Probiotics in the treatment of periodontal disease: A systematic review
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Abstract:
Over the years, probiotics have been used in the treatment of a variety of diseases. The use of probiotics in the treatment of periodontal disease has caught on over the last decade or so. This review was performed to determine whether administration of probiotics produced a lasting clinical benefit in the treatment of periodontal disease. A MEDLINE, Cochrane database and a hand search was performed on human randomized placebo controlled trials using probiotics in the treatment of periodontal disease. A total of thirteen papers which addressed the question of the use of probiotics in the treatment of periodontal disease were retrieved. Most of the studies reviewed showed only a short term benefit with regards to reduction in gingival inflammation and probing depth reduction. Lasting clinical benefits were not seen in any of the studies. At least four different combinations and strains of probiotics have been used in the studies. There also existed significant heterogeneity in the methodology of the studies reviewed. It was concluded that current regimens of probiotics in the treatment of periodontal disease produce only short-term clinical and microbiologic benefits.

Key words: Gingivitis, periodontitis, probiotics

INTRODUCTION

Periodontal disease is a biofilm associated polymicrobial disease that involves a complex interplay between the pathogenic bacteria and the host. The biofilm nature of the disease limits any long-term success in the treatment of this disease, as sooner or later, the biofilm is re-established.

Over the years, a number of treatments have been used as adjuncts to scaling and root planing to maximize benefits of periodontal therapy. These adjunctive treatments include the use of antibiotics and antiseptics, which have been used with a reasonable degree of success.

Probiotics have been used for a number of years in the field of general medicine for the treatment of inflammatory bowel disease, prevention of allergies, management of vaginal infections and for the prevention of respiratory tract infections.

In the treatment of dental disease, probiotics have been used for the last decade or so. Besides periodontal disease, they have also been used management of dental caries and halitosis.

Early attempts at the use of bacteria to manipulate the oral microflora were by Hillman and Shivers, who found that Streptococcus sanguis could inhibit the growth of Actinobacillus actinomycescomitans in gnotobiotic rats. In the following years, a number of animal studies were conducted using Lactobacillus spp. and Bifidobacterium spp. These studies found a reduction in periodontal disease following administration of these probiotic bacteria.

A few Russian studies pioneered in the use of probiotics for the treatment of periodontal disease in humans. Subsequently, over the last decade, numerous papers have been published trying to address the use of probiotics in the treatment of periodontitis.

In spite of the sheer volume of studies published, a few doubts still linger as to the effectiveness of the use of probiotics in the treatment of periodontal disease. A number of methodological issues have also been pointed out in these studies. The This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.
current paper attempts to review the available evidence on the effect of probiotics in the treatment of human periodontal disease.

**MATERIALS AND METHODS**

**Focused question**

Does probiotic administration produce clinical benefits in the treatment of periodontal disease?

**Search process**

A MEDLINE (PubMed) search was performed with the focused question. The search was restricted up to January 2016. Only studies evaluating the use of probiotics in the treatment of periodontal disease in humans were included in this review. Similar searches were also performed on the Cochrane database. In addition a hand search was also performed for the cross-references of the selected articles as well as other review articles. The keywords used in the searches on all databases and hand searches were “probiotics gingivitis” and “probiotics periodontitis.” Only placebo controlled trials which mentioned the probiotic strain used and available in full text in the English language were included. The guidelines given by CONSORT 2010 were applied to all the studies. The CONSORT 2010 guidelines form a 25 point checklist which addresses questions relating to the quality of reporting [Table 1]. A quality assessment of all the trials was done using the CONSORT guidelines and the studies were classified as excellent (≥20 items), good (13–19 items) and poor (≤12 items).

**RESULTS**

Out of the 25 studies retrieved from the MEDLINE and Cochrane databases and by way of hand search, 14 studies met the inclusion and exclusion criteria. Studies not published in the English language were excluded from this analysis.[14,15] Studies not mentioning the strain of bacteria used were excluded from the analysis.[12-35] Two studies were excluded as they did not allow a sufficient follow-up time.[16,20] Three other studies were excluded as they were not placebo controlled.[18-40] One other study was excluded as the methodology involved administration of probiotics to pregnant mothers before delivery, followed by administration of probiotics to the infant for the first 9 years of its life. This methodology was deemed too complex, and the criteria were not similar to the rest of the studies selected.[41]

The study by Mayanagi et al. assessed only microbiologic parameters without assessing clinical changes of the gingiva, so this study too was excluded from the analysis.[42] However this study was part of another study by Shimauchi et al.,[17] which was selected for the review. Of the 14 studies selected, it was found that five of these published studies assessed the use of probiotics in the treatment of gingivitis.[12-22] The remaining nine studies selected were on the use of probiotics in the treatment of periodontitis.[17,23-30]

In spite of exclusion of a number of studies from this review, there existed significant heterogeneity. As a result a meta-analysis of the data could not be performed. A thorough analysis of the remaining studies was performed. The details of this analysis are shown in Table 2.

