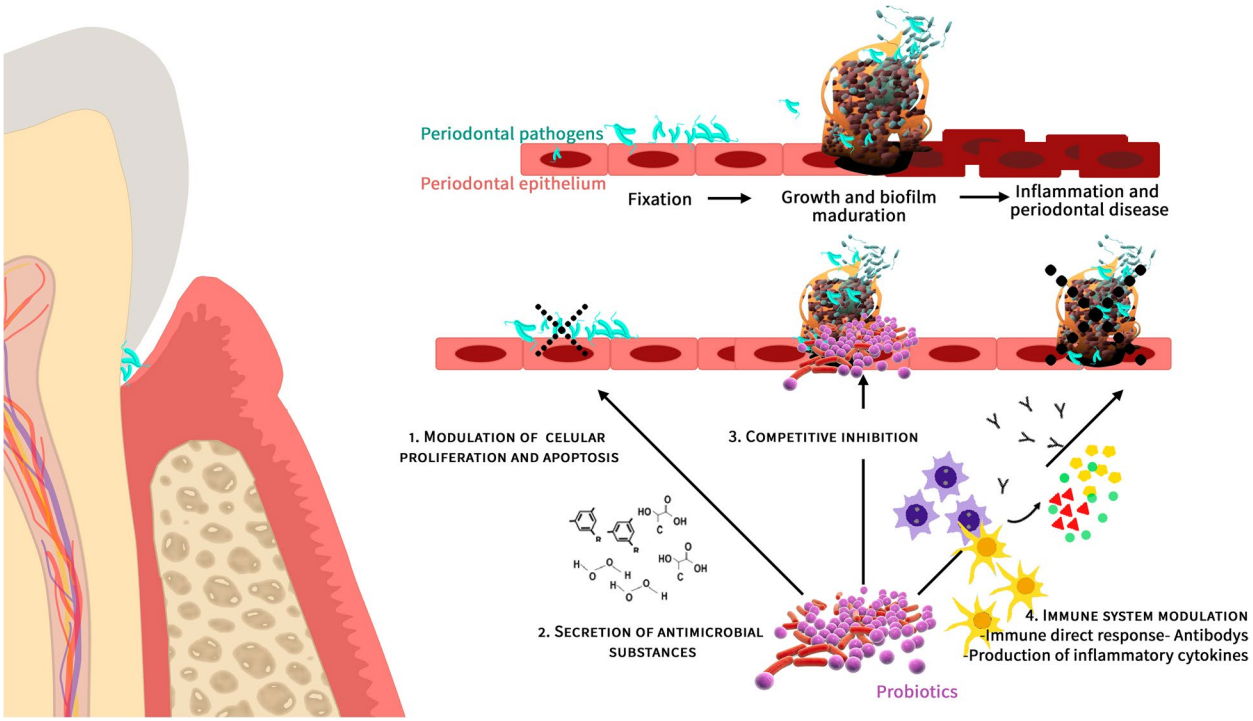

Fig. 1 Schematic diagram depicting the potential mechanisms of action of probiotics on the periodontal epithelium

Introduction

Periodontitis is a multifactorial biofilm-associated chronic disease, in which an imbalance of the oral ecosystem (dysbiosis) occurs, affecting periodontal tissues and showing a wide range of clinical, microbiological and immunological manifestations. It is associated with the dynamic interaction between infectious agents (mainly anaerobic bacteria), host immune response, environmental exposure and genetic predisposition [1–3]. It is characterized by the presence of gingival bleeding, periodontal pockets (> 3 mm) and loss of periodontal supporting tissues [2]. It is a disease with a high prevalence worldwide, and it is considered a public health problem and one of the main causes of tooth loss [4]. It also has systemic impact, being related to several systemic diseases, such cardiovascular diseases, diabetes, and adverse pregnancy outcomes [5, 6].

Mechanical plaque control measures such as scaling and root planing (SRP) are the current gold standard treatment for periodontitis, aiming to remove supra and subgingival plaque, reduce biofilm accumulation and bacterial colonization in the susceptible sites by this frequent debridement and/or surgical intervention. Antimicrobial agents as adjutants, have been proposed to achieve a greater reduction of the bacterial load. Among them, systemic and local antibiotics, antimicrobial photodynamic therapy, and probiotic therapy are the most common [7].

Probiotics are live micro-organisms that, when administered in adequate amounts, contribute to the health status of the host [8]. They have been used for the treatment of gastrointestinal disorders, inflammatory bowel disease, lactose intolerance, respiratory tract infections, lipid lowering, obesity, diabetes, allergies, and vaginal and urogenital infections [9]. Three mechanisms of action have been proposed to explain their role in health and disease: increasing the number of beneficial bacteria by preventing colonization by pathogenic species, producing antibacterial agents, and modulating host defences [10]. In periodontal disease, probiotics could regulate the secretion of gingival or crevicular fluid from the epithelium, preventing the adhesion of periodontopathogenic microorganisms. They may also play a nutrient-depleting competitive relationship with periodontopathogens and therefore change the subgingival flora to a more eubiotic one. Furthermore, they may play an important role in immunomodulation, by increasing the production of anti-inflammatory cytokines, modulating cell proliferation and apoptosis, producing antimicrobial agents, and modulating subgingival pH [11] (Fig. 1).

Despite previous systematic reviews on the use of probiotics in periodontal disease management, the evidence remains inconclusive due to various limitations, such as

small sample sizes, short follow-up durations, and methodological inconsistencies across studies. his meta-analysis was conducted to address these gaps and provide a more comprehensive and nuanced evaluation of the role of probiotics as an adjunct to periodontal therapy. By synthesizing data from studies with well-defined criteria and stratifying results based on the type of periodontal disease and follow-up times, it was aimed to offer more robust insights into the clinical outcomes associated with probiotic use. Specifically, this study focused to determine whether probiotics could be beneficial for improving outcomes such as plaque index, bleeding on probing, and probing pocket depth in both gingivitis and periodontitis patients, conducting a systematic review and meta-analysis of randomized controlled trials. The null hypothesis for this study was stated as follows: There would be no significant difference in clinical outcomes between patients receiving probiotics as an adjunct to periodontal treatment and those receiving a control or placebo treatment in the management of gingivitis and periodontitis.

Materials and methods

This systematic review and meta-analysis were performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines [12]. The protocol for the systematic review was registered with the PROSPERO database on February 4th, 2024 (registration number: CRD42024509910). No deviations from the registered protocol happened during the review process.

Eligibility criteria

The study was structured using the Population, Intervention, Comparison, Outcome framework, as detailed below:

P (population): Patients with gingivitis or periodontitis.
I (intervention): Adjunctive use of probiotics during non-surgical periodontal therapy.
C (comparison): Control/placebo groups during non-surgical periodontal therapy.
O (outcome): Clinical outcomes such as plaque index, bleeding on probing, and probing pocket depth.

Inclusion criteria were randomized clinical trials on the use of different probiotics for the treatment of both forms of periodontal disease (gingivitis or periodontitis) with non-surgical periodontal therapy, with control/placebo and probiotic/test groups, with a minimum sample size of 9 participants per group, and that were reported according to CONSORT guidelines [13]. Articles must have been published in the last 10 years, and only articles written in English were selected.

