Brazilian Dental Science

unesp
UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
Instituto de Ciência e Tecnologia
Campus de São José dos Campos

SYSTEMATIC REVIEW

DOI: https://doi.org/10.4322/bds.2023.e3619

Is the use of *Lactobacillus reuteri* probiotic efficient as adjunctive therapy in the treatment of periodontitis? A systematic review

O uso do probiótico *Lactobacillus reuteri* como terapia adjuvante no tratamento da periodontite é eficaz? Uma revisão sistemática

Tainá da Silva TRICOLY[1], Camila Lopes FERREIRA[1], Victória Clara da Silva LIMA[1], Andrea Carvalho de MARCO[1], Taciana Marco Ferraz CANEPPELE[1], Maria Aparecida Neves JARDINI[1]

1 - Universidade Estadual Paulista , Instituto de Ciência e Tecnologia, Departamento de Diagnóstico e Cirurgia, São José dos Campos, SP, Brazil.

How to cite: Tricoly TS, Ferreira CL, Lima VCS, Marco AC, Caneppele TMF, Jardini MAN. Is the use of *Lactobacillus reuteri* probiotic efficient as adjunctive therapy in the treatment of periodontitis? A systematic review. Braz Dent Sci. 2023;26(1):e3619. https://doi.org/10.4322/bds.2023.e3619

ABSTRACT

Objective: This systematic review had the purpose to validate the probiotic *Lactobacillus reuteri* as adjuvant therapy in the periodontal treatment of periodontitis, by the analysis of randomized controlled trial, controlled clinical trial, and observational studies. **Material and Methods:** Search keys related to the subject were defined, and the following databases were used as search strategies: MEDLINE via PubMed, Scopus, Web of Science, Cochrane Central Controlled Trials Registry, and EMBASE. The data selection and study were performed by two independent evaluators: first, they selected the article by title and abstract and subsequently qualified according to the bias risk analysis. A narrative synthesis has been performed based on the data obtained from the best-quality articles. After data extraction, their heterogeneity was analyzed, and a meta-analysis was performed. **Results:** In general, the results of the meta-analysis were positive for the use of probiotics as an adjuvant treatment. Considering the limitations of the comparisons between the analyzed articles studied, the conclusion was that probiotics may provide supplementary benefits to the treatment of periodontitis, with improvement in bleeding on probing rates and probing depth.

KEYWORDS

Lactobacillus reuteri; Periodontal diseases; Periodontitis; Probiotics; Systematic review.

RESUMO

Objetivo: Esta revisão sistemática teve como objetivo validar o uso do probiótico Lactobacillus reuteri como terapia adjuvante no tratamento periodontal da periodontite, por meio da análise de ensaios clínicos randomizados, ensaios clínicos controlados e estudos observacionais. **Material e Métodos:** Chaves de busca relacionadas ao assunto foram definidas, e as seguintes bases de dados foram utilizadas como estratégias de busca: MEDLINE via PubMed, Scopus, Web of Science, Cochrane Central Controlled Trials Registry e EMBASE. A seleção dos dados e o estudo foram realizados por dois avaliadores independentes: primeiro, selecionaram o artigo pelo título e resumo e posteriormente qualificaram de acordo com a análise de risco de viés. Uma síntese narrativa foi realizada com base nos dados obtidos dos artigos de melhor qualidade. Após a extração dos dados, sua heterogeneidade foi analisada e uma meta-análise foi realizada. **Resultados:** Em geral, os resultados da meta-análise foram positivos para o uso de probióticos como tratamento adjuvante. Considerando as limitações das comparações entre os artigos analisados estudados, concluiu-se que os probióticos podem trazer benefícios complementares ao tratamento da periodontite, com melhora nas taxas de sangramento à sondagem e na profundidade de sondagem.

PALAVRAS-CHAVE

Lactobacillus reuteri; Doença periodontal; Periodontite; Probióticos; Revisão sistemática.

INTRODUCTION

Periodontal disease is a chronic microbial infectious disease, defined as enduring inflammation and destruction of connective tissue and alveolar bone [1]. Nowadays, research scientists have evaluated distinct factors that must be examined in the analysis of periodontal disease, as well as the presence of pathogenic bacteria, the susceptibility of the host, and the reduction or absence of beneficial microorganisms [2-4].

Periodontitis is a relevant medical issue since its significant prevalence can result in tooth loss and dysfunction, chewing problems, and unsatisfactory aesthetics. In addition, it can be associated with social inequality and a decrease in the patient's quality of life. Periodontitis is responsible for a vast amount of edentulism and masticatory dysfunction, resulting in expensive dental care and adverse impacts on overall health [5]. Although gingivitis and periodontitis are originated and maintained by the microbial biofilm of dental plaque, host genetic and environmental aspects can also affect the disease progression [6].

The dental biofilm has a polymicrobial nature and over 700 species of bacteria are part of the oral microenvironment [7]. This resident microflora lives in symbiosis with the host and contributes directly and indirectly to its natural physiology, nutrition, and defense systems [8].

The first approach for periodontitis is a non-surgical treatment, which consists of scaling and root planning in association with oral hygiene instruction [9]. Mechanical therapies aim to improve clinical conditions, reducing the microbial load, either by physical removal or by disorganization of the subgingival biofilm [10]. Despite mechanical debridement has been considered the gold standard for the treatment of periodontitis, it's a technique that provides some obstacles, such as difficult access in cases of deep pockets, distortions in the root surface, as well as furcation areas [11], leading to the persistence of the disease process.

In order to achieve better root surface decontamination, different adjuvant treatments have been suggested, such as antibiotics [12], antiseptics [13], or microbial photodynamic therapy [14].

In this scenario, probiotics use were considered for the treatment of gingival and periodontal conditions [15,16]. The mechanisms related to the use of probiotics are the host's immunoinflammatory modulation [17], the attenuation of periodontal pathogen-induced interleukins expression in epithelial oral cells [18], and the reduction of pro-inflammatory cytokines [19].

The Food and Agriculture Organization (FAO) and the World Health Organization (WHO) define probiotics as "live microorganisms that, when present in acceptable amounts, provide health advantage to the host" [20]. Most parts of microorganisms used as probiotics are bacteria of the genus *Lactobacillus*, *Enterococcus*, *Bacillus,* and *Bifidobacterium* [21].