Upon evaluation it was found that four different strains of probiotic bacteria have been used in the treatment of periodontal disease. These included *Lactobacillus salivarius*,[17,42] a combination of *Lactobacillus rhamnosus* and *Bacillus subtilis*,[22] *Lactobacillus brevis*,[18-20,23-27,29] and *Lactobacillus reuteri*.[18-20,23-27,29] One of the studies examined the effects of a combination of *Streptococcus oralis*, *Streptococcus uberis* and *Streptococcus rattus*.[38]

Of the 14 studies reviewed for the CONSORT guidelines, two of them fulfilled all the criteria.[34,36]

One of the parameters that were poorly addressed in the CONSORT checklist was registration of the trial in the trial registry. Only one of the studies were registered in the trial registry.[24] Some of the trials did not mention the dates of recruitment of patients and follow-up,[18-21,25] while others did not mention how randomization and blinding/concealment were done.[17,19,23-25,28,29] The results of the application of CONSORT guidelines are given in Table 1.

The earliest study using probiotics in the treatment of periodontal disease was by Shimauchi et al. who used *L. salivarius* probiotic strain in the form of a tablet. They found no significant differences in the levels of gingival inflammation, plaque index and probing pocket depth between the probiotic and the control groups.[17]

The only study which used a combination of *L. rhamnosus* and *B. subtilis* used this mixture in the form of a lozenge given 4 times daily. They found that the plaque and gingival indices were reduced without having a major effect on the composition of the subgingival microflora.[22]

Two studies evaluated the effect of *L. brevis* in the treatment of periodontal disease. Shah et al. evaluated the use of *L. brevis* in the treatment of aggressive periodontitis and found that the patients who were given the probiotic lozenge showed improved clinical and microbiologic parameters for up to 60 days.[28] A more recent study by Lee et al. used *L. brevis* lozenges and found a significantly delayed onset of the gingival inflammation in the patients taking probiotics.[31]

Most studies evaluating the use of probiotics in the treatment of periodontal disease have used *L. reuteri*. Twetman et al. performed the earliest documented study with this strain and found significantly reduced gingival bleeding scores and gingival crevicular fluid (GCF) volumes at 4 weeks in the probiotic group.[18]

A later study by Iniesta et al. used the same probiotic strain administered once daily over a period of 4 weeks. The patients were then followed up for an additional 4 weeks. At the end of the 8 weeks follow-up, no significant clinical differences were seen between the test and control groups. However, the test site showed a significant reduction in periodontopathogens.[20]

Vivekananda et al. used *L. reuteri* lozenges chewed twice daily over a period of 42 days and found significant reductions...
Table 1: CONSORT checklist

| Item number | Item                                                                 | Number of studies fulfilling the criteria |
|-------------|----------------------------------------------------------------------|-----------------------------------------|
| 1           | How participants were allocated to interventions (e.g., “random allocation,” “randomised,” or “randomly assigned”) | 14                                      |
| 2           | Scientific background and explanation of rationale                   | 14                                      |
| 3           | Eligibility criteria for participants and the settings and locations where the data were collected | 14                                      |
| 4           | Precise details of the interventions intended for each group and how and when they were actually administered | 14                                      |
| 5           | Specific objectives and hypotheses                                    | 14                                      |
| 6           | Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors) | 14                                      |
| 7           | How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules | 8                                       |
| 8           | Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification) | 10                                      |
| 9           | Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned | 11                                      |
| 10          | Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups? | 11                                      |
| 11          | Whether or not participants, those administering the interventions, and those assessing the outcomes were aware of group assignment. If not, how the success of masking was assessed | 11                                      |
| 12          | Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses | 14                                      |
| 13          | Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons | 14                                      |
| 14          | Dates defining the periods of recruitment and follow-up               | 9                                       |
| 15          | Baseline demographic and clinical characteristics of each group       | 14                                      |
| 16          | Number of participants (denominator) in each group included in each analysis and whether the analysis was by “intention to treat.” State the results in absolute numbers when feasible (e.g., 10/20, not 50%) | 14                                      |
| 17          | For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% CI) | 14                                      |
| 18          | Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory | 14                                      |
| 19          | All important adverse events or side effects in each intervention group | 14                                      |
| 20          | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | 11                                      |
| 21          | Generalisability (external validity, applicability) of the trial findings | 14                                      |
| 22          | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | 14                                      |
| 23          | Registration number and name of trial registry                        | 2                                       |
| 24          | Where the full trial protocol can be accessed, if available           | 2                                       |
| 25          | Sources of funding and other support (such as supply of drugs), role of funders | 11                                      |