Search strategy

The search process was performed independently by two examiners (CBR and IC). This literature search was conducted in March 20, 2024 in Scopus, MEDLINE (through PubMed), Cochrane and EMBASE since the chosen databases are the most widely recognized and authoritative sources in the field of dentistry, periodontology, and clinical research, Cochrane Highly Sensitive Search Strategy for Randomized Controlled Trials was used as a search filter [14]. The descriptors were: "periodontal disease", "periodontitis" and "gingivitis"; and were combined in different equations with the term "AND probiotics". A secondary search was conducted by reviewing the references of all studies included in the final database, searching the TESEO database, and examining grey literature through the OpenGrey database to identify any relevant articles that may not have been captured in the primary search strategy.

The records obtained from the different databases were merged into a single database through a bibliographic management software (Mendeley Reference Manager, Elsevier, Amsterdam, Netherlands). Duplicate records were removed. The original search results were filtered on a title and abstract basis. Two reviewers (CBR and IC) screened independently and in duplicate all titles and abstracts against the eligibility criteria, using liberal acceleration. The full text of the included studies was assessed for eligibility by the same two reviewers in duplicate and independently. Any disagreement was resolved by discussion with a third reviewer (AMF). Cohen's kappa coefficient was used to assess inter-examiner agreement regarding search strategy. In case of missing information, the corresponding authors of the studies were contacted using the mail address provided in the paper. Studies that did not fulfil inclusion criteria and those in which the full text was not available after searching them by all available means, including contact with the corresponding author and request to the University Library, were excluded. Then, full-text review of these records was performed, checking for the fulfilment of the inclusion criteria, and data about the selected studies were gathered: first author, type of study, follow-up time, sample size, study groups, type of probiotic used, definition of periodontitis and main findings.

Quality assessment

The quality of the included studies was assessed by two independent authors (SNU and AMF) using the Version 2 of the Cochrane risk-of-bias tool for randomized trials

(RoB- 2) [15]. The RoB- 2 is organized into a fixed set of bias domains, each focusing on different aspects of trial design, conduct, and reporting. Bias domains and signaling questions of this tool as follows: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each study was classified as having a high risk of bias if it did not meet one or more domains, as uncertain if it partially met one or more domains, and as low risk if it met all domains. Consensus was reached by consulting a third author (IC) in case of discrepancies. Quality assessment results were not used as inclusion criteria for being included in the meta-analysis due to a potential selection bias.

Quality of evidence

The level of evidence was evaluated for plaque index, bleeding on probing, and probing pocket depth parameters using the Grading of Recommendations, Assessment, Development and Evaluation methodology through the GRADEpro Guideline Development Tool by two independent researchers (SNU and AMF) regarding the following domains: risk of bias, inconsistency, indirectness, imprecision, and other considerations (publication bias, significant effect, plausible confounding, and dose–response gradient) [16]. Each domain was deemed as "not serious", "serious", and "very serious," and the overall certainty of the evidence was graded into one of four levels: very low, low, moderate, or high.

Data-analysis

A meta-analysis was performed for each clinical outcome (plaque index (PI) in percentage, bleeding on probing (BOP) in percentage and periodontal probing depth (PPD) in millimetres) and according to the pathology (gingivitis/periodontitis), and to each group (probiotic/placebo). Following the same protocol from search strategy, the two same reviewers (CBR and IC) performed the data extraction, being any disagreement resolved by discussion with the same third reviewer (AMF) and calculating Cohen's kappa coefficient to assess inter-examiner agreement in the data extraction from the selected articles. In cases where the standard deviation was not reported directly, it was calculated from the confidence interval (CI). The Hedges formula with small sample bias correction [17] was used to calculate the standardized mean difference (SMD) and its variance, and individual effects were combined in a random effects model using the restricted maximum likelihood method [18].

Heterogeneity was assessed using the Higgins-I^2 coefficient [19] and the Cochran's-Q heterogeneity test, and studies that particularly contributed to heterogeneity were identified using the Galbraith plot. To control heterogeneity among studies, random-effects models were applied, as they provide more conservative estimates by incorporating between-study variability. This approach ensures a more robust assessment of the pooled effect size, as recommended for meta-analyses with observed heterogeneity. For analyses with very high heterogeneity, a sensitivity analysis was performed by removing those studies to assess the effect on overall heterogeneity and its influence on the pooled effect. The potential existence of publication bias was evaluated using the classical Egger's and Begg's tests, as well as the LFK index [20].

Finally, a subgroup analysis was performed to assess the influence of follow-up time on the pooled effect, using the median follow-up in weeks as the cut-off point to separate the results for each outcome. Meta-analyses were conducted using the"meta"package of the statistical software Stata v17 (StataCorp LLC, College Station, TX, USA).

Results

The initial search retrieved 573 articles, reduced to 158 after removing duplicates. These were reduced to 94 after reviewing the titles, and to 55 after reviewing the abstracts. After the final screening stage, 24 studies were included in the meta-analysis (Fig. 2). A list of the excluded studies and the reason for exclusion is provided in Supplemental Material 1. The Cohen's kappa coefficient values were calculated for inter-examiner agreement, obtaining 0.954 and 0.922 for search strategy and data extraction, respectively.

Selected articles were published 2012–2022, but 2015–2018 accumulated most of publications (60%). Of the 24 selected articles, 10 were about gingivitis and 14 about periodontitis, with a total of 951 participants allocated in the probiotic and placebo groups. In the studies about periodontitis, different case definitions were used, as shown in Table 1.

Quality assessment

Figure 3 presents the risk of bias assessment of included articles. Based on the assessment, 14 of the articles were considered to have a low risk of bias while 6 of them had a high risk of bias and 4 had some concerns. Except of two studies [26, 33], bias arising from the randomization process was low. One study was classified as having higher risk of bias due to the deviations from intended interventions since patients were of aware of their assigned intervention during the trial [33]. Some concerns have been detected as a result of the missingness in the outcome data in four articles [22, 26, 37, 39]. Moreover, some inappropriate methods or evaluation processes in measuring the outcome caused 2 articles to have been classified as

