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Probiotics in periodontal therapy: An enigmatic review

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Abstract
Background: Periodontitis is a microbially associated, host mediated inflammation. To improve the results of the classic periodontal treatment, probiotics have been suggested to decrease the number of bacteria and the expression of mediators of inflammation. Probiotics are microorganisms, mainly bacteria, which benefit the host's health.
Aim: The purpose of this review is to explore the literature to assess the effectiveness of different probiotic strains in the treatment of periodontal disease. In this study, we reviewed the literature on the efficacy of probiotics in the treatment of periodontitis.
Methodology: The electronic databases of PubMed, MeSH, Google Scholar, Web of Science and Scopus were searched. The inclusion criteria were: randomized clinical trials (RCTs) that assess the action of any probiotic strain in the treatment of periodontal disease, RCTs that assess the action of any probiotic strain on counting colony forming units (CFU) of periodontal pathogens, Reviews, Systematic reviews and meta-analysis.
Results: A total of 6 *In vitro* and 10 Clinical studies were reviewed after applying inclusion and exclusion criteria. The results shows that there was an improvement in the clinical as well as microbiological parameters.
Conclusion: Probiotics examined using *in vitro* and *in vivo*/preclinical models show promise for applications in a periodontal disease setting. Still further investigations has to be done for the evaluation of long term effects after the periodontal therapy.

Keywords: Probiotics, periodontitis, randomized control trials, colony forming unit

Introduction
The most prevalent chronic inflammatory disease of the oral cavity is periodontitis, which is caused and promoted by pathogenic plaque biofilms. It is one of the main reasons of tooth loss and are differentiated by the rapid degradation of periodontal attachment. There are about 800 different kinds of bacteria in the oral cavity, and periodontal disease is thought to be caused by the complex relationship between bacterial infection and host response, which can be influenced by behavioral factors like smoking [1, 2, 3].
Periodontitis risk factors include smoking, quantitative or functional decreases of polymorphonuclear leukocytes, immunosuppressive medicines or disorders linked with immunosuppression, diabetes, and genetic variants of genes related to cytokine production [4].
The main goal of the periodontal therapy is to eliminate the progression of the disease, which consists of removal of the bacterial etiological factor. The gold standard non-surgical therapy includes scaling and root planing (SRP) which is aimed to remove the dental plaque and calculus and to smooth the root surfaces infected by bacteria. The other supportive treatments includes antibiotics, local drug delivery, host modulation therapy, lasers, and other novel methods [5, 6].
But these treatments are not suffient to control disease even though they results in transient reduction of the inflammation and microbial load. Therefore, other supplemental tactics should be investigated. One among the other novel approaches being considered for the management of periodontitis include the administration of beneficial bacteria (probiotics) which has antimicrobial and anti-inflammatory properties [7, 8].

The first scientist to put forward the concept of beneficial bacteria was Ukrainian born Nobel laureate bacteriologist Ilya Ilyich Mechnikov, known as "the father of modern immunology. He proposed the hypothesis that lactic acid bacteria in yogurt may counteract harmful effects of gut pathogens by studying the general health of Bulgarian people living in the Rhodopes Mountains and mostly fed dairy products [9, 10]. Later in 1965 Lilly and Stillwell introduced the term "probiotics," meaning "for life". And the World Health Organization put forward the current definition for probiotics, as live microorganisms, most often bacteria (sometimes fungi), when consumed, confer beneficial effects to host [11, 12]. The bacterial strains that are considered as probiotics are often isolated from the human microbiota and are properly defined in terms of strain identity, composition, stability, and established health benefits. Lactobacillus, Bifidobacterium, Escherichia, Enterococcus and Bacillus genera which present in human skin, gastrointestinal tract, respiratory tract are most commonly used species of probiotics [13]. [Table: 1]

Table 1: Shows different probiotic bacterias.

