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REVIEW

Effects of probiotics in periodontal diseases: a systematic review

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Abstract
Objectives This study was designed to determine the effects of probiotics in prevention and/or treatment of periodontal diseases.
Materials and methods We performed broad searches in the MEDLINE, Embase, and Cochrane databases and selected articles that satisfied the description of randomized clinical trials comparing the administration of probiotics versus placebo or another intervention to prevent or treat periodontal diseases in adult patients.
Results Four randomized clinical trials were analyzed in the final review process. For the primary outcome, probing pocket depth, there would be no clinical beneficial effect of probiotics. For secondary outcomes, probiotics have shown small benefits on plaque index and gingival inflammation.
Conclusions Based on the results of this review, the effectiveness of probiotics on the prevention and treatment of periodontal diseases is questionable. There is currently insufficient evidence demonstrating the benefits of systematic preventative use of probiotics in patients with periodontal diseases.
Clinical relevance The use of probiotics are described to prevent or treat periodontal diseases in some clinical trials; therefore, a systematic review of the evidence for the effect of periodontal diseases is needed.

Keywords Systematic review · Probiotics · Periodontal diseases · Periodontitis · Gingivitis

Introduction

Periodontal diseases are divided into two general stages affecting a majority of adults: gingivitis and periodontitis

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[1]. These two categories are based on whether attachment loss has occurred. Gingivitis is the presence of gingival inflammation without loss of connective tissue attachment. Periodontitis is characterized by the presence of gingival inflammation with loss of connective tissue attachment and the resorption of coronal portions of tooth supporting alveolar bone [1]. Both diseases require the presence of plaque bacteria which are thought to induce pathological changes in the tissues by direct and indirect means [2]. Although conventional treatments are considered effective, efforts to improve periodontal therapies through complementary treatments are at research. Recently, there has been increasing interest in probiotic control against periodontal diseases, and a number of clinical trials have been conducted to elucidate the possible impact on oral health.

Probiotics are living microorganisms, principally bacteria, which provide beneficial effects for the host when administered in proper quantities [3]. Many clinical studies have shown the efficacy of certain probiotics in the prevention and treatment of systemic gastrointestinal diseases [4]. Probiotic bacteria can confer benefits for the host through the following mechanisms: (a) providing nutrients and cofactors, (b) competition with pathogens, (c) interaction with virulence factors of pathogens, and (d) stimulating the immune response of the host [5].

Plausible mechanisms of action for probiotics in periodontal diseases are based on modifications of the pathogenic potential of biofilm and include interfering in the growth and development of periodontal pathogens [6], the replacement of pathogenic microorganisms by beneficial bacteria [7], and prevention of colonization by periodontal pathogens [8]. However, this is a relatively new field, and data regarding the effectiveness of probiotics in oral diseases are scarce.

The objective of this systematic review was to analyze the available scientific evidence on the effects of probiotics in patients with periodontal diseases (compared with other conventional interventions and the administration of placebo).

Materials and methods

This review was conducted according to a previously developed protocol, which is available from the authors.

Focused question What is the clinical impact of probiotic therapy, compared to conventional intervention or to placebo, in the prevention or treatment of periodontal diseases?

Search process We searched the MEDLINE (1948-February 2011), Embase (1980-February 2011), and *CENTRAL databases* (1993–February 2011). We also performed a hand search of the Journal of Periodontology and the Journal of Clinical Periodontology. We reviewed cross references from relevant papers and abstracts of conferences related to the subject of the review. Finally, we contacted research groups in the area and laboratories that prepared probiotics to obtain information about possible studies being developed and preliminary results. No language restrictions were applied.