CI – Confidence interval

in plaque and gingival inflammation. It was also seen that pocket depth, attachment levels and periodontopathogens were significantly reduced.[26] A later study by Teughels et al. using the same regimen over a 3-month period found similarly improved results in the clinical and microbiologic parameters in the group of patients who were administered the probiotic.[27] However, later studies by other authors found no significant differences in clinical parameters between the probiotic and the control groups.[20,25] Nevertheless, one of these studies found significant improvements in biochemical parameters of GCF in probiotic group.[23] A key point that needs to be noted is that the patients in these studies were only followed up for 2–3 weeks while those in the earlier studies were followed up for longer intervals.
Table 2: List of studies using probiotics in the treatment of periodontal disease

| Study                  | Type of infection       | Type of intervention before start of treatment (day 0) | Probiotic strain and concentration | Groups                                | Frequency and duration | Follow-up | Results                                                                 |
|------------------------|-------------------------|-------------------------------------------------------|-----------------------------------|--------------------------------------|------------------------|-----------|-------------------------------------------------------------------------|
| Shimauchi et al.       | Healthy volunteers without severe periodontitis | Brushing and oral hygiene instructions                | L. salivarius WB21 (2×10⁹) chewing tablet | Probiotic group and xylitol group    | 3/day for 56 days     | 56 days   | No significant differences in PI, GI, BOP, PPD and salivary lactoferrin between groups PI, GI lower in probiotic group No changes in levels of bacteria Significantly lower PI, GI, PPD, CAL and periodontopathogens in the group receiving doxycycline + probiotic and probiotic alone groups |
| Toiviainen et al.      | Healthy volunteers      | Brushing and oral hygiene instructions                | L. rhamnosus and B. subtilis lozenge | Probiotic and placebo groups         | 4/day for 28 days     | 30 days   | No significant differences in PI, GI, BOP, PPD and salivary lactoferrin between groups PI, GI lower in probiotic group No changes in levels of bacteria Significantly lower PI, GI, PPD, CAL and periodontopathogens in the group receiving doxycycline + probiotic and probiotic alone groups |
| Shah et al.            | Aggressive periodontitis | SRP on day 0                                          | L. brevis CD2 1×10⁸ Lozenge        | Probiotic + doxycycline (A) Probiotic alone (B) Doxycycline alone (C) | 2/day for 2 weeks     | 60 days   | No significant differences in PI, GI, BOP, PPD and salivary lactoferrin between groups PI, GI lower in probiotic group No changes in levels of bacteria Significantly lower PI, GI, PPD, CAL and periodontopathogens in the group receiving doxycycline + probiotic and probiotic alone groups |
| Lee et al.             | Experimental gingivitis | SRP and administration of probiotic                   | L. brevis CD2 1×10⁸ Lozenge        | Probiotic and placebo groups         | 3/day for 14 days     | 14 days   | No significant differences in PI, GI, BOP, PPD and salivary lactoferrin between groups PI, GI lower in probiotic group No changes in levels of bacteria Significantly lower PI, GI, PPD, CAL and periodontopathogens in the group receiving doxycycline + probiotic and probiotic alone groups |
| Twetman et al.         | Gingivitis              | Brushing and oral hygiene instructions                | L. reuteri ATCC 55730 ATCCPTA 5289 (2×108) (Prodentis) Chewing gum | Placebo + probiotic (A) Probiotic + probiotic (B) Probiotic + only placebo group (C) Probiotic and placebo groups | 2/day for 30 days     | 30 days   | No significant differences in PI, GI, BOP, PPD and salivary lactoferrin between groups PI, GI lower in probiotic group No changes in levels of bacteria Significantly lower PI, GI, PPD, CAL and periodontopathogens in the group receiving doxycycline + probiotic and probiotic alone groups |
| Iniesta et al.         | Gingivitis              | Tooth polishing                                       | L. reuteri ATCC 55730 ATCCPTA 5289 (2×10⁸) (Prodentis) Chewing gum | Probiotic and placebo groups         | 1/day for 56 days     | 56 days   | No significant differences in PI, GI, BOP, PPD and salivary lactoferrin between groups PI, GI lower in probiotic group No changes in levels of bacteria Significantly lower PI, GI, PPD, CAL and periodontopathogens in the group receiving doxycycline + probiotic and probiotic alone groups |
| Vivekananda et al.     | Chronic periodontitis   | Split mouth SRP One quadrant received SRP and probiotic while the other received probiotic alone or placebo alone FMD and placebo or FMD and probiotic | L. reuteri ATCC 55730 ATCCPTA 5289 (2×10⁹) (Prodentis) Lozenge | Probiotic and placebo groups         | 2/day for 42 days     | 42 days   | No significant differences in PI, GI, BOP, PPD and salivary lactoferrin between groups PI, GI lower in probiotic group No changes in levels of bacteria Significantly lower PI, GI, BOP, PPD, CAL and periodontopathogens in the group receiving doxycycline + probiotic and probiotic alone groups |
| Teughels et al.        | Chronic periodontitis   | SRP on day 0                                          | L. reuteri ATCC 55730 ATCCPTA 5289 (2×10⁸) (Prodentis) Lozenge | Probiotic and placebo groups         | 2/day for 90 days     | 90 days   | No significant differences in PI, GI, BOP, PPD, CAL and periodontopathogens in the group receiving doxycycline + probiotic and probiotic alone groups |
| Szkaradkiewicz et al.  | Chronic periodontitis   | SRP on day 0                                          | L. reuteri ATCC 55730 ATCCPTA 5289 (2×10⁸) (Prodentis) Lozenge | Probiotic and placebo groups         | 2/day for 14 days     | 14 days   | No significant differences in PI, GI, BOP, PPD and salivary lactoferrin between groups PI, GI lower in probiotic group No changes in levels of bacteria Significantly lower PI, GI, BOP, PPD, CAL and periodontopathogens in the group receiving doxycycline + probiotic and probiotic alone groups |