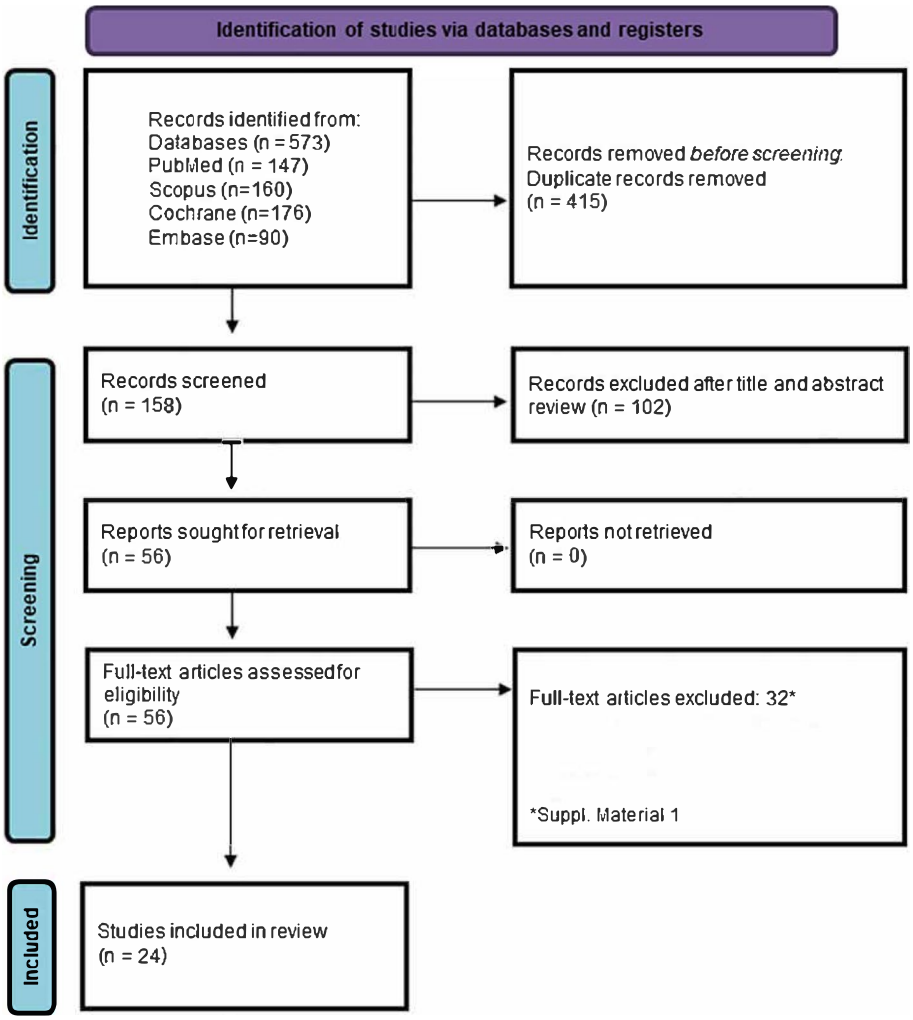

Fig. 2 PRISMA Flow diagram of the identification and selection process

having some concerns [22, 33]. Finally, the domain "selection of the reported result" was considered as having high risk of bias for four articles due to the deficiencies in the presenting outcome data [7, 38–40].

Quality of evidence

The results of the evaluation of quality of evidences using GRADEpro for plaque index, bleeding on probing, and probing pocket depth parameters are shown in Table 2. The certainty of evidence was found to be overall of low quality of selected studies that received "serious" risk of bias. Since the results were consistent across studies and the evidences answer directly the health care question for all three parameters, inconsistency and indirectness domains were deemed as "not serious". Furthermore, imprecision domain was also considered as "serious" due to the uncertain estimated effects that show potential harm or benefit [7, 38–40]. Moreover, any considerations such as large effect, plausible confounding, and dose response gradient were not identified. Additionally, no data verification could be performed that would upgrade the certainty of the evidence.

Metanalysis results

Figure 4A describes the results of the meta-analysis for the PI outcome. In the gingivitis studies a significant high heterogeneity was found ($I^2 = 94.83\%$, $p < 0.001$), and a lower PI was found in the Probiotic group compared to control/placebo (SMD = − 0.51), although no statistically significant differences were found (95% CI [− 1.37; + 0.35], $p = 0.248$). Regarding the studies performed in periodontitis patients, no heterogeneity was found ($I^2 = 0.00\%$, $p = 0.496$), and the meta-analysis showed that PI was lower in the probiotic group compared to control/placebo group (SMD = − 0.35; 95% CI [− 0.54; − 0.15),

Table 1 Summarized data of the articles about probiotics and periodontitis included in the meta-analysis

First author and year	Pathology	Study type	Follow-up (Weeks)	Sample Size	Probiotic	Periodontitis case-definition	Study groups	Main findings
Iniesta et al. 2012 [21]	Gingivitis	RCT-DB-Placebo	8	40	*Lactobacillus reuteri*	-	Group 1: Probiotics (20) Group 2: Placebo (20)	No observed differences in PI or BOP between groups
Hallström et al. 2013 [22]	Gingivitis	RCT-DB-Placebo	3	18	*Lactobacillus reuteri*	-	Group 1: Probiotics (9) Group 2: Placebo (9)	*Prevotella intermedia* counts reduced in probiotic group
Toiviainen et al. 2015 [23]	Gingivitis	RCT-DB-Placebo	4	60	*Lactobacillus rhamnossus* *Bifidobacterium lactis*	-	Group 1: Probiotic (29) Group 2: Placebo (31)	No significant differences in PI, BOP or PPD between groups
Schlagenhauf et al. 2016 [24]	Gingivitis	RCT-DB-Placebo	7	45	*Lactobacillus reuteri*	-	Group 1: Probiotic (24) Group 2: Placebo (21)	No difference in cytokine concentration were detected with the use of the probiotic
Alkaya et al. 2017 [25]	Gingivitis	RCT-DB-Placebo	8	40	*Bacillus subtilis* *Bacillus megaterium* *Bacillus pumulus*	-	Group 1: Probiotic (20) Group 2: Placebo (20)	PI and BOP significantly decreased in the probiotic group
Jagadeesh et al. 2017 [26]	Gingivitis	RCT-DB-Placebo	3	30	*Bacillus coagulans*	-	Group 1: Probiotics (15) Group 2: Placebo (15)	PI and BOP were significantly lower in the probiotic group
Kuru et al. 2017 [27]	Gingivitis	RCT-DB-Placebo	4	51	*Bifidobacterium animalis*	-	Group 1: Probiotics (26) Group 2: Placebo (25)	No differences observed in PI or BOP
Montero et al. 2017 [28]	Gingivitis	RCT-DB-Placebo	6	59	*Lactobacillus planatarum, brevis* *Pediococcus acidilactici*	-	Group 1: Probiotics (29) Group 2: Placebo (30)	BOP and PPD were significantly lower in the probiotic group
Sabatini et al. 2017 [29]	Gingivitis	RCT-DB-Placebo	4	80	*Lactobacillus reuteri*	-	Group 1: Probiotic (40) Group 2: Placebo (40)	Lower PI, BOP and PPD, and lower IL- 1β levels in the probiotic group
Keller et al. 2018 [30]	Gingivitis	RCT-DB-Placebo	6	47	*Lactobacillus rhamnossus* *Lactobacillus curvatus*	-	Group 1: Probiotic (23) Group 2: Placebo (24)	No changes were observed in BOP, although a significant decrease of sites with severe inflammation was observed
Teughels et al. 2013 [31]	Periodontitis	RCT-DB-Placebo	12	30	*Lactobacillus reuteri*	≥ 14 teeth affected and bone loss > 1/2 of the root length, or ≥ 6 mm	Group 1: Probiotic (15) Group 2: Placebo (15)	Probiotic group presented a greater improvement in PPD and CAL
Vicario et al. 2013 [32]	Periodontitis	RCT-DB-Placebo	4	20	*Lactobacillus reuteri*	PPD > 4 mm and CAL > 5 mm in ≥ 2 non-adjacent teeth	Group 1: Probiotic (10) Group 2: Placebo (10)	Significant improvement in PI, BOP and PPD in the probiotic group

Table 1 (continued)