Search strategies were based on the following terms: (1) probiotics, (2) periodontal diseases, (3) type of probiotics, and (4) randomized clinical trials (RCTs). Each one of these terms was explored and adapted to the syntax of each of the databases. (Supporting Information)

Selection criteria for the studies

– Inclusion criteria

Type of studies: Randomized clinical trials
Subjects: Anyone who received probiotics as a preventive or treatment agent for periodontal diseases (gingivitis or periodontitis).
Type of treatment intervention: Oral probiotic administration compared with placebo, no treatment, or another active intervention. Randomized clinical trials were included when they (1) tested one or more probiotic agents as an adjunct to scaling and root planing [SRP] alone or with a placebo and (2) had a control group that received the same SRP as the treatment group. We considered any type of probiotic with any type of administration method. Some of the included probiotics were, but not limited to *Lactobacillus rhamnosus* GG, *Lactobacillus salivarius* WB21, *Lactobacillus acidophilus*, *Bifidobacterium* DN-173 010, *Lactobacillus reuteri*, and *Lactobacillus casei*.
Types of outcome measures: Primary outcome variables were probing pocket depth (PPD), measured in millimeters from the gingival margin to the depth of probe penetration, and clinical attachment level (CAL), measured in millimeters from the cement-enamel junction to the depth of probe penetration. Secondary outcomes included measurements of plaque index, gingival inflammation, and bleeding on probing (BOP). All studies were examined for reports of adverse effects either by the clinician [clinical examination] or by the patient [interviews/questionnaire] at each recall visit, including the presence of halitosis. There was no restriction regarding the method for measuring any of the outcomes. We only included trials that reported any of these outcomes with a minimum follow-up of 4 weeks.

– Exclusion criteria

Studies were not used in the present review if the clinical trials included patients with a compromised general state of health.

Process for selection of studies and data collection Two reviewers performed the titles and abstract screening independently (AG, AP). Interobserver agreement was assessed by calculating kappa scores (kappa=0.9). In a second stage, we evaluated the full text of the articles selected, and we eliminated all articles that did not fulfill all the selection criteria (Table 1). Extraction of data was performed using a previously designed chart (Tables 2 and 3). Two reviewers independently analyzed all of the articles that fulfilled the selection criteria (NY, IA), and we applied the Cochrane Collaboration tool for evaluating the risk of bias [9]. Disagreements in all stages were solved by discussion and with the help of an arbiter. We contacted authors when necessary for clarification of data or to obtain missing data.

Assessment of heterogeneity We assessed clinical heterogeneity based on the setting, patients, intervention, and outcome measurement characteristics. We used the risk of bias tool [9] to evaluate methodological heterogeneity. We planned to assess statistical heterogeneity using the chi-square test and the I^2 statistic.

Data analysis We planned to undertake the meta-analyses using a random effects model if the clinical heterogeneity were judged to be low; otherwise, only qualitative descriptions were done. Measures of effect, subgroup, and sensitivity analysis planned are described with details in the protocol of the review.

Results

The initial search resulted in 100 articles; however, 87 of these articles were excluded after reviewing the abstracts because they did not have the proper clinical trial design or because they were duplicates. After analyzing the full text from 13 clinical trials, 8 were excluded because they did not fulfill all of the selection criteria (see Table 2 and the flow diagram in Fig. 1). Our final review included five articles; however, two articles were a separate report of the same randomized clinical trial [10, 11]. Therefore, a total of four trials were included in this review (Tables 2 and 3).

Among the articles selected, one studied the administration of probiotics using *L. salivarius* (*L. salivarius*] in pills [10], two studied the administration of *L. reuteri* (*L. reuteri*) (one by pills and the other in the form of gum) [12, 13], and one investigated treatment with *L. casei* (*L. casei*) administered in milk. All the studies were placebo-controlled, except for the study published by Staab et al. [14], which administered no treatment to the control group.

Risk of bias of the included studies The four studies were subjected to critical analysis following the Cochrane Collaboration tool for evaluating the risk of bias, and we classified two articles as having a low risk of bias [10, 12] and two articles as having a high risk of bias [13, 14] (Table 4). The domain in which the trials were judged to have the lower risk of bias was "randomization". All the studies reported the randomization method properly. In contrast, the domain classified as having the higher risk of bias was "free of other sources of bias". The four studies were funded by private laboratories. Other important sources of bias were the short follow-up period [13], experimentally induced gingivitis, and samples conformed by dental and medical students [14].