Contd...
Vicario et al. utilized a 30 days regimen of probiotics given once daily and found significant improvements in periodontal status.\textsuperscript{[21]}

Ince et al.\textsuperscript{[23]} and Tekce et al.\textsuperscript{[24]} used the same above mentioned regimen of \textit{L. reuteri} given for 3 weeks in the treatment of chronic periodontitis. The patients were then followed up for 1 year. Clinical, microbiologic and GCF biochemical parameter evaluated at various points of time found a significant improvement in the test group.

Two studies assessed the effect of probiotic lozenges in the treatment of experimental gingivitis. The study by Hallström et al. found no significant differences in the gingival inflammation.\textsuperscript{[19]} This study used \textit{L. reuteri} in a lozenge form as the probiotic. The other study by Lee et al. used \textit{L. brevis} lozenges and found a significantly delayed onset of the gingival inflammation in the test group.\textsuperscript{[21]}

A most recent study assessed the use of a combination of \textit{S. oralis}, \textit{S. uberis} and \textit{S. rattus} in the treatment of periodontitis. The combination was given in the form of a probiotic tablet to be chewed twice daily for 3 months. At the end of 3 months no significant clinical differences were seen between the test and the control group. The only significant differences seen were in the levels of periodontopathogens in the test group which was significantly reduced.

**DISCUSSION**

This systematic review attempted to address the question as to whether probiotics can produce significant clinical benefits in the treatment of periodontal disease.

None of the studies showed a poor quality of reporting. Ten of the reviewed studies showed a good quality of reporting, while three showed an excellent quality of reporting.