Micro organism	Species
Lactobacillus	*L. acidophilus, L. casei, L. crispatus, L. fermentum, L. gasseria, L. johnsoniia, L. lactis, L. paracasei, L. plantarum, L. reuteri, L. rhamnosus, L. salivarius.*
Bifidobacterium	*B. adolescentis, B. animalisa, B. bifidum, B. breve, B. infantis, B. lactis, B. longuma B. thermophilus*
Streptococcus	*S. lactis, S. cremoris, S. salivarius, S. intermedius*
Others	*Enterococcus faecalis, E. faecum, Bacillus, Escherichia coli.*

The mechanism of action for the Probiotics are as follows [4, 8, 15].

1. Preventing the growth or adherence of pathogenic bacteria.
2. Probiotics are involved in the production of antimicrobial substances which inhibit the growth of periodontal pathogens.
3. Probiotics can modulate the host's innate and adaptive immune response by reducing the production of pro-inflammatory cytokines

Probiotics can be easily available in the form of lozenges, tablets, cheese, yogurt, rinses, capsules and liquid. The dairy based probiotic products includes fermented milk, cheese, ice cream, yogurts, buttermilk and milk powder [14, 16]. Non dairy food products includes soy based products, nutrition bars, cereals. Probiotic strains provides health benefits to the consumers which are confirmed in a range of randomized clinical trials [17, 18, 19].

Over the years, the scientific interest to discover, asses and analyse species with probiotic properties has intensively grown. This article aims to assess the effectiveness of different probiotic strains in the treatment of periodontal disease.

Materials and Methods

We evaluated several *in vitro* and clinical research on the use of probiotics in the treatment of periodontal disease. The databases of PubMed, Web of Science, Science Direct, Scopus, clinicaltrials.gov, and Google Scholar were used to conduct an electronic literature search. Individual medical subject heading (MeSH) terms such as probiotics, periodontitis, gingivitis, and periodontal diseases were used in the search.

Inclusion criteria

- Randomized clinical trials (RCTs) that assess the action of any probiotic strain in the treatment.
- Reviews, *In vitro* studies, Systematic reviews and Meta analysis were also included.
- Findings published in English.

Exclusion criteria

- Studies conducted in animals
- Patients with a healthy periodontium
- Experimental periodontitis.

Results

Data selection and Interpretation

Clinical studies

10 clinical studies investigating the use of probiotics in the management of periodontal disease were discussed in this study.

A total of 40 patients were selected and randomly divided into two groups. Group I received scaling and root planing (SRP) plus *L. reuteri*-containing lozenges, and Group II received SRP plus placebo. The plaque index (PI), Gingival index (GI), Bleeding on probing (BoP), Probing depth (PD) and relative attachment level were measured. Microbiological sampling was performed at baseline and on days 21, 90, 180 and 360 and were analysed by culturing. After treatment, the measured PI, GI, BoP and PD were significantly (p<0.05) lower in Group I compared with Group II at all time points. Similar observations were made for total viable cell counts and proportions of obligate anaerobes with exception of day 360. In Group I, significantly fewer patients required surgery on ≥3 sites [20].

In a randomized clinical trial, 41 chronic periodontitis patients were recruited and monitored clinically, immunologically, and microbiologically at baseline (before SRP) and 30 and 90 days after SRP. All patients were randomly assigned to a Test (SRP + Probiotic, n = 20) or Control (SRP + Placebo, n = 21) group. The probiotic lozenges of Bifidobacterium species were used twice a day for 30 days. The results showed test group presented a decrease in probing pocket depth and a clinical attachment gain higher than Control group at 90 days. The Test group demonstrated fewer periodontal pathogens of red and orange complexes, as well as lower proinflammatory cytokine levels when compared to the Control group [21].