Lactobacillus reuteri is a lactic-acid, gram-positive, and facultative anaerobe microorganism [22] found in the gastrointestinal and urogenital tracts of humans, in breast milk, and in the gastrointestinal tract of some animals, such as rats, chickens, and pigs [23]. Immunomodulation of the host's intestinal microbiota, suppression of pro-inflammatory cytokines [22,24], histamine production [25], and increase in vitamin B12 synthesis [26] are some examples of favorable consequences related to the use of this probiotic. Studies have also elucidated the important benefits of *L. reuteri* for bone health, indicating reduced osteoclastogenesis, an increase in bone mineral density, which leads to a decrease in the risk of fractures [27], an increase in circulation of vitamin D, and, consequently, higher absorption of calcium by the organism [28].

Lactobacillus reuteri is a part of the oral microbiota in humans, and it has antibacterial action by transforming glycerol into reuterin (3-hydroxypropionaldehyde (3-HP), a substance that has a broad antimicrobial spectrum [29], inducing oxidative stress in pathogenic microorganisms [30]. In addition, this probiotic has shown an effect on the maintenance of healthy microbial flora, by preventing the excessive growth of other pathological microorganisms [31].

Different studies have analysed the results of probiotics in the treatment of periodontal diseases in humans [19,29,32-40]. For most of these studies, the use of the probiotic demonstrated a reduction in bleeding on probing (BoP), plaque index (PI), gingival index (GI), probing depth (PD) and number of mandatory anaerobes microorganisms.

Given the results of studies found in the literature, the use of probiotic therapy adjuvant to the treatment of periodontal disease in humans is developing as a probable treatment option. This present systematic study may contribute to future studies, allowing new clinical trials design, identification and correction of methodology gaps and determine clinical guidelines on this subject.

MATERIAL AND METHODS

Protocol and registration

This systematic study followed the international parameters of transparency in Systematic Review and PRISMA Statement Meta-Analysis [39] and was registered in the PROSPERO base (https://www.crd.york.ac.uk/prospero/) n0 CRD42021236186.

Eligibility criteria

The selected studies for analysis followed the PICO criteria:

Population: Patients with periodontal disease

Intervention: Patients who received adjuvant periodontal treatment with the probiotic Lactobacillus reuteri

Comparison: Patients who received non-surgical periodontal treatment (scaling and root planing - SRP) exclusively or in combination with placebo

Outcome: Improvement in the main clinical periodontal parameters (PD and BoP)

Inclusion criteria

1) Studies published in English
2) Controlled and randomized clinical trials (RCT)
3) Studies that evaluated the treatment of patients with periodontitis comparing SRP + probiotic *Lactobacillus reuteri* versus SRP + placebo or SRP only
4) Results reported in terms of probing pocket depth

Exclusion criteria

1) If patients with systemic disease were included
2) If they were duplicated or secondary study

Search strategy

In this present study, randomized clinical trials, controlled clinical trials and observational studies were investigated. To be the most comprehensive as possible, there was no restriction regarding the time after treatment or the year of publication. The authors performed an examination of the MEDLINE collection of data via PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, and EMBASE, for articles published until April 2020. The search was updated on January 2023. All studies were identified by the inclusion criteria and there was no need for additional contact with authors to identify other information.

Considering the components of the questions, terms and synonyms that could enhance the accuracy of the study were found. Initially, the word in Portuguese was inserted in the Health Sciences Descriptors (DeCS) and the descriptor in English was obtained. The terms found were associated to the terms “AND”, “OR” or “NOT” to constitute the following search strategy: “Probiotics and Periodontal Disease” and Periodontal Disease, Probiotics” according to MeSH and, the uniterms will be: (“probiotics”[MeSH Terms] OR “probiotics”[All Fields]) AND (“periodontal diseases”[MeSH Terms] OR (“periodontal”[All Fields] AND “diseases”[All Fields]) OR “periodontal diseases”[All Fields] OR (“periodontal”[All Fields] AND “disease”[All Fields]) OR (“periodontal disease”[All Fields])).

Data extraction

Two reviewers were responsible for searching the scientific articles (an undergraduate student and a Ph.D. candidate), previously calibrated by a third reviewer (Principal Investigator). The inter-examiner test (Kappa) was applied to assess agreement (twice) of the selected titles and abstracts obtaining a result of 0,89. At each stage there was a meeting between the three reviewers to analyse discrepancies, that were resolved by the third reviewer. All titles and abstracts of eligible papers were assessed by the “Covidence” program and thoroughly analysed.

The details for systematic review selection are shown in Figure 1, as recommended in the literature [42].

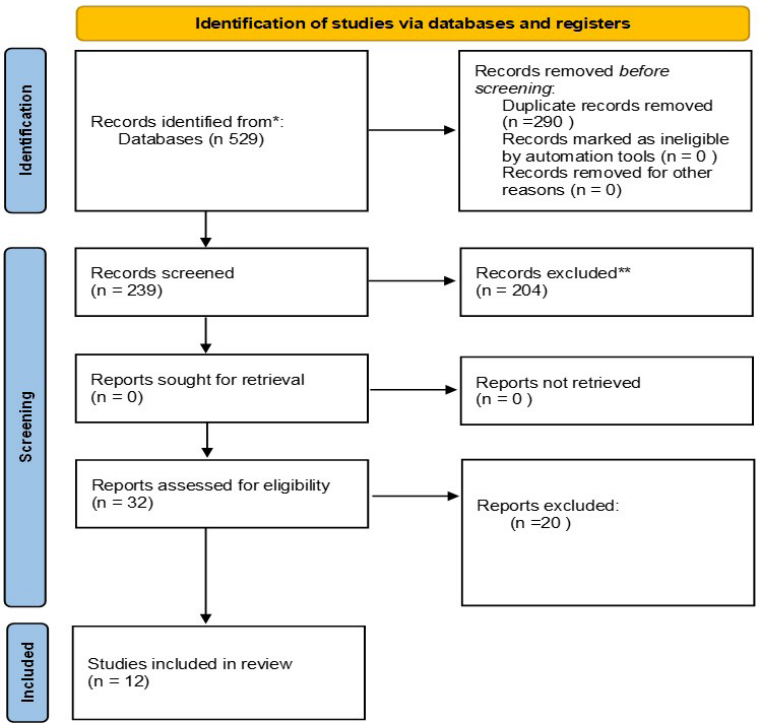

Figure 1 - PRISMA flowchart. From: Page et al. [41]. (*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.)

Data item

Data extracted from each study were grouped in: 1) Author; 2) Publication year; 3) Type of study; 4) Number of patients; 5) Age; 6) Total dose (daily dose multiplied by the consumption time in colony forming units [CFU]); 7) Frequency and duration of consumption; 8) Follow-up time.