Effects of probiotics Due to the clinical heterogeneity of the studies, we considered that it was not appropriate to perform meta-analyses. Trials that evaluated the same outcomes did

Table 1 Articles excluded from the final review

Author	Title of article	Reason for exclusion
Hatakka et al. 2007	Probiotics reduce the prevalence of oral *Candida* in the elderly—a randomized controlled trial	Only had to do with a study of *Candida*
Caglar et al. 2005b	Effect of yogurt with *Bifidobacterium* DN-173 010 on salivary mutans streptococci and lactobacilli in young adults	Only had to do with a study of caries
Montalto et al. 2004	Probiotic treatment increases salivary counts of *Lactobacilli*—a double-blind, randomized, controlled study	Only had to do with a study of caries
Riccia et al. 2007	Anti-inflammatory effects of *Lactobacillus brevis* (CD2) on periodontal disease.	No between groups comparison for the clinical outcomes
Iwamoto et al. 2010	Effects of probiotic *Lactobacillus salivarius* WB21 on halitosis and oral health—an open-label pilot trial	Not a randomized study.
Zahradnik et al. 2009	Preliminary assessment of safety and effectiveness in humans of ProBiora3™, a probiotic mouthwash	Not a randomized study.
Tsubura et al. 2009	The effect of *Bacillus subtilis* mouth rinsing in patients with periodontitis	Not a randomized study.
Krasse et al. 2006	Decreased gum bleeding and reduced gingivitis by the probiotic *Lactobacillus reuteri*	Follow-up for fewer than four weeks (see selection criteria).

Table 2 Demographic and clinical characteristics of the studies included in the review

Study	No.	Men	Women	Age (averages)	Clinical characteristics
Shimauchi et al. 2008[a]	66	57	9	32–61 (44.9)	Systemically healthy individuals, smokers and nonsmokers without severe periodontitis and without caries requiring treatment.
Mayanagi et al. 2009[a]	66	57	9	32–61 (44.9)	Systemically healthy individuals, smokers or nonsmokers without severe periodontitis and without caries requiring treatment.
Vivekananda et al. 2010	30	19	11	34–50 (42)	Systemically healthy individuals with chronic periodontitis.
Twetman et al. 2009	42	26	16	———— (24)	Systemically healthy individuals with moderate gingivitis.
Staab et al. 2009	50	25	25	———— (24.4)	Systemically healthy individualswithout periodontitis, smokers and nonsmokers. Gingivitis induced during the study.

[a] These articles were a separate report of the same randomized clinical trial

so using different measurement methods, different times of follow-up, and/or reporting biases were observed. In consequence, we judged that the results were not comparable.

- *Probing pocket depth* (*PPD*): Two trials evaluated this outcome. Although Shimauchi et al. [10] reported their results using graphs from which it was not possible to extract the exact PPD value, they state that there were no statistically significant differences between the experimental and control groups at 8 weeks after the treatment was applied. However, they did find a statistically significant beneficial effect of probiotics in smokers. Vivekananda et al. [12] reported that there was a statistically significant beneficial effect of probiotics only when combined with scaling and root planing. A reduction of 0.1 mm (SD 0.2) and a gain of 0.04 mm (SD 0.23) in PPD were observed in the experimental and control groups, respectively, at 42 days after the intervention.
- *Clinical attachment level* (*CAL*):Only one trial reported this outcome [12]. The authors did not find statistically significant differences between the groups.
- *Plaque index* (*PI*): This outcome was reported in three trials [10, 12, 14]. Details can be observed in Table 5. Two of the three trials reported statistically significant differences in PI when comparing probiotics against placebo.
- *Gingival inflammation* (*GI*): Two trials measured this outcome using the Loe and Silness method. Shimauchi et al. [10] found no statistically significant differences between the groups at 8 weeks after the intervention. His results are reported only in graphs. In contrast, Vivekananda et al. [12] showed a reduction from baseline of 0.53 (SD 0.12) and 0.14 (SD 0.14) in the GI of the probiotic and placebo group, respectively, at 42 days of follow-up. This difference was statistically significant.
- *Bleeding on probing* (*BOP*): Two trials reported this outcome. Shimauchi et al. [10] measured BOP percentage, using the Ainamo and Bay method and showed no statistically significant differences between the experimental and control groups at 8 weeks after the intervention. Twetman et al. [13] reported the proportion of sites positive to BOP and found statistically significant differences between the groups at the second week, but not at the fourth week after the intervention. The other two authors also measured bleeding; however, they used different methods (see Table 6).
- *Adverse effects*: Two studies investigated possible side effects related to the use of probiotics [10, 13]. None of them reported adverse side effects.