First author and year	Pathology	Study type	Follow-up (Weeks)	Sample Size	Probiotic	Periodontitis case-definition	Study groups	Main findings
Szkaradkiewicz et al. 2014 [33]	Periodontitis	RCT-DB-Placebo	3	38	*Lactobacillus reuteri*	PPD >4 mm in ≥2 non-adjacent teeth	Group 1: Probiotic (24) Group 2: Placebo (18)	Greater improvement in clinical variables (BOP, PPD and CAL), and a greater reduction in proinflammatory cytokines expression
Ince et al. 2015 [34]	Periodontitis	RCT-DB-Placebo	52	30	*Lactobacillus reuteri*	≥2 teeth with interproximal PPD of 5–7 mm and gingival index ≥2 in each quadrant	Group 1: Probiotic (15) Group 2: Placebo (15)	Significant differences in PI, BOP, CAL and PPD were found in favour of the probiotic-treated group
Laleman et al. 2015 [35]	Periodontitis	RCT-DB-Placebo	24	48	*Streptococcus oralis KJ3, Streptococcus uberis KJ2, Streptococcus rattus JH145*	Diagnosis of moderate or severe adult periodontitis (Van der Velden, 2005)	Group 1: Probiotic (24) Group 2: Placebo (24)	No significant differences were found between groups
Tekce et al. 2015 [36]	Periodontitis	RCT-DB-Placebo	52	40	*Lactobacillus reuteri*	≥2 teeth with interproximal PPD of 5–7 mm	Group 1: Probiotic (20) Group 2: Placebo (20)	PI, BOP, and PPD were significantly lower in the probiotic group
Morales et al. 2016 [4]	Periodontitis	RCT-DB-Placebo	48	28	*Lactobacillus rhamnosus SP1*	≥5 teeth with CAL and PPD ≥5 mm	Group 1: Probiotic (14) Group 2: Placebo (14)	Probiotic group showed greater improvement in PPD than placebo group
Penala et al. 2016 [37]	Periodontitis	RCT-DB-Placebo	12	32	*Lactobacillus reuteri y Lactobacillus salivarius*	≥4 teeth with PPD ≥5 mm and CAL ≥4 mm	Group 1: Probiotic (16) Group 2: Placebo (16)	PI, BOP and PPD improved significantly in the group treated with probiotics
Invernici et al. 2018 [7]	Periodontitis	RCT-DB-Placebo	12	41	*Bifidobacterium animalis subsp lactis HN019*	≥30% sites with PPD ≥4 mm and CAL ≥4 mm, BOP in ≥5 teeth with CAL and PPD ≥5 mm	Group 1: Probiotic (20) Group 2: Placebo (21)	PPD and CAL decreased significantly in the probiotic group
Grusovin et al. 2020 [10]	Periodontitis	RCT-DB-Placebo	12	20	*Lactobacillus reuteri*	CAL ≥5 mm and ≥3 teeth with radiographic bone loss ≥30%	Group 1: Probiotic (10) Group 2: Placebo (10)	PPD, CAL and BOP decrease in the probiotic group
Invernici et al. 2020 [38]	Periodontitis	RCT-DB-Placebo	12	30	*Bifidobacterium animalis subsp lactis HN019*	≥30% sites with PPD ≥4 mm and CAL ≥4 mm, BOP in ≥5 teeth with CAL y PPD ≥5 mm	Group 1: Probiotic (15) Group 2: Placebo (15)	Lower PI and BOP in the probiotic group. *P. gingivalis* levels decreased
Laleman et al. 2020 [39]	Periodontitis	RCT-DB-Placebo	24	39	*Lactobacillus reuteri*	PPD ≥6 mm or PPD of 5 mm with BOP	Group 1: Probiotic (19) Group 2: Placebo (20)	PPD in the probiotic group was significantly lower and less sites required surgery after treatment
Pudgar et al. 2021 [40]	Periodontitis	RCT-DB-Placebo	12	40	*Lactobacillus brevis, Lactobacillus plantarum*	PPD ≥5 mm in ≥4 teeth in 4 different quadrants	Group 1: Probiotic (20) Group 2: Placebo (20)	BOP decreased but diseased sites presented les healing chance

Table 1 (continued)

First author and year	Pathology	Study type	Follow-up (Weeks)	Sample Size	Probiotic	Periodontitis case-definition	Study groups	Main findings
Ramos et al. 2022 [41]	Periodontitis	RCT-DB-Placebo	12	45	*Lactobacillus reuteri*	≥ 3 sites with moderate pockets with BOP and ≥ 3 sites with deep pockets with BOP	Group 1: Probiotic (15) Group 2: Placebo (15) Group 3: Antibiotic (15)	No additional benefit for subgingival instrumentation was found in any of the groups

RCT Randomized Controlled Trial, *DB* Double-blinded, *PPD* Probing Pocket Depth, *CAL* Clinical Attachment Loss, *PI* Plaque Index, *BOP* Bleeding on probing

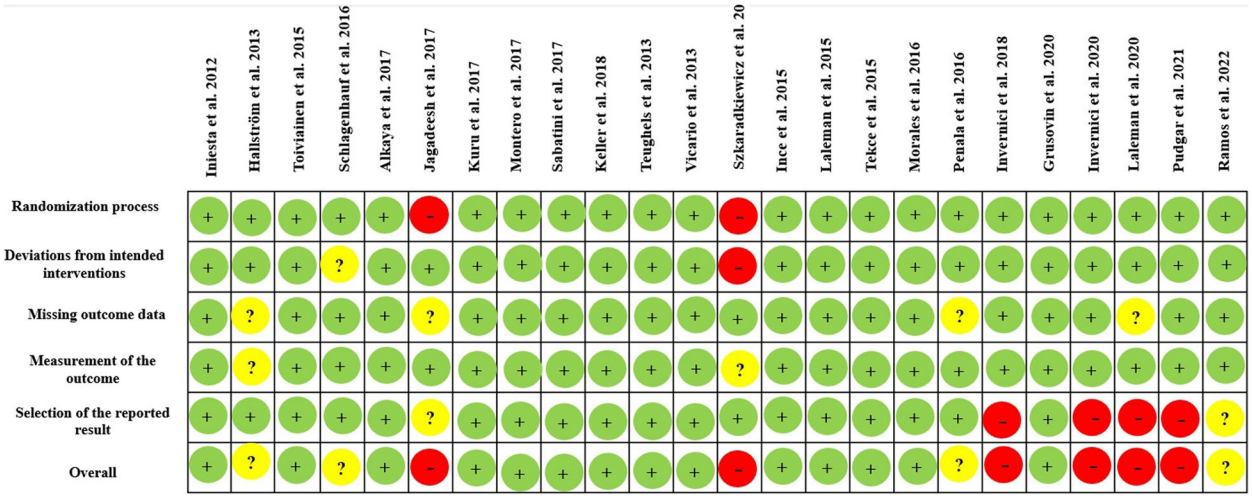

Fig. 3 Results from the risk of bias assessment

and that this difference was statistically significant ($p=$ 0.001).

Figure 4B describes the meta-analysis results for BOP outcome. In the gingivitis studies a significant high heterogeneity was again found ($I^2=$ 95.70%, $p<$ 0.001), and a lower, but statistically non-significant, BOP was found in the Probiotic group compared to control/placebo (SMD =− 0.49, 95% CI [− 1.66; +0.68], $p=$ 0.409). In periodontitis studies, a mild heterogeneity was found ($I^2=$ 53.07%, $p=$ 0.011), and the meta-analysis showed a lower and significant BOP in the probiotic group compared to control/placebo group (SMD =− 0.32, 95% CI [− 0.58; − 0.05], $p=$ 0.021).