Risk of bias in individual studies

The character of the involved studies was evaluated using the Cochrane Library Risk Tool for Randomized Clinical Trials (RoB 2) (updated on March 15th, 2019), by a calibrated examiner (MJ) and by a second examiner (CF) for ensure agreement on the scoring system. The studies were divided in low, moderate, high, or imprecise risk of bias, which were based on five domains: (a) resulting from the randomization process; (b) due to deviations from the proposed intervention; (c) due to lack of outcome data; (d) in measuring results; (e) in the selection of results. (Figure 2)

Research and evaluation results

After search, 12 articles were selected (Table 1).

During data extraction, the different treatment protocols were grouped by similarities, and a meta-analysis was performed for the two outcomes mentioned.

Meta analysis

The data was analysed by the Studio R software (version 3.4.4), using the R statistical language. For the analysed outcomes (PD and BoP), the results were presented as difference in means (MD), with a confidence interval of 95%.

The Cochran Q test was used to evaluate the statistical heterogeneity of the treatment results, associated with the I^2 inconsistency test, where figures above 50% were treated as indicative of significant heterogeneity. In case of significant clinical heterogeneity ($I^2 > 50\%$), subgroup analysis was used to plot the results. Subgroup analysis are secondary analyses, in which studies were divided into groups according to common characteristics and the analysed outcomes were performed to determine whether any significant treatment effects occur according to this characteristic. Subgroup analysis of included studies were performed for follow-up time characteristics.

For the meta-analysis of PD and BoP outcomes, the articles were organized according to follow-up time, 3 and 6 months.

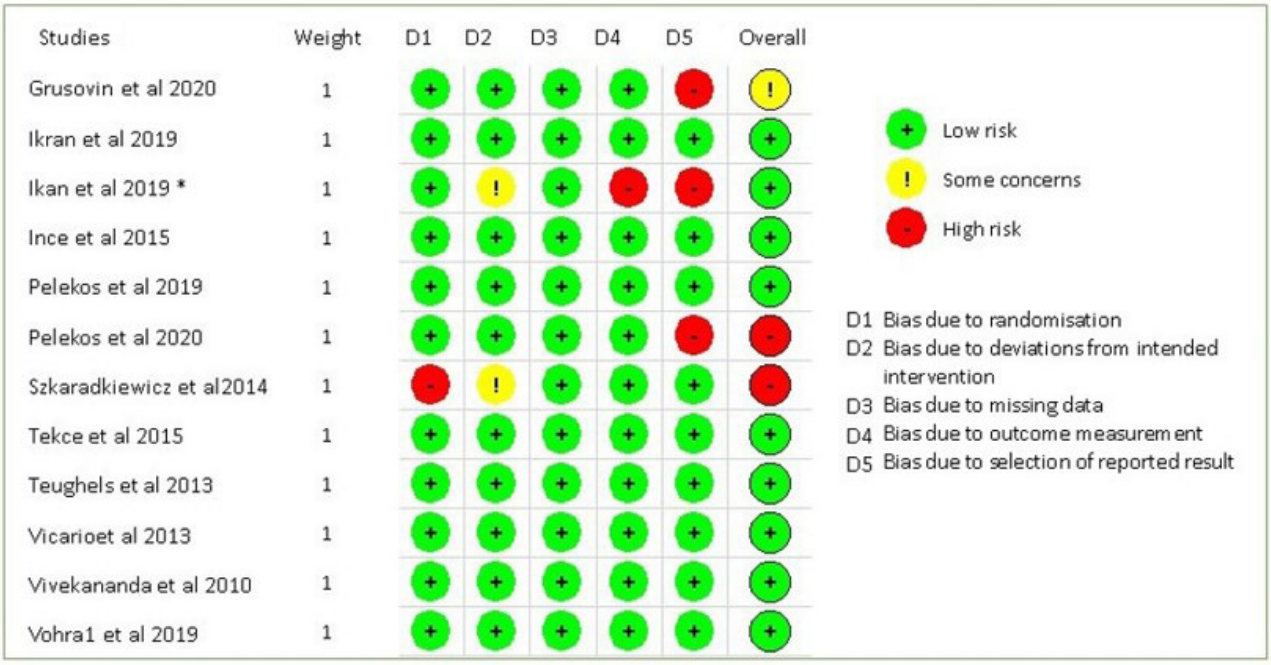

Figure 2 - Traffic light plots.

Table I - General characteristics of included studies

Author	Year	Study design	Sample	Age	Vehicle full dose	Frequency	Follow up
Grusovin et al. [39]	2019	Pilot study, double blind and randomized	20 patients	31-70 years	168 tablets	Twice a day	3, 6, 9 and 12 months
Ikram et al. [43]	2018	Clinical trial, double blind and randomized	30 patients	Olden than 30 years	168 tablets	Twice a day	6 and 12 weeks
Ikram et al. [44]	2019	Clinical trial, double blind and randomized	28 patients	Older than 30 years	-	Once a day	6 and 12 weeks
Ince et al. [45]	2015	Clinical trial, double blind and randomized	30 patients	35-50 years	42 tablets	Twice a day	Days 0, 21, 90, 180 and 360
Pelekos et al. [46]	2019	Clinical trial, double blind and randomized	59 patients	Older than 18 years	56 tablets	Twice a day	Days 0, 90 and 180
Pelekos et al. [47]	2020	Clinical trial, double blind and randomized	40 patients	-	56 tablets	Twice a day	Days 90 and 180
Szkaradkiewicz et al. [48]	2014	-	38 patients	31-46 years	28 pills	Twice a day	Two weeks after pills administration
Tekce et al. [49]	2015	Clinical trial and randomized	40 patients	35-50 years	42 tablets	Twice a day	Days 21, 90, 180 and 360
Teughels et al. [37]	2013	Clinical trial and randomized	30 patients	Older than 35 years	168 tablets	Twice a day	3, 6, 9 and 12 weeks
Vicario et al. [36]	2013	Clinical trial, double blind and randomized	19 patients	Older than 18 years	30 tablets	Once a day	After 30 days
Vivekananda et al. [35]	2010	Clinical trial, double blind and randomized	30 patients	34-50 years	42 tablets	Twice a day	Days 0 and 42
Vohra et al. [50]	2019	Clinical trial, double blind and randomized	127 patients	50 years	42 tablets	Twice a day	3 and 6 months

STUDIES DESCRIPTION

In a double-blind clinical trial, Ikram et al. [43] gathered thirty participants diagnosed with chronic periodontitis who underwent SRP. Half of the patients received *L. reuteri* for 3 months, and the other half received amoxicillin and metronidazole for 7 days. The study concluded that there was a similar improvement in both groups, indicating that adjuvant probiotic agents showed similar efficacy to therapeutic agents. In a second double-blind clinical trial, Ikram et al. [44] continued their study involving the use of *L. reuteri*, the new data showed an improvement in the treatment when using the probiotic, and they could conclude that the probiotic approach is effective and a promising alternative in adjuvant periodontal therapy. Also with thirty patients, Ince et al. [45] concluded that the analysed clinical parameters improved when using the probiotic *L. reuteri,* in 2015.