Publication bias Due to the small number of trials included in this review, it was not possible to statistically assess publication bias.

Discussion

The goal of this systematic review was to determine whether the use of probiotics has clinical beneficial effects in the prevention and treatment of periodontal diseases. The evidence available does not allow making a clear statement regarding the effectiveness of probiotics, because for the same outcomes, different trials showed different results. Nevertheless, it seems that for the primary outcome, PPD, there would be no clinical beneficial effect of probiotics. Even though probiotics have shown benefits on PI and GI, these benefits are small, inconsistent across trials, and not clinically relevant, which does not allow making a clear statement regarding the effectiveness of this intervention.

The studies included in this review demonstrated large variability in the type of probiotic used, the probiotic concentration and pharmaceutical form, and the clinical characteristics of the patients in which they were tested. Furthermore, all of the studies were financed by laboratories involved in the production of probiotics, which raises concerns regarding the confidence in the apparent treatment benefits.

Table 3 General characteristics of the studies

Study	Probiotic type and pharmaceutical form	Placebo controlled	Experimental group	Control group	*N*°.	Results	Follow-up time
Shimauchi et al. 2008[a]	Tablet of *Lactobacillus salivarius* WB21 (6.7×10^8 CFU/tab) and Xylitol (280 mg/tab)	Yes	34	32	66	- Probing pocket depth[b] - Bleeding on Probing - Gingival index - Plaque index[c] -Changes in levels of lactobacillus in saliva and supra- and subgingival plaque[c] - Changes in levels of lactoferrin[c] - Side effects	8 weeks (57 days)
Mayanagi et al. 2009[a]	Tablet of *Lactobacillus salivarius* WB21 (6.7×10^8 CFU/tab) and Xylitol (280 mg/tab)	Yes	34	32	66	- Probing pocket depth[b] - Bleeding on probing - Gingival index - Plaque index[c] -Changes in pathogenic periodontal flora (supra- and subgingival) due to smoking habit[c] - Side effects	8 weeks (57 days)
Vivekananda et al. 2010	Tablet of Prodentis with *Lactobacillus reuteri* (1×10^8 CFU DSMI 17938+ 1×10^8 CFU ATCC PTA 5289)	Yes	15	15	30	- Probing pocket depth[d] - Plaque index[c] - Gingival index[c] - Level of insertion - Gingival bleeding index[c] - Variation in quantity of pathogens[c]	42 days
Twetman et al. 2009	Gum with two strains of *Lactobacillus reuteri*: ATCC 55730 and ATCC PTA 5289 (1×10^8 CFU/gum)	Yes	15[e] 14[f]	13	42	- Bleeding on probing[c] - Volume of crevicular fluid -Levels of inflammatory mediators in crevicular fluid[c] - Side effects	4 weeks
Staab et al. 2009	Probiotic milk with *Lactobacillus casei*. (dose of 65 ml)	No	25	25	50	- Papillary bleeding index - Plaque index - Interproximal plaque index - Activity of polymorphonuclear elastase[c], myeloperoxidase (MPO) and quantity of metalloproteinase (MMP-3) matrix in the crevicular fluid[c]	8 weeks

N° sample size

[a] These articles were a separate report of the same randomized clinical trial

[b] Beneficial effect of the probiotic only in the smoker group (statistically significant difference)

[c] Beneficial effect of the probiotic (statistically significant difference)

[d] Beneficial effect of the probiotic only when were combined with scaling and root planing (statistically significant difference)

[e] Experimental group (15 individuals) received one dose probiotic + one dose of placebo per day

[f] Experimental group (14 individuals) received two doses of probiotic per day

It should be noted that one of the trials recruited patients with no signs of periodontitis and evaluated the effects of probiotic drink milk after inducing gingivitis by interrupting mechanical plaque control for 96 h [14]. We acknowledge that this is a clinical scenario unlikely to be real; however, this study fulfilled the selection criteria and answered the clinical question of interest, and thus it was included.