Figure 4C describes the meta-analysis results for PPD. In the gingivitis studies, only two of them reported PPD as an outcome, and a no heterogeneity was found between them ($I^2=$ 0.00%, $p=$ 0.977). Lower values of probing were found in the probiotic group compared to control/placebo, but the difference was statistically non-significant (SMD =− 0.23, 95% CI [− 0.63; +0.18], $p=$ 0.272). In periodontitis studies, a mild heterogeneity was found ($I^2=$ 51.68%, $p=$ 0.020), and a lower, but statistically non-significant, PPD was found in the probiotic group compared to control/placebo group (SMD =− 0.25, 95% CI [− 0.53; +0.03], $p=$ 0.077).

A sub-analysis was performed for each outcome variable, considering the follow-up time of each study. As cut-off value for each outcome, the median follow-up time was chosen for stratification. Results of these sub-analyses for the studies on gingivitis are shown in Supplementary Material. Results of this sub-analyses for the studies on periodontitis are shown in Figs. 5, 6 and 7.

Figure 5 shows the results for the PI for the studies on periodontitis, after meta-analysing according to subgroups with follow-up times of less than or equal to 8 weeks and more than 8 weeks. Only 2 studies presented a follow-up time lower or equal to 8 weeks, and presented low heterogeneity ($I^2=$ 33.73%, $p=$ 0.219) and a lower but statistically non-significant difference in the probiotic group (SMD =− 0.51, 95% CI [− 1.17; +0.15], $p=$ 0.130). However, studies with a follow-up time greater than 8 weeks showed no heterogeneity ($I^2=$ 0.00%, $p=$ 0.473) and statistically significant lower values of PI for the probiotic group (SMD =− 0.33, 95% CI [− 0.54; − 0.12], $p=$ 0.002).

Regarding the results of the sub-analysis on BOP for the studies on periodontitis, shown in Fig. 6, subgroups were meta-analysed according to follow-up time of less than or equal to 12 weeks, and greater than 12 weeks. For the studies with a follow-up time lower or equal to 12 weeks, a mild heterogeneity was found ($I^2=$ 59.55%, $p=$ 0.012), and lower and statistically significant levels of BOP were found in the probiotic group (SMD =− 0.48, 95% CI [− 0.86; − 0.11], $p=$ 0.012). Studies with a follow-up time greater than 12 weeks showed no heterogeneity ($I^2=$ 0.00%, $p=$ 0.436), but no statistical difference in BOP was found between probiotic and control/placebo group (SMD =− 0.07, 95% CI [− 0.36; +0.21], $p=$ 0.614).

Sub-analysis results on PPD for the studies on periodontitis are shown in Fig. 7, subgroups were meta-analysed according to follow-up time of less than or equal to 12 weeks, and greater than 12 weeks, as median follow-up value. For the studies with a follow-up time lower or equal to 12 weeks, a mild heterogeneity was found ($I^2=$ 44.94%, $p=$ 0.095), and lower levels of BOP were found in the probiotic group (SMD =− 0.42, 95% CI [− 0.77; +0.07], $p=$ 0.019), being this difference statistically significant. Meta-analysis for PPD in studies

Table 2 Assessment of quality of evidence using GRADEpro

Certainty Assessment						
№ of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Certainty of evidence**
Plaque Index						
21	Serious[a]	Not serious[b]	Not serious[c]	Serious[d]	None	⊕⊕◯◯ Low
Bleeding on Probing						
20	Serious[a]	Not serious[b]	Not serious[c]	Serious[d]	None	⊕⊕◯◯ Low
Probing Pocket Depth						
14	Serious[a]	Not serious[b]	Not serious[c]	Serious[d]	None	⊕⊕◯◯ Low

GRADEpro: Grading quality of evidence and strength of recommendations

aMost of the studies showed some limitations that downgraded the quality of the evidence

bThe results were consistent across studies

cThe evidence directly answered the questions that have been investigated

dThe results of some studies had some deficiencies and contradictions in terms

with a follow-up time greater than 12 weeks showed mild heterogeneity ($I^2 = 51.77\%$, $p = 0.083$), and no statistical difference in PPD between probiotic and control/placebo group (SMD = − 0.03, 95% CI [− 0.44; + 0.38], $p = 0.886$).

Heterogeneity and publication bias

Analyses of the heterogeneity and publication bias were performed for the cases in which heterogeneity was detected. Regarding the studies about gingivitis, for PI one study showed contributed to heterogeneity [29]. The value of LFK index for this meta-analysis (− 1.46), showed a potential publication bias, as this value was outside the range between − 1 and 1. For BOP, one study contributed to heterogeneity [25], and the LFK index value (− 1.38), suggested the presence of publication bias, although Begg's and Egger's tests did not reach that conclusion (Supplementary Material 2).

Regarding the studies on periodontitis, in the meta-analysis for PI several studies contributed to heterogeneity [32, 37, 39, 41]. According to the LFK index value (− 1.22), there was evidence of publication bias, but the Begg's and Egger's tests obtained non-significant results. For BOP, one study contributed to heterogeneity [33]. The LFK index value (− 0.26) showed that there was no publication bias. Considering PPD, statistically significant heterogeneity was found referring the p-value which corresponds to the test for detecting a significant combined effect rather than the homogeneity test (*p-hetero* = 0.020, *p-effect* = 0.077). The LFK index value (− 0.31), showed no evidence of publication bias (Supplementary Material 3).

Discussion

This systematic review and meta-analysis aimed to evaluate the clinical effects of probiotics as an adjunct in periodontal therapy and provide valuable educational insights for clinicians, researchers, and students in the field of periodontology. In this sense, this review enhances the knowledge base regarding adjunctive treatment options, emphasizing their role within evidence-based periodontal therapy. The findings also highlight the distinction between statistical significance and clinical relevance, fostering a deeper understanding of how treatment effects should be interpreted in real-world dental practice. Moreover, by identifying gaps in the current literature, this study informs future research priorities, encouraging students and researchers to design more robust and clinically relevant studies in periodontology. Considering the identified limitations and potential biases in the included studies, the results of this systematic review and meta-analysis suggest a possible improvement in certain periodontal parameters in patients with gingivitis and periodontitis when probiotic therapy is used as an adjunct.