In another clinical study thirty chronic periodontitis patients were examined and divided into 2 groups. Test group received scaling and root planing (SRP) and probiotic containing lozenges and Control group received SRP and placebo lozenges. Clinical parameters were assessed and Gingival crevicular fluid (GCF) sample was collected for the analysis of matrix metalloproteinases-8 (MMP-8) and tissue inhibitor of metalloproteinases-1 (TIMP-1) with ELISA. All evaluations were performed at baseline and on days, 21, 90, 180 and 360. Values of attachment gain were higher in test group compared with control group. The baseline clinical and biochemical parameters for these patients were similar for both groups (p>0.05). After treatment, PI, GI and BoP were significantly lower in test group when compared with control

group at all time points. Also treatments led to a significant decrease in the GCF volumes (µl) and MMP-8 concentrations (ng/ml) and a significant increase in TIMP-1 concentrations (ng/ml) [22].

In another study thirty chronic periodontitis patients were recruited and monitored clinically and microbiologically at baseline, 3, 6, 9 and 12 weeks after therapy. All patients received one-stage full-mouth disinfection and randomly assigned over a test (SRP + probiotic, n = 15) or control (SRP + placebo, n = 15) group. The probiotic lozenges consisted of *L. reuteri* were used two times a day for 12 weeks. At 12th week, clinical parameters were significantly reduced in both groups, and attachment gain (p<0.05) is seen in test group than control group and also more *Porphyromonas gingivalis* reduction was in probiotic group [23].

A total of 60 patients were randomly selected and divided into 3 groups. Group A received SRP + chlorhexidine-based toothpaste) (control), Group B (SRP + probiotics-based toothpaste) and Group C (SRP + probiotics-based toothpaste + probiotics-based chewing-gum). At baseline and after 3 and 6 months, periodontal clinical parameters along with microbiological analysis of Red Complex and Orange Complex bacterias were recorded. No significant differences in the clinical parameters were found in group A after 3 and 6 months. But some significant differences were found in Group B and C for other clinical indexes tested after 3 and 6 months. In microbiological analysis no significant differences were detected compared to baseline values for any group, except in Group B and C at 6 months only for the percentage of the orange complex pathogens [24].

In another randomized clinical study a total of 25 chronic periodontitis patients, aged 25 to 58 years, categorized into two groups: the first group SRP while the second group SRP and probiotic lozenges containing five bifid bacteria including Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum, *Lactobacillus rhamnosus*, and Lactobacillus salivarius, twice a day for 30 days. Clinical parameters were assessed and GCF sample collected at baseline and 30 days after periodontal management. There was a significant improvement in periodontal parameters after SRP treatment with and without probiotic lozenges in both groups. There was a decrease in GCF/ MMP-8 levels after 30 days in patients managed by SRP only (p = 0.017) compared with the baseline in both groups, whereas a highly significant decrease in patients treated by SRP and probiotics (p = 0.001) [25].

In a single-blinded, randomized, controlled clinical pilot study, 48 patients with (stages II and III, grade B) periodontitis randomly assigned into 3 groups. Group subgingival debridement (SD) alone, Group 2 with SD with light-activated disinfection (LAD), and Group 3 SD with LAD plus probiotic lozenges with a daily dose of 62.5 mg *L. brevis* and 62.5 mg *L. plantarum* per day for 3 months. Clinical parameters were evaluated and Subgingival plaque samples were collected at baseline, 3 months, and 6 months following treatment. group 3 demonstrated greater reductions in BOP, GIs, and red complex bacteria *P. gingivalis* and *T. forsythia* compared with other groups at 6 months (p<0.05) [26].

Another study was conducted on 38 adults, 31-46 years with moderate chronic periodontitis patients divided into 2 groups. Group 1 with SRP with probiotic tablets containing *L. reuteri* strain and Group 2 SRP. Gingival crevicular fluid (GCF) was sampled from all patients. Results obtained indicated application of oral treatment with tablets containing probiotic strain of *L. reuteri* induces in most patients with chronic periodontitis reduction of pro-inflammatory cytokine response and improvement of clinical parameters [27].