Szkaradkiewicz et al. [48] recruited 38 patients and divided them into two groups. For two weeks, one of the groups had probiotic administration, while another one had placebo administration. Subsequently, the control of the patients was performed and, it was concluded that there was a significant reduction in the clinical indices of PI (plaque index), GI (gingival index) and BI (bleeding index) in the test group. As well, in 2012 Vicario et al. [36] concluded that the administration of probiotics proved to be an effective strategy for reducing inflammation and clinical symptoms of periodontitis.

Using the same approach of dividing into an experimental and a control group, Tekce et al. [49] analysed the microbiological and periodontal parameters on administered *L. reuteri* in patient with periodontitis, and concluded that the probiotic helped to delay local recolonization and improves clinical outcomes after periodontal intervention. Teughels et al. [37] had also analyzed microbiological parameters and their work showed an important change in the amount of P. gingivalis bacteria and an improvement in periodontal parameters. In 2012, Vivekananda et al. [35] recruited thirty patients and analyzeddetermined parameters. They were able to conclude that the administration of *L. reuteri* as an adjuvant therapy inhibited bacterial plaque and had anti-inflammatory and antimicrobial effects.

In 2019, Vohra et al. [50] evaluating 127 patients concluded that the SRP treatment was effective, regardless of the use of the probiotic. In 2019, Grusovin et al. [39] obtained positive results regarding PPD (pocket probing depth), CAL (clinical attachment loss) and BoP after administration of the probiotic *L.reuteri*.

Pelekos et al. [47] analysed possible changes in the use of L. *reuteri*, specifically in periodontal pockets with PD >5mm in molars. According to their study, the molar pockets were benefited from the administration of the probiotic concluding that new approaches related to the probiotic dose, duration and administration way should be taken. Previously, in 2019, Pelekos et al. [46] had already studied L. reuteri in another clinical trial, but the results were inconclusive and only showed a trend towards successful treatment with the use of probiotics. Likewise, correlating this study to other from Grusovin et al. [39], Ikram et al. [44], Pelekos [46,47] and Teughels et al. [37] had showed a non-statistically significant improvement in the periodontal treatment using probiotics.

META ANALYSIS

DISCUSSION

This review considered 12 clinical studies that evaluated the parameters of probing depth and bleeding on probing after 3 and 6 months. Initially, 526 results were found, but 290 were duplicated. With the new number of 239 studies, 204 were excluded due to irrelevance, leaving 32 articles for analysis. After a deeper reading of these 32 articles, 20 were excluded because they did not fit the parameters of this systematic review, leaving 12 studies for analysis.

The following studies: Ikram et al. [43], Pelekos et al. [46,47], Teughels et al. [37] and Vivekananda et al. [35] also analysed clinical attachment level indices. Ince et al. [45] and Tekce et al. [49] analysed gingival recession indices. As the analysed data were not presented in all articles, only probing depth and bleeding on probing data were considered in the meta-analysis performed in this study.

All studies analysed the risk of bias and, among them, 8 had low risk [35-37,44-46,49,50]. The study made by Grusovin et al. [39] had a median risk of bias, and the last two studies, Pelekos et al. [47] and Szkaradkiewicz et al. [48], had a high risk of bias.