Probiotics and pathogens compete for binding sites, resulting in competitive exclusion of pathogenic microorganisms. In the case of *Lactobacillus reuteri*, a probiotic with proven efficacy in different bacterial infections, its mechanism of action involves the competitive exclusion of pathogenic microorganisms [42–44]. Its mechanism of action consists in the production of reuterin, an antimicrobial substance that inhibits a broad spectrum of pathogenic bacteria [36]. Other probiotics produce, in addition to reuterin, other substances such as bacteriocin

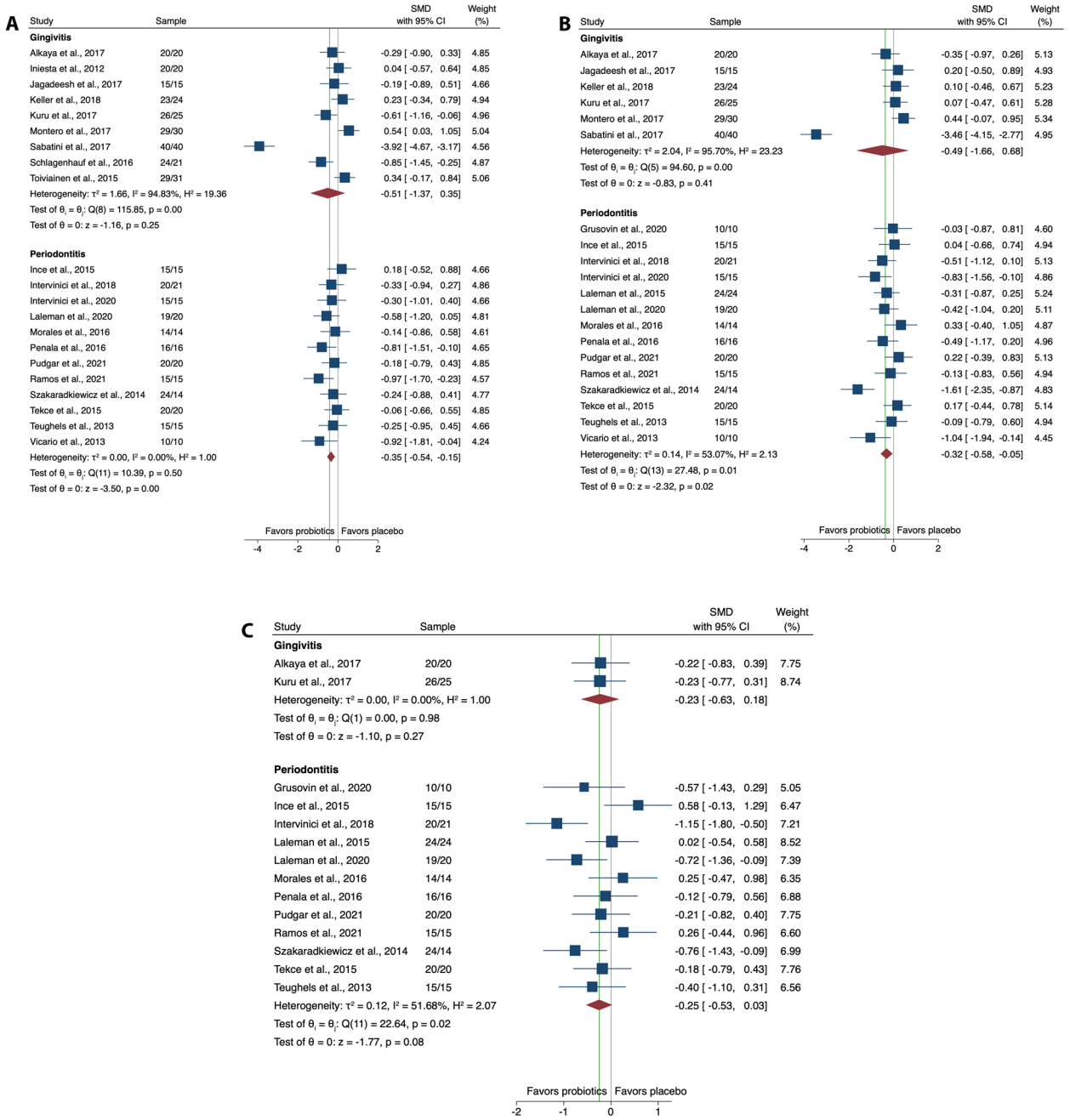

Fig. 4 Forest-plots of the results of the meta-analysis, subdivided in studies for gingivitis and periodontitis, for plaque index (**A**), bleeding on probing (**B**) and probing pocket depth (**C**)

and reutericillin [45]. These molecules have also been associated with a lower expression of some pro-inflammatory cytokines [46]. Probiotics can also produce lactic acid, which would reduce pH in the medium, preventing the development of other bacterial species [47].

In patients with gingivitis, only two studies [25, 28] used probiotics as adjunctive therapy after mechanical plaque removal by the practitioner, as they claim that the effect of probiotics is better if bacteria were previously removed. *Lactobacillus reuteri* was used as a probiotic in 4 of the trials [21, 22, 24, 29]. In two of them [24, 29], there was a significant reduction in PI and BOP in patients taking the probiotic, while the other two trials [21, 22] showed no significant differences when comparing the test group with the placebo group. Other probiotics used were *Bifidobacterium animalis* [27] and

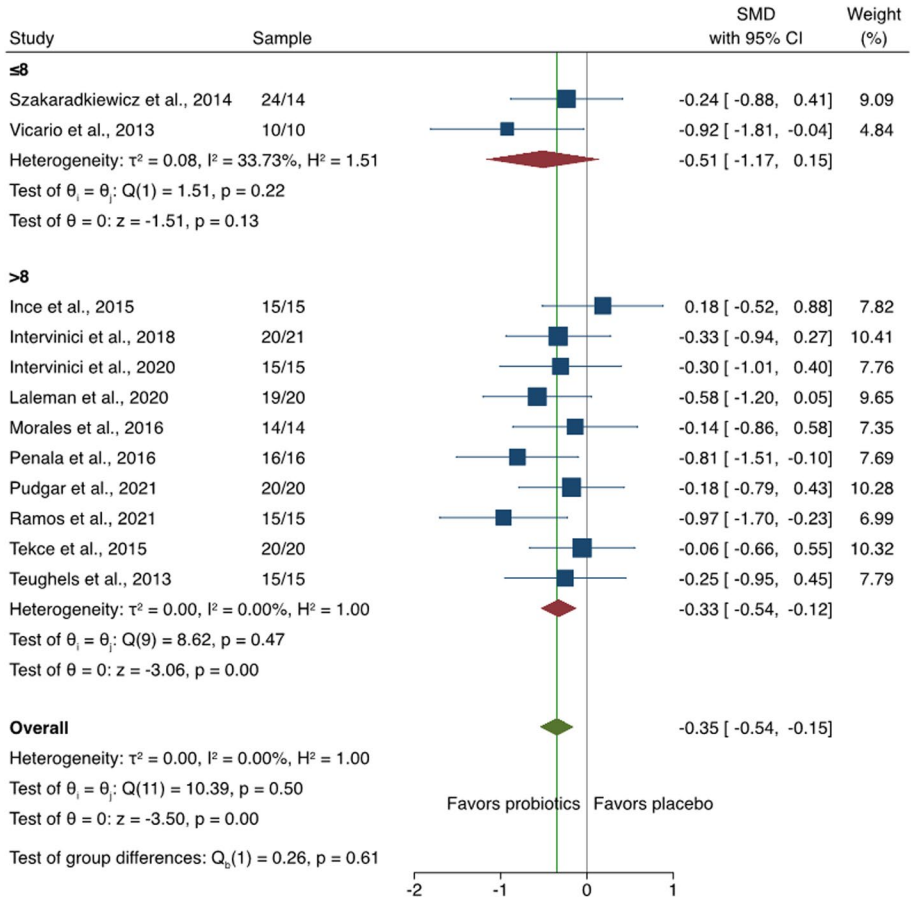

Fig. 5 Forest-plot of the results of the meta-analysis for plaque index in the periodontitis studies, subdivided into studies with short follow-up time (less than or equal to 8 weeks) and studies with long follow-up time (more than 8 weeks)

Bifidobacterium lactis [23]. The latter was used in combination with *Lactobacillus rhamnossus* and, in both studies the results showed significant reductions for PI and gingival index in those who had taken the probiotic *versus* placebo. In three other trials [25, 28, 30], the authors used a combination of different *Lactobacillus* species, and none found differences between the study groups. However, almost 50% showed an improvement in sites with severe inflammation.