Forty-nine adult patients with peri-implant mucositis were consecutively recruited and divided as 22 subjects in test group and 24 in the control group. After initial mechanical debridement topical application of droplet of experimental oil containing *Lactobacillus reuteri* strains were given to test group and placebo oil and placebo lozengeswere given to control group. Pocketprobing depth (PPD), plaque index (PI) and bleeding on probing (BOP) recorded at baseline and after 1, 2, 4, 12 and 26 weeks. After 4 and 12 weeks, all clinical parameters mproved in both test and the placebo group. PPD and BOP were reduced compared with baseline (p<0.05), but no significant differences were displayed between the groups [28].

Thirty chronic periodontitis patients were included in a study and Split-mouth design was performed for the SRP. *L. reuteri* Prodentis lozenges were given 29to the patient. The clinical parameters recorded at day 0, day 21, and day 42. were PI, GI, BI, probing pocket depth (PPD),clinical attachment level (CAL). At day 42, the PI, GI, and GBI were reduced by all treatment modalities [29]. [Table no. 2]:

Table 2: Clinical studies showing the effects of probiotic in periodontal therapy.

Authors, Year	No. of participants	Periodontitis Treatment	Probiotics Used	Main results
Vivekananda MR, 2010 [30]	30	scaling and root planing (SRP)	*L. reuteri* lozenges	Decrease in PI, GI, and GBI
Teughels W, 2013 [23]	30	scaling and root planing (SRP)	*L. reuteri* containing lozenges	Decrease in PI, GI, BoP, CAL and PD
Szkaradkiewicz AK, 2014 [27]	38	scaling and root planing (SRP)	*L. reuteri* containing tablets	Decrease in BI, PPD, CAL
Tekce M *et al*, 2015 [20]	40	scaling and root planing (SRP)	*L. reuteri* containing lozenges	Decrease in PI, GI, BoP and PD
Ince *et al*, 2015 [20]	30	scaling and root planing (SRP)	*L. reuteri* containing lozenges	Decrease in PI, GI, BoP
Hallström H, 2016 [28]	49	scaling and root planing (SRP)	experimental oil containing *Lactobacillus reuteri* strains	PPD and BOP were significantly reduced
Invernici MM *et al*, 2018 [21]	41	scaling and root planing (SRP)	Bifidobacterium containing lozenges	Decrease in PD & CAL
Alshareef A *et al*,2020 [25]	25	scaling and root planing (SRP)	bifid bacteria containg lozenges	Decrease in BI, PI, PPD, CAL
Andrea Butera *et al*,	60	scaling and root	*Lactobacillus* & Bifidobacterium containing	Decrease in CAL and PD

2021 [4]		planing (SRP)	toothpaste and chewing gum	
Patyna M, 2021 [26]	48	subgingival debridement	*L. brevis and L. plantarum* containing lozenges	Decrease in BOP, GIs, and red complex bacteria

Antimicrobial Studies

The antibacterial activity of propolis against periodontal pathogenic bacteria *in vitro* was examined in 6 of the studies.

In vitro testing of antibacterial activity of oral probiotics like *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, and *Streptococcus salivarius* against periodontal pathogens Fusobacterium nucleatum (FN), *Porphyromonas gingivalis* (PG), and *Aggregatibacter actinomycetemcomitans* (AA) using agar welldiffusion assay were evaluated in study, results shows *Streptococcus salivarius* K-12 was most effective against *A. actinomycetemcomitans*. For both *F. nucleatum* and *P. gingivalis* effect of all probiotics was comparable with *P. gingivalis* exhibiting slightly more sensitivity [30].

The interaction assay was conducted with *P. gingivalis* and *L. reuteri* preparations in tubes containing Brain Heart Infusion broth was conducted in a study and Survival was evaluated over 7 days. The results shows reduction in *P. gingivalis* after the interaction with *L. reuteri* [31].