The study published by Vivekanada et al. [12] not only evaluated the effects of probiotic tablets versus placebo, but also included a second intervention, scaling and root planing. The researchers allocated each of the patients to either probiotic or placebo tablets and also randomized mouth quadrants to receive scaling and root planing or no treatment. The authors performed paired and unpaired *t* tests to compare pairs of treatment combinations and found many statistically

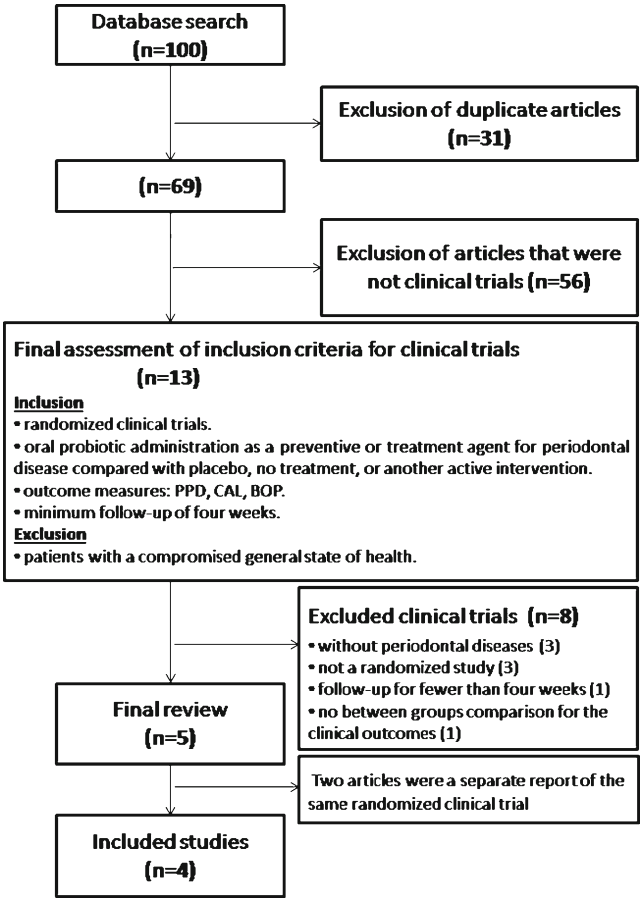

Fig. 1 Flow diagram

significant differences; however, no adjustment of the significance level was made for multiple comparisons.

Four problems arose that made it impossible to perform a meta-analysis of the variables shared by the studies included in this review. First, clinical heterogeneity was high. The populations studied could have had important clinical differences, because they were affected by different periodontal diseases, ranging from severe periodontitis to plaque-induced gingivitis. Second, the types of probiotic studied varied across the trials. Third, and the most important issue, the variables were not reported properly in one of the studies [10]. Information on the outcomes of interest was only found in graphs, which did not allow obtaining the exact value of the final measurement in each group. Based on the small number of included studies with adequate report, imputation methods were not considered appropriate for undertaking a meta-analysis. In addition, a sensitivity analysis could not be properly conducted for testing the robustness of the assumptions made for imputing data. We tried to contact the authors, but we did not receive any responses. Finally, the length of follow-up was different across the trials, preventing from comparisons.

To our knowledge, this is the first systematic review trying to answer this clinical question. However, only four trials and 188 patients are contributing to the results and conclusions of this review, number that is very small when compared to the number of patients suffering periodontal diseases. Also, not all the trials reported on all the outcomes of interest. Moreover, only two trials reported on the primary outcome PPD. This traditional diagnostic method provides a useful overall assessment of the depth of periodontal pockets, which are the principal habitats of periodontal pathogens [15]. PPD is an essential component of periodontal examination because it indicates the presence of an abnormal gingival sulcus associated with periodontal tissue destruction and gives a good assessment of the distribution of periodontally affected teeth [15].