Regarding the use of probiotics in the treatment of periodontitis, they are used as an adjunctive therapy to SRP in all the trials included in the review, and not as a unique treatment. Most of the studies showed an improvement of the probiotics at 52 weeks [10, 34, 36]. In trials where both groups showed comparable clinical results, the follow-up periods ranged from 4 to 12 weeks [31–33]. In another study, Pudgar et al. used a combination of *Lactobacillus brevis* and *Lactobacillus plantarum* [40], with less improvement than *L. reuteri*, as it reduced BOP but also reduced the chances of healing of sites with PPD >4 mm [41]. *Bifidobacterium animalis subsp lactis* HN019 was tested in two trials, showing a greater decrease in PPD than the placebo group. In addition, both reported significant lower levels of periodontal pathogens and, one of them, lower levels of proinflammatory cytokines [38, 48].

The results of the meta-analyses performed for each outcome, considering subgroups according to the follow-up period, showed interesting findings in the periodontitis studies. PI decreased after probiotic use, except in studies with less than 8 weeks of follow-up. Most studies had a follow-up period equal to or longer than 8 weeks, and PI significantly decreased with probiotic use in these studies (SMD = − 0.35; p = 0.002) (Fig. 5), suggesting that the effectiveness of probiotics in preventing plaque accumulation occurs in the long term.

In the case of Laleman et al., unlike most periodontitis studies, no decrease in the PI value was found after the application of the probiotic (*Lactobacillus reuteri*). The authors concluded that the rinsing effect of the crevicular fluid in the gingival sulcus might have prevented the probiotic from remaining in contact with the inflamed tissue

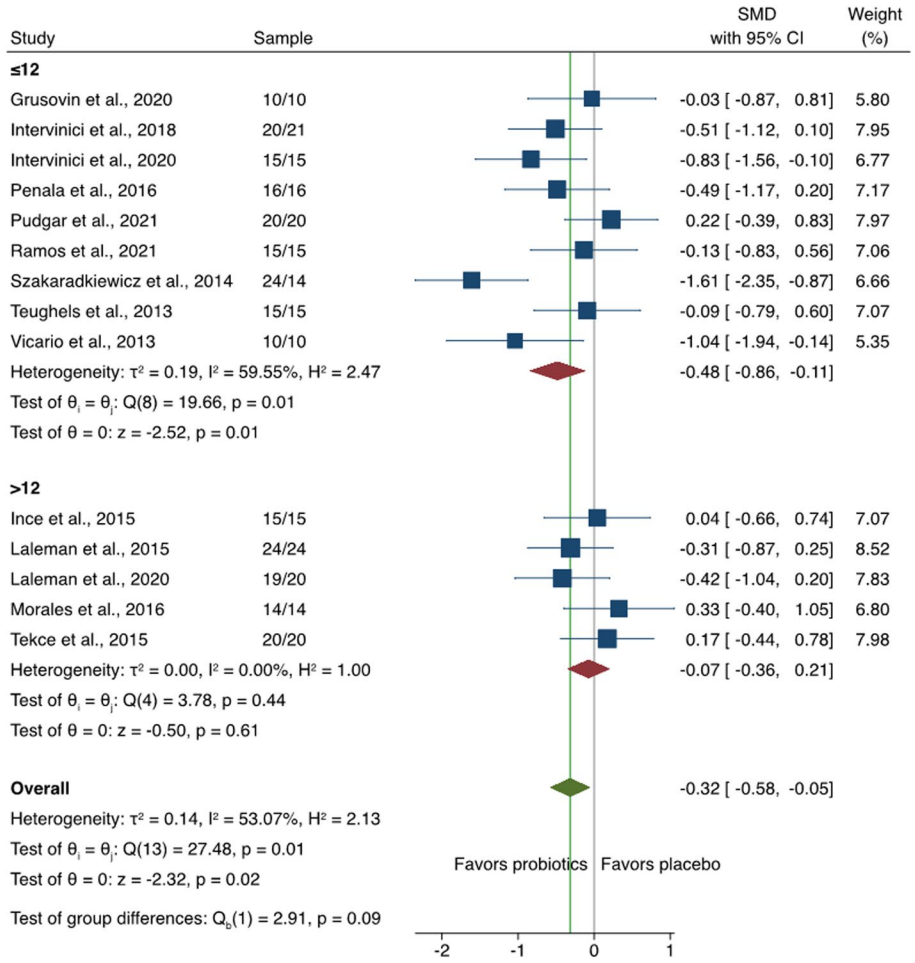

Fig. 6 Forest-plot of the results of the meta-analysis for bleeding on probing in the periodontitis studies, subdivided into studies with short follow-up time (less than or equal to 12 weeks) and studies with long follow-up time (more than 12 weeks)

long enough to exert an effect. Additionally, SRP was re-done after probiotic application in this study, which, according to existing literature, could hinder the effectiveness of the treatment [39].

In the study by Penala et al., the probiotic tablets were administered four times over 4 weeks and as a rinse for 2 weeks [37]. This administration protocol might explain the differences in PI compared to other studies, as it would affect the release and effectiveness of the probiotic. In the study by Penala et al., the probiotic tablets were administered 4 times in 4 weeks and as a rinse for 2 weeks [37]. This may explain the differences in PI when compared to other studies, since the administration protocol would also affect the release and the effect of the probiotic. As for the work of Ramos et al., the follow-up time was significantly longer (12 weeks) compared to other studies, explaining the added heterogeneity despite a decrease in PI [41]. The study by Vicario et al. also reported a significant improvement in PI values in the placebo group (PI increased from 62.9 ± 24.21% to 67.4 ± 16.57%). This could be explained by the fact that, despite not receiving any oral hygiene measures or interventions, participants altered their regular oral hygiene habits simply because they were enrolled in the study [32]. Other factors, such as attentional bias, which can influence the observation of certain effects in the placebo group in clinical trials, might have contributed to this heterogeneity [49].