In another study effect of probiotics Lactobacillus strains and *Streptococcus salivarius* strains were evaluated against periodontal pathogens like *P. intermedia*, *P. gingivalis*, *A. actinomycetemcomitans* and *F. nucleatum* using an agar-based inhibition assay. The results showed that there was a strongest decreases of *P. intermedia*, *P. gingivalis* and *F. nucleatum*, but a weaker inhibition of *A. actinomycetemcomitans* other strains [32].

Another study using Sub-gingival plaque samples from periimplantitis patients to identify various peri-implantitis microorganisms. The effect of probiotic *Lactobacillus reuteri* was assessed on *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, *Streptococcus salivaris* and *Staphylococcus aureus* were found in the subgingival sample and all microorganisms were afected by *L. reuteri* except *Aggregatibacter actinomycetemcomitans* [33].

An *in vitro* assessment of probiotic *L. salivarius* on peri-implantitis pathogens was included in study using serial tube dilution method. Minimum inhibitory concentration was calculated for *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, *Streptococcus salivarius*, and *Staphylococcus aureus*. The results showed that all the pathogens were susceptible to probiotic. *S. salivarius* except AA comitans [34].

The inhibitory effect of probiotic *Streptococcus salivarius*, *Streptococcus oralis* and *Lactobacillus reuteri* on anaerobic periodontal bacteria and *Aggregatibacter actinomycetemcomitans* was evaluated in study. The results *S. salivarius* showed most constant inhibitory potential against all pathogens and *Streptococcus oralis* subsp. had significant inhibitory effects on *P. intermedia* and *A. actinomycetemcomitans*. But the overall best inhibitor of the periodontal pathogens was *L. reuteri* [35]. [Table no.3]

Table 3: *In vitro* studies showing the effects of probiotic against periodontal pathogens.

Study and Year	Probiotic strain	Results
Moman R, 2020 [30]	*Lactobacillus rhamnosus*, *Lactobacillus reuteri*, *Streptococcus salivarius*	*Streptococcus salivarius* was the most effective against *A. Actinomycetem* comitans.
Geraldo BM *et al*, 2020 [31]	*L. reuteri*	Reduction in *P. gingivalis* CFU/mL up to 86%.
Mulla M, 2021 [31]	*Lactobacillus reuteri*	*Lactobacillus reuteri* has antimicrobial property against all periodontal pathogens except *A. Actinomycetem* comitans.
Mulla M, 2021 [31]	*L. salivarius*	*L. salivarius* shows antimicrobial property against *Porphyromonas gingivalis*, *Prevotella intermedia*, *Streptococcus salivarius*, and *Staphylococcus aureus* except *A. Actinomycetem* comitans.
Jansen PM, 2021	*Streptococcus salivarius*, *Streptococcus oralis* and *Lactobacillus reuteri*	*S. salivarius* showed inhibitory potential against all pathogens and *Streptococcus oralis* subsp. had significant inhibitory effects on *P. intermedia* and *A. actinomycetemcomitans*.
Van Holm W,2023 [32]	Lactobacillus strains and *Streptococcus salivarius* strains	Decreases of *P. intermedia*, *P. gingivalis* and *F. nucleatum*, but a weaker inhibition of *A. actinomycetemcomitans*

Discussion

The aim of this review was to determine the effectiveness of probiotics in treatment of periodontal disease. The findings shows that probiotics are beneficial in improving clinical as well as microbiological parameters.

The study by Vivekananda MR and colleagues showed effect of *L. reuteri* probiotic lozenges in improving the clinical parameters like PI, GI, and GBI in 30 patients [29]. Teughels W *et al* in another study used *L. reuteri* containing lozenges and showed reduction in clinical parameters as well as reduction in *Porphyromonas gingivalis* [23].