A similar assessment of quality of reporting has been used in earlier reviews.\textsuperscript{[6]}

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**Table 2: Contd...**

| Study               | Type of infection | Type of intervention before start of treatment (day 0) | Probiotic strain and concentration | Groups                          | Frequency and duration | Follow-up | Results                                                                                                                                 |
|---------------------|-------------------|-------------------------------------------------------|-----------------------------------|--------------------------------|------------------------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Hallström et al.    | Experimental gingivitis | SRP and administration of probiotic | \textit{L. reuteri} ATCC 55730 ATCCPTA 5289 (2×10⁸) (Prodentis) Lozenge \textit{L. reuteri} ATCC 55730 ATCCPTA 5289 (2×10⁸) (Prodentis) Lozenge | Probiotic and placebo groups | 2/day for 21 days | 21 days | No significant differences in PI, GI, BOP and GCF biomarkers |
| Vicario et al.      | Chronic periodontitis | No treatment provided on day 0 | \textit{L. reuteri} ATCC 55730 ATCCPTA 5289 (2×10⁸) (Prodentis) Lozenge | Probiotic and placebo groups | 1/day for 30 days | 30 days | Significantly lower scores of PI, BOP and PPD in probiotic group |
| Ince et al.         | Chronic periodontitis | SRP on day 0 | \textit{L. reuteri} ATCC 55730 ATCCPTA 5289 (2×10⁸) (Prodentis) Lozenge | Probiotic and placebo groups | 2/day for 3 weeks | 360 days | Significantly lower PI, GI, BOP, PPD, CAL and GCF biomarkers in the probiotic group |
| Tecke et al.        | Chronic periodontitis | SRP on day 0 | \textit{L. reuteri} ATCC 55730 ATCCPTA 5289 (2×10⁸) (Prodentis) Lozenge | Probiotic and placebo groups | 2/day for 3 weeks | 360 days | Significantly lower PI, GI, BOP, PPD, CAL and periodontopathogens in the probiotic group |
| Laleman et al.      | Chronic periodontitis | FMD on day 0 | \textit{S. oralis} KJ3, \textit{S. uberis} KJ2, \textit{S. rattus} JH145 Chewable tablet | Probiotic and placebo groups | 2/day for 3 months | 3 months | No significant differences in PI, GI, BOP and PPD between groups. Significantly lower levels of \textit{P. intermedia} in saliva of test group |

\text{PI – Plaque index; GI – Gingival index; BOP – Bleeding on probing; PPD – Probing pocket depth; CAL – Clinical attachment level; FMD – Full-mouth disinfection; GCF – Gingival crevicular fluid; L. reuteri – \textit{Lactobacillus reuteri}; L. salivarius – \textit{Lactobacillus salivarius}; L. rhamnosus – \textit{Lactobacillus rhamnosus}; B. subtilis – \textit{Bacillus subtilis}; L. brevis – \textit{Lactobacillus brevis}; S. oralis – \textit{Streptococcus oralis}; S. uberis – \textit{Streptococcus uberis}; S. rattus – \textit{Streptococcus rattus}; P. intermedia – \textit{Prevotella intermedia}; SRP – Scaling and root planing}
Application of the CONSORT guidelines revealed that most studies were not registered. Only one of the thirteen studies reviewed were registered.[46] There is significant evidence that has found that prior registration of trials reduces the risk of publication bias.[18,14]

While some of the early studies did not mention how the sample size was calculated[17,19,20,22,25,29] the later studies, however, addressed this problem and showed sample size calculation.[21,23,24,26,28] It has been shown that not mentioning how the sample size was calculated may lead to studies with a small sample size that is not representative of the problem in hand.[45]

Many studies also failed to address how the randomization, allocation, concealment and blinding were performed during the course of the study.[17,19,21,25,29] Not mentioning these items on the checklist may lead to an increased risk of selective reporting.[16,47] Many of the newer studies addressed most of the items on the CONSORT checklist.

Of the four strains of probiotic used, one study using L. salivarius found no significant difference in the periodontal parameters at the end of the study (2 months)[27] while another which used a combination of L. rhamnosus and B. subtilis showed significant improvements at 1 month.[22] Two studies used L. brevis in the treatment of periodontal disease, while one of the studies showed improved periodontal parameters in the test group at 2 months,[25] the other found no differences between the test and the placebo groups at 2 weeks.[25]

The maximum number of studies has been conducted using L. reuteri.[18,20,23-27,29] Among the nine studies which have been conducted with this strain, three of the studies showed no significant difference in periodontal parameters between the test and the control group.[10-20] The other six studies showed a statistically significant variation in the periodontal parameters in the patients who received probiotics.[23-27,29]

A most recent study by Lallem et al. used a combination of S. oralis, S. uberis and S. rattus in the treatment of periodontitis and found no significant differences between the groups.[30]

As one can see, the results from the published studies are significantly heterogeneous making it difficult to draw conclusions. One of the observations made during the course of this review was that while some studies performed a scaling and/or polishing at the start of the study (day 0), others did not. A similar observation was made in an earlier review which led the authors to quote that pretreatment tends to reduce the levels of oral indigenous microbiota and thereby create more sites for colonization by probiotic bacteria.[46] It is only logical to assume this may have also been one of the reasons variability in results between these studies.