Regarding Bleeding on Probing, meta-analysis showed a decrease in its value after probiotic administration (SMD = − 0.32; p = 0.021) (Fig. 6). Bleeding on Probing decreased after probiotic use, except in studies with more than 12 weeks of follow-up, suggesting that the effectiveness of the probiotics in bleeding happened at short-term. Galbraith's test concluded that one study contributed to the heterogeneity of the probiotics [33]. This study added heterogeneity to the meta-analysis due to the subdivision of patients of the probiotic into those

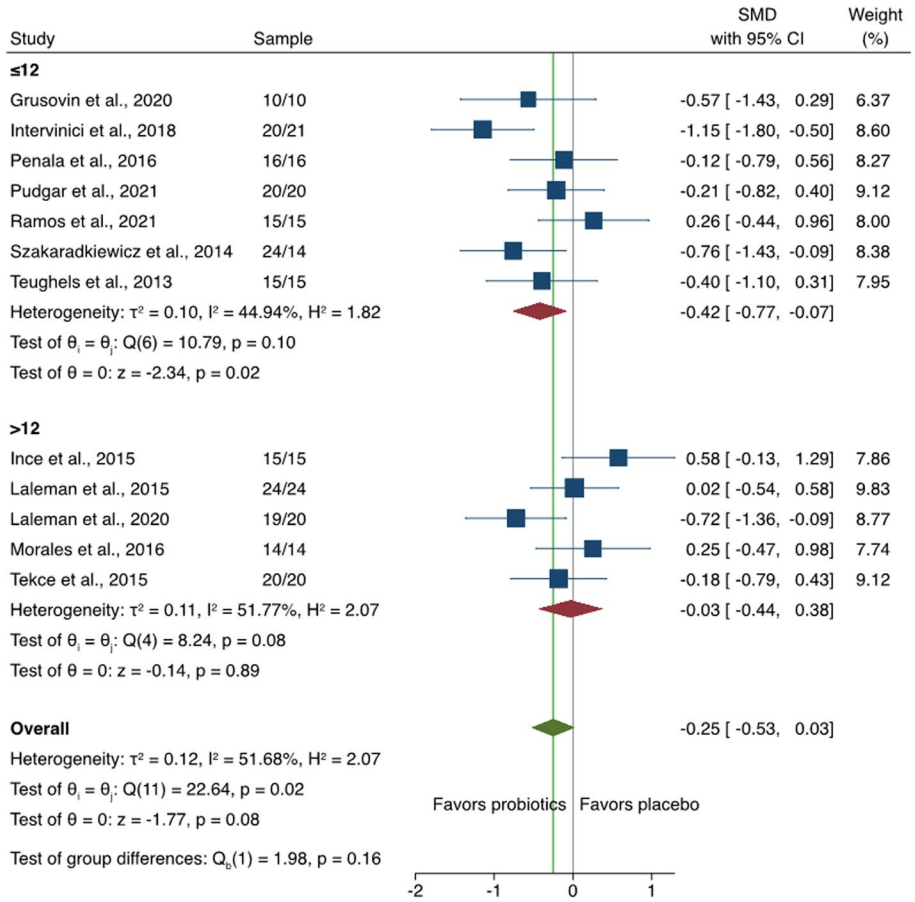

Fig. 7 Forest-plot of the results of the meta-analysis for probing pocket depth in the periodontitis studies, subdivided into studies with short follow-up time (less than or equal to 12 weeks) and studies with long follow-up time (more than 12 weeks)

who showed an improvement in clinical parameters (group 1A), and those who showed no improvement in clinical parameters (group 1B). Authors state that a potential inadequate colonization by the probiotic (*Lactobacillus reuteri*) in group 1B might happened. They also state that subjects from this group may have required probiotic administration for a longer period, in order achieve an anti-inflammatory effect and an improvement of clinical parameters [50].

In the studies that assessed PPD in periodontitis, the meta-analysis showed that there was no statistically significant difference between probiotic and placebo groups, although there was a greater decrease in the probiotic group (SMD = − 0.25; p = 0.077). However, in studies with a follow-up equal to or less than 12 weeks, there was a greater and significant decrease in PPD in the probiotic group, suggesting that the effectiveness of the probiotics in this outcome happened at short-term (SMD = − 0.42; p = 0.019) (Fig. 7). Galbraith's test concluded that only one study contributed to heterogeneity [7]. This may be explained by the fact that patients were subdivided into those with moderate periodontal pockets (PPD 4–6 mm) and deep periodontal pockets (PPD > 6 mm). PPD decrease was greater in the case of deep pockets, with a mean PPD of 7.27 ± 0.29 at baseline, that was reduced to 3.75 ± 1.32 after treatment. In patients with moderate pockets, mean PPD values at baseline were 4.47 ± 0.20, and were reduced to 3.19 ± 0.52 after follow-up. These results show a much greater improvement (3.5 mm reduction) compared to other studies also performed in deep pockets [31, 35], where a smaller PPD improvement was observed (2.88 and 2.37 mm, respectively). It should also be noted that other probiotic bacterial strains (*Lactobacillus* and *Streptococcus*) were used in these previous studies, whereas *Bifidobacterium* strains were used in this study.

Regarding the current evidence of topic, discrepancies controversy in the literature. These differences may be attributed to variations in the inclusion criteria of the reviews, leading to a different number of studies being included in previous meta-analyses. Some systematic reviews agree with the results of our study, suggesting

that a greater improvement in periodontal clinical variables is more prone to occur in patients with deep pockets [3, 51]. Other reviews showed that these clinical effects were not so clear, and the adjunctive use of probiotics in SRP showed no significant clinical effects [52, 53]. Moreover, heterogeneity observed in the results of this meta-analysis can be attributed to several factors, including differences in study design, population characteristics, intervention protocols, follow-up periods, differences in quality among studies, and outcome assessment methods. We now provide an updated review on the topic and also perform sensitivity analyses that provide new insights on the sources of heterogeneity.

The findings should be interpreted with caution due to the limitations of the study. Firstly, The forest plots indicate only minor effects across the analysed studies, suggesting that the investigated intervention may have a limited clinical impact. Additionally, the observed heterogeneity—though moderate—may reflect variations in study protocols, operator experience, or measurement techniques. Moreover, the systematic review included only articles in English and may have potentially missed studies in other languages, despite having consulted grey literature sources. Although some degree of publication bias was suggested by the LFK index for plaque index and bleeding on probing in gingivitis studies, this was not confirmed by Egger's or Begg's tests. For periodontitis, evidence of publication bias was minimal. Therefore, given the robustness of our sensitivity analyses and the use of random-effects models, the potential impact of publication bias on our overall conclusions is considered limited. In addition, many of the follow-up periods are short, and with longer studies the results could change. Also, the influence of microbiological or immunological parameters on the clinical outcomes after probiotic administration were not considered in this meta-analysis. In addition, most of the included studies had certain limitations that affected the overall quality of the evidence and therefore, these limitations may introduce some uncertainty in the results. In this sense, it is crucial that while probiotics may provide an adjunctive benefit in periodontal therapy, further large-scale, high-quality randomized controlled trials are needed to confirm their clinical relevance. These steps would be essential to strengthening the evidence base and providing more conclusive insights.

Conclusions

This systematic review and meta-analysis showed that while certain periodontal parameters showed statistically significant improvements with probiotic use, the clinical relevance of these findings remains uncertain due to the variability in study designs, follow-up durations, and treatment protocols. The observed heterogeneity and risk of bias in several included studies further highlight the need for high-quality, well-standardized clinical trials to determine the true effectiveness and long-term benefits of probiotic therapy in periodontal treatment. Future research should focus on optimizing treatment protocols, assessing patient-centered outcomes, and establishing clearer clinical guidelines for probiotic use in periodontology.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Authors' contributions

CBR designed the concept and methodology; CBR collected data, MRB and SNU analysed the data; IC has provided the resources; visualization was done by CBR, AMF and IC. Writing original draft preparation was done by IC, AMF and CBR. FM have substantially revised the manuscript and done the final editing. All authors have read and agreed to the published version of the manuscript.

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Data availability

The datasets used and/or analysed during the current systematic review and meta-analysis will be available in the Figshare depository.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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