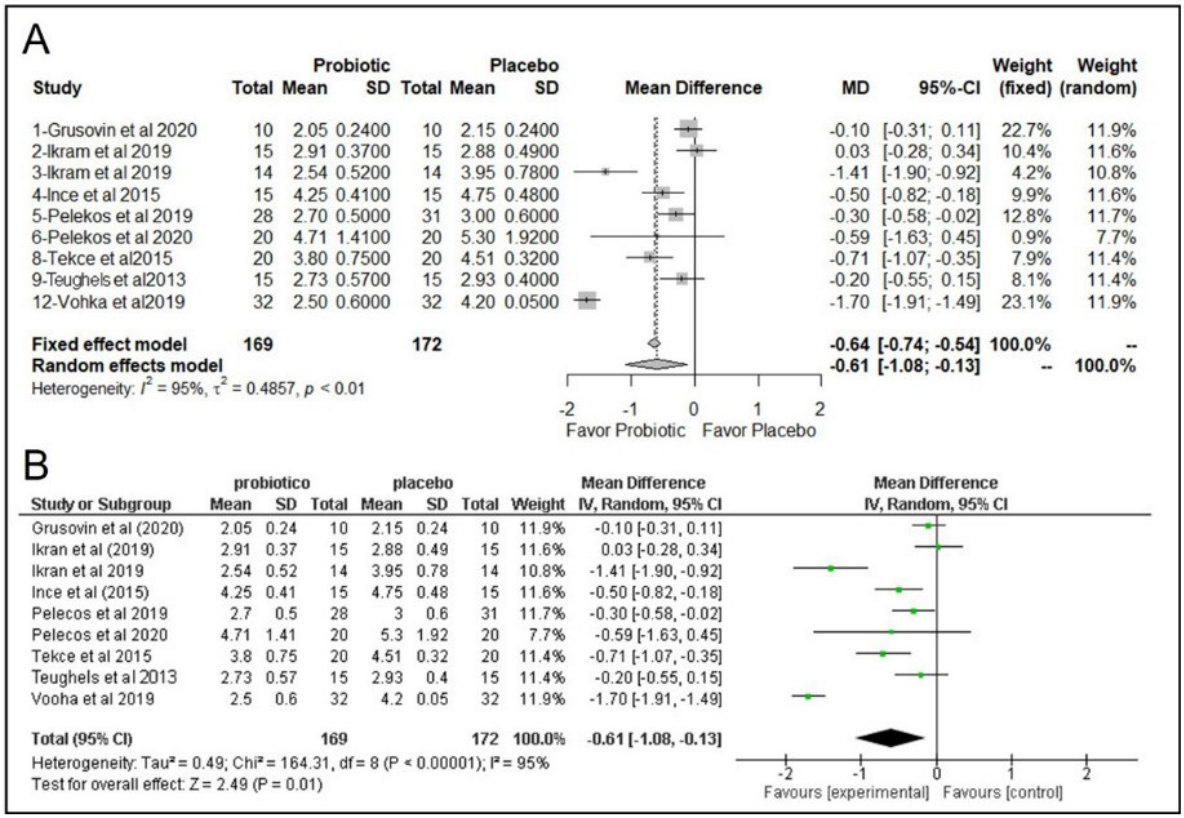

Figure 3 - Forest plot - 3-month follow-up on probing depth reduction (A) and decrease in bleeding on probing (B). (A) reduction in probing depth and (B) decrease in bleeding on probing comparing scaling and root planing (SRP) and adjuvant probiotics versus scaling and root planing (SRP). CI, confidence interval; SD, standard deviation.

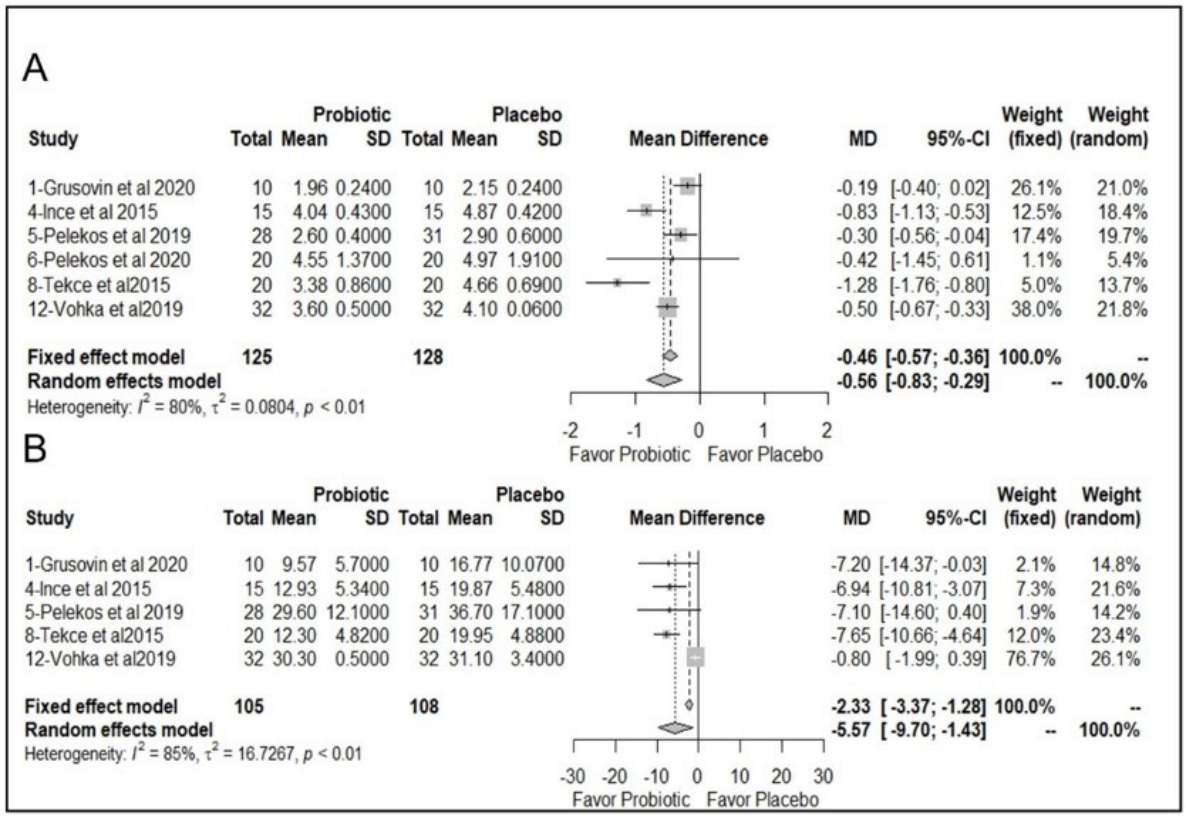

Figure 4 - Forest plot - 6-month follow-up on probing depth reduction (A) and decrease in bleeding on probing (B). (A) reduction in probing depth and (B) decrease in bleeding on probing comparing scaling and root planing (SRP) and adjuvant probiotics versus scaling and root planing (SRP). CI, confidence interval; SD, standard deviation.

All the included studies had established inclusion criteria, and the distribution of probiotics was similar in all, ranging from 1 or 2 times a day through lozenges. Only Szkaradkiewicz et al. [48] used tablets methods and, Ikram et al. [43] administered *L. reuteri* in sachet form, after brushing.

At the 3-month follow-up for PD, 9 articles were selected for the meta-analysis, resulting in a favorable use of probiotics as adjuvant to SRP, compared to groups that did not use probiotics (-0.61, 95% CI [-1.08; -0.13], I^2=95%; p = 0.01).

The articles by Vicario et al. [36], Vivekananda et al. [35] and Szkaradkiewicz et al. [48] did not analyse the data at 3 months and, therefore, were not included in the meta-analysis. Among the ones that were analysed, four showed significant improvement in probing depth with the use of *L.reuteri* [44,45,49,50].

Regarding the parameter bleeding on probing, there was no meaningful difference in the use of the probiotic *L.reuteri* in the 3 months results (Figure 3). Virtually, all the articles analysed obtained unfavourable or neutral results for the use of probiotics (-6.16, 95% CI [-14.56; 2.24], I^2=97%; p < 0.01). Only two articles, among those analysed, showed positive results for the use of probiotics: Ince et al. [45] and Tekce et al. [49].

The follow-up evaluation after 6 months showed that the number of articles that presented these data were six for PD, and five articles for BoP (Figure 4). For PD, among those analysed, most showed probing depth gain [45,46,49,50], while Grusovin et al. [39] and Pelekos et al. [47] showed no meaningful difference but had a favourable result for the use of probiotics (-0.56, 95% CI [-0.83; -0.29], I^2=80%; p < 0.01). For BoP parameters, three of them did not show an important difference for the use of probiotics, these results were presented in Grusovin et al. [39], Pelekos et al. [46] and Vohra et al. [50]. However, in general, the analysis was positive regarding the use of probiotic as an adjunctive therapy in the treatment of periodontal disease (-5.57, 95% CI [-9.70; -1.43], I^2=85%; p < 0.01).