Szkaradkiewicz AK and colleagues studied the effect of probiotic tablets containing *L. reuteri* strain in 38 subjects and the result showed that there was a significant reduction of pro-inflammatory cytokine response and improvement of clinical parameters (BI, PPD, CAL) [27]. Also forty-one chronic periodontitis patients were evaluated by Invernici MM *et al* for the efficacy of lozenges containing Bifidobacterium species clinically, immunologically, and microbiologically. And this study showed that the test group presented a decrease in probing pocket depth and a clinical attachment gain significantly higher than those of the Control group. And significantly fewer periodontal pathogens of red and orange complexes, as well as lower proinflammatory cytokine levels than the control group [21].

In another study conducted by Tekce M *et al* in 40 chronic periodontitis subjects showed that there was an improvent in the PI, GI, BoP and PD after the administration of *L. reuteri* containing lozenges [20]. Hallström H study in 49 patients with peri-implant mucositis, administrated with topical application of droplet of an experimental oil containing *Lactobacillus reuteri* strains have provided improvement in the

Pocketprobing depth (PPD), plaque index (PI) and bleeding on probing (BOP) after 12 weeks [28].

48 patients with (stages II and III, grade B) periodontitis were evaluated by Patyna Mand colleagues showed that the probiotic lozenges with a daily dose of 62.5 mg *L. brevis* and 62.5 mg *L. plantarum* improved the BOP, GIs, and red complex bacteria *P. gingivalis* and *T. forsythia* counts within 6 months [26].

The Antimicrobial effect of probiotis against periodontal pathogens has been studied in 6 of the *in vitro*. Moman R and colleagues on their study stated that *A. actinomycetemcomitans* showed the greatest sensitivity to all probiotics and *Streptococcus salivarius* was the most effective probiotics against *A. actinomycetemcomitans* [30].

Geraldo BM *et al* on their study evaluated for the antimicrobial effect of *L. reuteri* on *Porphyromonas gingivalis* showed that there was a reduction in *P. gingivalis* CFU/mL upto 86%. Thus they concluded that *Lactobacillus reuteri* has an antimicrobial activity against *P. gingivalis* [31].

Mulla M and colleagues stated probiotic strain including *L. reuteri* showed antimicrobial effects against periodontal pathogens including *Porphyromonas gingivalis*, *Prevotella intermedia*, *Streptococcus salivaris* and *Staphylococcus aureus* which was found in subgingival plaque except *Aggregatibacter actinomycetemcomitans* [33].

Mulla M and colleagues assessed effect of probiotic *L. salivarius* on peri-implantitis pathogen, results showed *L. salivarius* antimicrobial property against *Porphyromonas gingivalis*, *Prevotella intermedia*, *Streptococcus salivarius*, *Staphylococcus aureus* except *A. Actinomycetem* comitans [34].

Jansen PM and colleagues reported *S. salivarius* showed most constant inhibitory potential against all anerobic pathogens and *Streptococcus oralis* subsp. had inhibitory effects on *P. intermedia* and *A. actinomycetemcomitans.* But overall best inhibitor of periodontal pathogens was *L. reuteri* [35].

Van Holm W *et al* showed that strongest decreases of *P. intermedia*, *P. gingivalis* and *F. nucleatum*, a weaker inhibition of *A. actinomycetemcomitans* than other strains against Lactobacillus strains and *Streptococcus salivarius* strains [32].

In the present literature we found in each study, a different number of participants were chosen. Future research must be conducted with purpose of gaining a better understanding of the performance of probiotics in improvement of clinical and microbiological aspects of periodontal diseases. Moreover, a larger sample size with a longer follow-up should be employed in further studies.

Conclusion

In summary, probiotics examined using *in vitro* and *in vivo*/preclinical models show promise for applications in a periodontal disease setting This review suggests that the use of probiotics leads to an improvement in gingivitis and periodontitis with changes in clinical parameters, including periodontal pocket depth, clinical attachment loss and bleeding on probing. However, effects of probiotics on a long-term changes after periodontal therapy has to be investigated further in future.

Conflict of Interest

Not available

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Not available

Reference

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