Despite these limitations, we believe that this is the best possible summary of evidence of the topic. However, it highlights the necessity of well-designed non-industry funded randomized controlled trials to answer this clinical question. The outcomes of interest for patients and clinicians and the methods and time points for measuring these outcomes must be standardized. In addition, the reporting of the trials must be enhanced, which can be easily attainable

Table 4 Bias assessment for the studies

Study	Randomization	Concealment of randomization sequence	Blind	Proper reporting of incomplete outcomes	Free of bias for selective outcomes	Free of other sources of bias
Shimauchi et al. 2008. Mayanagi et al. 2009[a]	Yes	Yes	Yes, double blind (does not specify who was blind)	Yes	No	No
Vivekananda et al. 2010	Yes	Yes	Yes, double blind (does not specify who was blind)	Yes	Yes	No
Twetman et al. 2009	Yes	Yes (but inadequate because distinguishable by color)	Yes	No	No	No
Staab et al. 2009	Yes	No	No	Yes	Yes	No

[a] These articles were a separate report of the same randomized clinical trial

Table 5 Plaque Index (PI)

Study	Method	Baseline characteristics probiotics group	Baseline characteristics placebo group	Final characteristics probiotics group	Final characteristics placebo group	Time	*P* value
Vivekananda 2010[a]	Silness and Löe 1964	1.79 (0.36)	1.77 (0.20)	0.41 (0.16)[b]	0.17 (0.14)[b]	42 days	S.D
Shimauchi 2008	Silness and Löe 1964	0.7 (0.1)	0.6 (0.1)	N.P.	N.P.	8 weeks	S.D
Staab 2009	Turesky 1970	0.76 (0.23)	0.68 (0.23)	2.52 (0.61)	2.14 (0.30)	8 weeks	N.S.

Values are given as mean (SD)

NP Not possible to extract numeric values, because the final results were expressed in graphs

Time follow-up time

N.S No statistically significant difference

S.D Statistically significant difference

[a] Vivekananda et al. performed paired *t* tests

[b] The reduction of the outcome is expressed, not the final outcome

following the guidelines of the CONSORT [16]. Finally, we also recommend conducting trials with appropriate sample sizes in order to have enough power to detect differences among the groups. There was only one trial in which a sample size calculation was done.

Conclusions

Based on the results of this review, the effectiveness of probiotics on the prevention and treatment of periodontal diseases is questionable. For the primary outcome, PPD, there would be no clinical beneficial effect of probiotics. For secondary outcomes, probiotics have shown small benefits on PI and GI.

There remains no evidence about whether probiotics are effective or ineffective in the prevention and treatment of periodontal diseases. The results of this systematic review confirm that more studies are necessary to evaluate the efficacy of probiotics with correct methodological design, in broader population samples, and over longer periods of time. Comparative trials of different strains of probiotic species would also be interesting, and these results could be compared with those of other interventions, such as antiseptics and antibiotics. In addition, future studies should utilize appropriate forms of administration for oral pathologies and investigate the frequency of application and concentration of probiotic bacteria necessary for particular modes of administration.

Table 6 Bleeding on probing (BOP) and other bleeding indices

Study	Method	Baseline characteristics probiotics group	Baseline characteristics placebo group	Final characteristics probiotics group	Final characteristics placebo group	Time	*P* value
Shimauchi 2008[a]	Bleeding on probing, BOP. (Ainamo and Bay 1975)	19.2 (2.4)	13.9 (2.5)	N.P.	N.P.	8 weeks	N.S.
Twetman 2009[b]	They reported positive site for BOP/total of sites.	112 /208 112/208	68/96 68/96	16/208 38/208	45/96 64/96	2 weeks 4 weeks	S.D.N.S.
Vivekananda[c] 2010[a]	Gingival bleeding index, GBI.(Ainamo 1975)	81.6 (18.4)	87.9 (13.5)	48.3 (14.4)*	12.0 (8.7)*	42 days	S.D.
Staab 2009[a]	Papilla bleeding index, PBI. (Saxer and Mühlemann 1975)	0.67 (0.30)	0.80 (0.27)	1.17 (0.57)	1.12 (0.36)	8 weeks	N.S.

NP Not possible to extract numeric values, because the final results were expressed in graphs

Time Follow-up time

N.S No statistically significant difference

S.D Statistically significant difference

[a] Values are given as mean (SD)

[b] Values are given as: positive site for BOP/total of sites

[c] Vivekananda et al. performed paired *t* tests

Conflicts of interest and source of funding statement None of the authors of this review declares a conflict of interest or obtained any kind of financing or support from any company related to the production of probiotics. This investigation did not receive any private financial support.

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