Probiotics are dietary supplements used to preserve or promote health [51]. The probiotic evaluated in the present review, *L.reuteri*, is a bacterium capable of producing antimicrobial molecules and remodelling the host's commensal microbiota [22]. It had also shown an effect against periodontopathogens, *A. actinomycetemcomitans, P.gingivalis., F. nucleatum, T. forsythia*, and other oral pathogens, such as *S.mutans* [52].

Previous systematic reviews have shown positive results regarding the use of *L.reuteri* in non-surgical periodontal therapy [53,54], while the review by Akram et al. [55] analysed its use in cases of gingivitis and, concluded that there is no enough evidence on the reduction of inflammatory levels to support the use.

The primary limitation of this study is the high heterogeneity found. This may be due to the clinical and methodological diversities, such as the differences between the methodologies used for administering probiotics, the follow-up time, the difference in the form of distribution of probiotics, such as lozenges, sachets and tablets, and the different amounts and final dose that each study uses, consequently each patient receives. Thus, more randomized clinical studies with similar methodologies are needed to analyse the behaviour of L.reuteri as an adjuvant in non-surgical periodontal treatment.

CONCLUSION

Considering the limitations of this present study, it was concluded that probiotics may provide supplementary benefit to the treatment of periodontitis, with improvement in bleeding on probing rates and probing depth.

Author's Contributions

TST, CLF, VCSL: Conceptualization, Methodology. ACM, TMFC, MANJ: Formal Analysis, Investigation, Resources, Writing – Original Draft Preparation. TC, MANJ: Data Curation. TST, CLF, VCSL, MANJ: Writing – Original Draft Preparation. TST, CLF, VCSL, ACM, TMFC, MANJ: Writing – Review & Editing, Supervision. TST, TMFC, MANJ: Visualization.

Conflict of Interest

The authors declare no conflicts of interest.

Funding

Scholarship PIBIC Reitoria Edital 1/2020 -PIBIC.

Regulatory Statement

This study was conducted in accordance with all the provisions of the local research subjects oversight committee guideline.