There was significant heterogeneity in the studies and this may have been the reason for the mixed results. This heterogeneity was due to a number of factors. These included:

- Different strains of bacteria being used
- Lack of consensus on whether pretreatment in the form of scaling and/or polishing was provided on day 0.

Furthermore, six of the eight studies which showed positive results in the probiotic group were funded in part or in full by the pharmaceutical industry.[17,20,23,24,27] Although the methodologies of these studies were clear and some of the studies clearly stated that the company was not involved in data management,[18,24] it has been found that pharmaceutical industry funding of clinical trials is strongly associated with pro-industry results.[40]

Registration of trials only partly reduces publication bias. A statistical assessment of publication bias was not possible due to the heterogeneity of the studies.[49] This was one of the limitations of this review. Another limitation of this review was that only publications in the English language were considered. Similar limitations were found in earlier reviews as well.[31,49,50]

Research with probiotics in the treatment of periodontal disease is still in its infancy. Some pertinent questions still need to be answered.

**How many times daily should probiotics be administered?**

From the studies reviewed in this paper, there was little consensus amongst the authors as to how many times a day probiotics need to be administered. The frequency of administration varied from once daily to 4 times daily.

**Which strain of bacteria is the most beneficial?**

As can be seen from this review, at least four different strains of probiotics have been used for the treatment of periodontal disease. The studies using the strains using L. salivarius and a combination of L. rhamnosus and B. subtilis were too few in number. Only one study examines the use of streptococci in humans. Thus it is difficult to conclude whether these strains are effective.

Most studies have been conducted with probiotic strains using L. reuteri. Two other studies used L. brevis probiotic strain of bacteria. From the results of this review it is not known which of the aforementioned strains of probiotic is most effective, though L. reuteri and L. brevis have shown the most promising results.

**Which mode of application is the most effective?**

Probiotics from the different studies have been used in the form of chewable tablets, lozenges and chewing gum. As the duration of exposure of each of these vehicles can differ, it is not known which vehicle is the most effective means of delivering probiotics in the oral cavity.

**Does a booster dose of probiotics need to be administered every now and then?**

Long-term results from current data[23,24] indicate that most of the effects of probiotic administration cannot be maintained for >6 months. This could mean that probiotics need to be administered often to prevent disease recurrence.

**Can probiotics move beyond microbiological and inflammatory benefits into clinical tangible benefits?**

Most studies included in this review show a definite benefit in GCF biochemical parameters and microbiological parameters.
Can positive results be obtained in an everyday scenario and in studies without industry sponsorship?

As seen from this review, many studies showing positive results using probiotics were funded in some way by the pharmaceutical industry. A pertinent question that needs to be answered is whether similar results can be produced in an everyday scenario without industry sponsorship. A recent study also observed that most studies (current or past) tried to examine product specific effects rather than species-specific effects (L. reuteri or L. salivarius or streptococcus containing probiotics).\(^{[30]}\)

How safe are probiotics?

There is also considerable controversy regarding the safety of probiotics when used long-term. Though there are studies confirming the safety of probiotics when used long-term,\(^{[49,51]}\) at least one strain of probiotic (L. rhamnosus) has shown an increased risk of bacteremia and endocarditis in animal studies and in human case reports.\(^{[32-34]}\) As observed in an earlier review,\(^{[49]}\) probiotics are currently regulated as dietary supplements and not subjected to the same rigorous standards as drugs.

CONCLUSIONS

With the available evidence, it is, as yet, difficult to conclude whether probiotics offer any clinical benefit in the treatment of periodontal disease. Most studies show a limited and temporary improvement in periodontal parameters when probiotics are given. Well-designed clinical studies with larger sample sizes and long-term follow-ups are required. The possibility of administering a booster dose for better long-term results may also be considered. Future studies will also have to adhere to a uniform methodology to avoid heterogeneity.

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Conflicts of interest

There are no conflicts of interest.

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