REFERENCES

1. Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS, et al. A new classification scheme for periodontal and peri-implant diseases and conditions: introduction and key changes from the 1999 classification. J Clin Periodontol. 2018;45(Suppl 20):S1-8. http://dx.doi.org/10.1111/jcpe.12935. PMid:29926489.
2. Slots J, Rams TE. New views on periodontal microbiota in special patient categories. J Clin Periodontol. 1991;18(6):411-20. http://dx.doi.org/10.1111/j.1600-051X.1991.tb02309.x. PMid:1890221.
3. Socransky SS, Haffajee AD. The bacterial etiology of destructive periodontal disease: current concepts. J Periodontol. 1992;63(4s):322-31. http://dx.doi.org/10.1902/jop.1992.63.4s.322.
4. Wolff L, Dahlen G, Aeppli D. Bacteria as risk markers for periodontitis. J Periodontol. 1994;65(5s):498-510. http://dx.doi.org/10.1902/jop.1994.65.5s.498.
5. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol. 2018;89(Suppl 1):S173-82. http://dx.doi.org/10.1002/JPER.17-0721. PMid:29926951.
6. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Dis Primers. 2017;3(1):17038. http://dx.doi.org/10.1038/nrdp.2017.38. PMid:28805207.
7. Berezow AB, Darveau RP. Microbial shift and periodontitis. Periodontol 2000. 2011;55(1):36-47. http://dx.doi.org/10.1111/j.1600-0757.2010.00350.x. PMid:21134227.
8. Marsh PD. Are dental diseases examples of ecological catastrophes? Microbiology. 2003;149(Pt 2):279-94. http://dx.doi.org/10.1099/mic.0.26082-0. PMid:12624191.
9. Keestra JA, Grosjean I, Coucke W, Quirynen M, Teughels W. Non-surgical periodontal therapy with systemic antibiotics in patients with untreated chronic periodontitis: a systematic review and meta-analysis. J Periodontal Res. 2015;50(3):294-314. http://dx.doi.org/10.1111/jre.12221. PMid:25142259.
10. Haffajee AD, Teles RP, Socransky SS. The effect of periodontal therapy on the composition of the subgingival microbiota. Periodontol 2000. 2006;42(1):219-58. http://dx.doi.org/10.1111/j.1600-0757.2006.00191.x. PMid:16930312.
11. Jepsen S, Deschner J, Braun A, Schwarz F, Eberhard J. Calculus removal and the prevention of its formation. Periodontol 2000. 2011;55(1):167-88. http://dx.doi.org/10.1111/j.1600-0757.2010.00382.x. PMid:21134234.
12. Feres M, Figueiredo LC, Soares GM, Faveri M. Systemic antibiotics in the treatment of periodontitis. Periodontol 2000. 2015;67(1):131-86. http://dx.doi.org/10.1111/prd.12075. PMid:25494600.
13. Van der Sluijs M, Van Der Sluijs E, Van Der Weijden F, Slot DE. The effect on clinical parameters of periodontal inflammation following non-surgical periodontal therapy with ultrasonics and chemotherapeutic cooling solutions: a systematic review. J Clin Periodontol. 2016;43(12):1074-85. http://dx.doi.org/10.1111/jcpe.12613. PMid:27509308.
14. Segarra-Vidal M, Guerra-Ojeda S, Vallés LS, López-Roldán A, Mauricio MD, Aldasoro M, et al. Effects of photodynamic therapy in periodontal treatment: A randomized, controlled clinical trial. J Clin Periodontol. 2017;44(9):915-25. http://dx.doi.org/10.1111/jcpe.12768. PMid:28667678.
15. Teughels W, Durukan A, Ozcelik O, Pauwels M, Quirynen M, Haytac MC. Clinical and microbiological effects of Lactobacillus reuteri probiotics in the treatment of chronic periodontitis: a randomized placebocontrolled study. J Clin Periodontol. 2013;40(11):1025-35. http://dx.doi.org/10.1111/jcpe.12155. PMid:24164569.
16. Longo M, Ramos TCS, Nunes CMM, Santamaria MP, Jardini MAN. Probiotic therapy as a novel approach in the prevention and treatment of gingivitis: a review. Braz Dent Sci. 2018;21(4):367-76. http://dx.doi.org/10.14295/bds.2018.v21i4.1600.
17. Stamatova I, Meurman JH. Probiotics and periodontal disease. Periodontol 2000. 2009;51(1):141-51. http://dx.doi.org/10.1111/j.1600-0757.2009.00305.x. PMid:19878473.
18. Sliepen I, Van Damme J, Van Essche M, Loozen G, Quirynen M, Teughels W. Microbial interactions influence inflammatory host cell responses. J Dent Res. 2009;88(11):1026-30. http://dx.doi.org/10.1177/0022034509347296. PMid:19828891.
19. Twetman S, Derawi B, Keller M, Ekstrand KIM, Yucel-Lindberg LAY, Stecksén-Blicks C. Short-term effect of chewing gums containing probiotic Lactobacillus reuteri on the levels of inflammatory mediators in gingival crevicular fluid. Acta Odontol Scand. 2009;67(1):19-24. http://dx.doi.org/10.1080/00016350802516170. PMid:18985460.
20. Brown AC, Valiere A. Probiotics and medical nutrition therapy. Nutr Clin Care. 2004;7(2):56-68. PMid:15481739.
21. Bron PA, van Baarlen P, Kleerebezem M. Emerging molecular insights into the interaction between probiotics and the host intestinal mucosa. Nat Rev Microbiol. 2011;10(1):66-78. http://dx.doi.org/10.1038/nrmicro2690. PMid:22101918.
22. Mu Q, Tavella VJ, Luo XM. Role of Lactobacillus reuteri in human health and diseases. Front Microbiol. 2018;9:757. http://dx.doi.org/10.3389/fmicb.2018.00757. PMid:29725324.
23. Spinler JK, Sontakke A, Hollister EB, Venable SF, Oh PL, Balderas MA, et al. From prediction to function using evolutionary genomics: human-specific ecotypes of lactobacillus reuteri have diverse probiotic functions. Genome Biol Evol. 2014;6(7):1772-89. http://dx.doi.org/10.1093/gbe/evu137. PMid:24951561.
24. Schepper JD, Collins FL, Rios-Arce ND, Raehtz S, Schaefer L, Gardinier JD, et al. Probiotic lactobacillus reuteri prevents postantibiotic bone loss by reducing intestinal dysbiosis and preventing barrier disruption. J Bone Miner Res. 2019;34(4):681-98. http://dx.doi.org/10.1002/jbmr.3635. PMid:30690795.
25. Thomas CM, Hong T, van Pijkeren JP, Hemarajata P, Trinh DV, Hu W, et al. Histamine derived from probiotic lactobacillus reuteri suppresses tnf via modulation of pka and erk signaling. PLoS One. 2012;7(2):e31951. http://dx.doi.org/10.1371/journal.pone.0031951. PMid:22384111.
26. Gu Q, Zhang C, Song D, Li P, Zhu X. Enhancing vitamin B12 content in soy-yogurt by Lactobacillus reuteri. Int J Food Microbiol. 2015;206:56-9. http://dx.doi.org/10.1016/j.ijfoodmicro.2015.04.033. PMid:25955289.
27. Collins FL, Rios-Arce ND, Schepper JD, Parameswaran N, McCabe LR. The potential of probiotics as a therapy for osteoporosis. Microbiol Spectr. 2017;5(4):5.4.20. http://dx.doi.org/10.1128/microbiolspec.BAD-0015-2016. PMid:28840819.
28. D'Amelio P, Sassi F. Gut microbiota, immune system, and bone. Calcif Tissue Int. 2018;102(4):415-25. http://dx.doi.org/10.1007/s00223-017-0331-y. PMid:28965190.
29. Iniesta M, Herrera D, Montero E, Zurbriggen M, Matos AR, Marín MJ, et al. Probiotic effects of orally administered Lactobacillus reuteri-containing tablets on the subgingival and salivary microbiota in patients with gingivitis. A randomized clinical trial. J Clin Periodontol. 2012;39(8):736-44. http://dx.doi.org/10.1111/j.1600-051X.2012.01914.x. PMid:22694350.
30. Schaefer L, Auchtung TA, Hermans KE, Whitehead D, Borhan B, Britton RA. The antimicrobial compound reuterin (3-hydroxypropionaldehyde) induces oxidative stress via interaction with thiol groups. Microbiology (Reading). 2010;156(Pt 6):1589-99. http://dx.doi.org/10.1099/mic.0.035642-0. PMid:20150236.

31. Jones SE, Versalovic J. Probiotic Lactobacillus reuteri biofilms produce antimicrobial and anti-inflammatory factors. BMC Microbiol. 2009;9(1):35. http://dx.doi.org/10.1186/1471-2180-9-35. PMid:19210794.
32. Krasse P, Carlsson B, Dahl C, Paulsson A, Nilsson A, Sinkiewicz G. Decreased gum bleeding and reduced gingivitis by the probiotic Lactobacillus reuteri. Swed Dent J. 2006;30(2):55-60. PMid:16878680.
33. Riccia DN, Bizzini F, Perilli MG, Polimeni A, Trinchieri V, Amicosante G, et al. Anti-inflammatory effects of Lactobacillus brevis (CD2) on periodontal disease. Oral Dis. 2007;13(4):376-85. http://dx.doi.org/10.1111/j.1601-0825.2006.01291.x. PMid:17577323.
34. Harini PM, Anegundi RT. Efficacy of a probiotic and chlorhexidine mouth rinses: a short-term clinical study. J Indian Soc Pedod Prev Dent. 2010;28(3):179-82. http://dx.doi.org/10.4103/0970-4388.73799. PMid:21157050.
35. Vivekananda MR, Vandana KL, Bhat KG. Effect of the probiotic Lactobacilli reuteri (Prodentis) in the management of periodontal disease: preliminary randomized clinical trial. J Oral Microbiol. 2010;2(1):2. http://dx.doi.org/10.3402/jom.v2i0.5344. PMid:21523225.
36. Vicario M, Santos A, Violant D, Nart J, Giner L. Clinical changes in periodontak subjects with the probiotic Lactobacillus reuteri Prodentis: a preliminar randomized clinical trial. Acta Odontol Scand. 2013;71(3-4):813-9. http://dx.doi.org/10.3109/00016357.2012.734404. PMid:23176716.
37. Teughels W, Durukan A, Ozcelik O, Pauwels M, Quirynen M, Haytac MC. Clinical and microbiological effects of Lactobacillus reuteri probiotics in the treatment of chronic periodontitis: a randomized placebo-controlled study. J Clin Periodontol. 2013;40(11):1025-35. http://dx.doi.org/10.1111/jcpe.12155. PMid:24164569.
38. Dhaliwal PK, Grover V, Malhotra R, Kapoor A. Clinical and microbiological investigation of the effects of probiotics combined with scaling and root planing in the management of chronic periodontitis: a randomized, controlled study. J Int Acad Periodontol. 2017;19(3):101-8. PMid:31473697.
39. Grusovin MG, Bossini S, Calza S, Cappa V, Garzetti G, Scotti E, et al. Clinical efficacy of Lactobacillus reuteri-containing lozenges in the supportive therapy of generalized periodontitis stage III and IV, grade C: 1-year results of a double-blind randomized placebo-controlled pilot study. Clin Oral Investig. 2020;24(6):2015-24. http://dx.doi.org/10.1007/s00784-019-03065-x. PMid:31620939.
40. Elazim MMA, Kabil NS, Wassel MO, Nasser MS. Investigation of the effect of breast milk, probiotic supplemented and plain milk formulas on some oral bacteria in infants: an observational and in-vitro study. Braz Dent Sci. 2022;25(2):e3099. http://dx.doi.org/10.4322/bds.2022.e3099.
41. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:71. http://dx.doi.org/10.1136/bmj.n71.
42. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535. http://dx.doi.org/10.1136/bmj.b2535. PMid:19622551.
43. Ikram S, Hassan N, Raffat MA, Mirza S, Akram Z. Systematic review and meta-analysis of double-blind, placebo-controlled, randomized clinical trials using probiotics in chronic periodontitis. J Investig Clin Dent. 2018;9(3):e12338. http://dx.doi.org/10.1111/jicd.12338. PMid:29604177.
44. Ikram S, Hassan N, Baig S, Borges KJJ, Raffat MA, Akram Z. Effect of local probiotic (Lactobacillus reuteri) vs systemic antibiotic therapy as an adjunct to non-surgical periodontal treatment in chronic periodontitis. J Investig Clin Dent. 2019;10(2):e12393. http://dx.doi.org/10.1111/jicd.12393. PMid:30663271.
45. Ince G, Gürsoy H, İpçi ŞD, Cakar G, Emekli-Alturfan E, Yılmaz S. Clinical and biochemical evaluation of lozenges containing lactobacillus reuteri as an adjunct to non-surgical periodontal therapy in chronic periodontitis. J Periodontol. 2015;86(6):746-54. http://dx.doi.org/10.1902/jop.2015.140612. PMid:25741580.
46. Pelekos G, Ho SN, Acharya A, Leung WK, McGrath C. A double-blind, paralleled-arm, placebo-controlled and randomized clinical trial of the effectiveness of probiotics as an adjunct in periodontal care. J Clin Periodontol. 2019;46(12):1217-27. http://dx.doi.org/10.1111/jcpe.13191. PMid:31479530.
47. Pelekos G, Acharya A, Eiji N, Hong G, Leung WK, McGrath C. Effects of adjunctive probiotic L. reuteri lozenges on S/RSD outcomes at molar sites with deep pockets. J Clin Periodontol. 2020;47(9):1098-107. http://dx.doi.org/10.1111/jcpe.13329. PMid:32511775.
48. Szkaradkiewicz AK, Stopa J, Karpiński TM. Effect of oral administration involving a probiotic strain of Lactobacillus reuteri on pro-inflammatory cytokine response in patients with chronic periodontitis. Arch Immunol Ther Exp (Warsz). 2014;62(6):495-500. http://dx.doi.org/10.1007/s00005-014-0277-y. PMid:24509697.
49. Tekce M, Ince G, Gursoy H, Dirikan Ipci S, Cakar G, Kadir T, et al. Clinical and microbiological effects of probiotic lozenges in the treatment of chronic periodontitis: a 1-year follow-up study. J Clin Periodontol. 2015;42(4):363-72. http://dx.doi.org/10.1111/jcpe.12387. PMid:25728888.
50. Vohra F, Bukhari IA, Sheikh SA, Albaijan R, Naseem M, Hussain M. Effectiveness of scaling and root planing with and without adjunct probiotic therapy in the treatment of chronic periodontitis among shamma users and non-users: A randomized controlled trial. J Periodontol. 2019;91(9):1177-85. http://dx.doi.org/10.1002/JPER.19-0464. PMid:31985066.
51. Bizzini B, Pizzo G, Scapagnini G, Nuzzo D, Vasto S. Probiotics and oral health. Curr Pharm Des. 2012;18(34):5522-31. http://dx.doi.org/10.2174/138161212803307473. PMid:22632388.
52. Baca-Castañón ML, De la Garza-Ramos MA, Alcázar-Pizaña AG, Grondin Y, Coronado-Mendoza A, Sánchez-Najera RI, et al. Antimicrobial effect of lactobacillus reuteri on cariogenic bacteria streptococcus gordonii, streptococcus mutans, and periodontal diseases actinomyces naeslundii and tannerella forsythia. Probiotics Antimicrob Proteins. 2015;7(1):1-8. http://dx.doi.org/10.1007/s12602-014-9178-y. PMid:25422124.
53. Martin-Cabezas R, Davideau JL, Tenenbaum H, Huck O. Clinical efficacy of probiotics as an adjunctive therapy to non-surgical periodontal treatment of chronic periodontitis: a systematic review and meta-analysis. J Clin Periodontol. 2016;43(6):520-30. http://dx.doi.org/10.1111/jcpe.12545. PMid:26970230.
54. Song D, Liu XR. Role of probiotics containing Lactobacillus reuteri in adjunct to scaling and root planing for management of patients with chronic periodontitis: a meta-analysis. Eur Rev Med Pharmacol Sci. 2020;24(8):4495-505. PMid:32373987.
55. Akram Z, Shafqat SS, Aati S, Kujan O, Fawzy A. Clinical efficacy of probiotics in the treatment of gingivitis: a systematic review and meta-analysis. Aust Dent J. 2020;65(1):12-20. http://dx.doi.org/10.1111/adj.12733. PMid:31682012.

Maria Aparecida Neves Jardini
(Corresponding address)
Universidade Estadual Paulista, Instituto de Ciência e Tecnologia, Departamento de Diagnóstico e Cirurgia. São José dos Campos, SP, Brazil.
Email: maria.jardini@unesp.br

Date submitted: 2022 Aug 17
Accept submission: 2023 Jan 23