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Review Article

Probiotics in Treatment and Prevention of Periodontal Diseases: A Systemic Review

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ABSTRACT

Aim: *Aim of this systematic review was to analyse the available scientific evidence on the effects of probiotics in prevention and treatment of periodontal diseases*

Materials and methods: *A broad literature search was performed using both electronic database and hand search in library. The important databases like COCHRANECENTRAL, MEDLINE, GOOGLE SCHOLAR, EMBASE were used for online data search. Hand search was performed in the central library of the institute to identify the relevant articles, articles that satisfied the inclusion criteria with description of randomized clinical trials comparing the administration of probiotics versus placebo or another intervention to prevent or treat periodontal diseases in adult patients were selected.*

Results: *The initial search resulted in 73 articles; however, 45 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 analysing the full text from 27 clinical trials, 12 were excluded because they did not fulfil all the selection criteria. Our final review included 15 articles. Included outcome measures were probing pocket depth, bleeding on probing, clinical attachment loss, plaque index and gingival inflammation. Included studies were subjected to critical analysis following the Cochrane Collaboration tool for evaluating the risk of bias.*

Conclusion: *Probiotics had a beneficial effect on reducing probing pocket depth, gingival inflammation, bleeding on probing when compared with placebo. Lactobacillus was the most commonly used probiotic genus, in which L.reuteri strain had most beneficial effects.*

Key words: *Probiotics, Periodontitis, Gingivitis.*

INTRODUCTION

The term probiotic is a relatively new word meaning 'for life' and it is currently used when referring to bacteria associated with beneficial effects on humans and animals[1]. A number of potential benefits arising from the use of probiotics have been demonstrated, including increased resistance to infectious diseases, alleviation of lactose intolerance, prevention of gut diseases, diarrhea and vaginal and urogenital infections, reduced allergy and respiratory infections, reduced serum cholesterol concentration, increased resistance to cancer chemotherapy and decreased risk of colon cancer.[2] The application of health promoting bacteria for therapeutic purposes is one of the strongest emerging fields not only in medical but dental science.[3]

Probiotics are claimed to be effective in reduction of dental caries, Gingivitis and Periodontal disease, Halitosis. Probiotics have a capacity to adhere and to colonize various surfaces of oral cavity, thereby probiotics can modify the surrounding environment by modulating the pH and/or

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oxidative reduction potential, which may compromise the ability of pathogens to become established.[4]

Periodontitis is a multifactorial disease that encompasses the hard and soft tissue, microbial colonization (with or without invasion), inflammatory responses and adaptive immune responses.[5] The clinical manifestation of periodontal disease result from a complex interplay between the etiologic agents, specific bacteria found in the dental plaque and the host tissues. The oral bacteria lives in harmony with its host, but under specific conditions like increased mass and/ or pathogenicity, suppression of beneficial bacteria and/or reduced host response, they can cause disease6. Conventional treatment modalities of periodontal disease include non-surgical and surgical management, which emphasizes mainly on mechanical debridement, often accompanied by antibiotics. These treatment modalities are aimed at eliminating the entire microflora irrespective of their pathogenicity.[5]

Although current modalities of periodontal therapy aim at eliminating all plaque microorganisms, the Specific Plaque Hypothesis states that only certain microorganisms found in dental plaque are responsible for periodontal disease. The advent of probiotics into the field of Periodontics would possibly open new horizons to address the above concerns as an attractive alternative to antibiotics and to target particular periodontal pathogens, thus increasing the long-term success of periodontal therapy.[7]

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

MATERIALS AND METHODS

Focused question: what is the prognosis of periodontal diseases when we compare probiotic therapy to conventional intervention or to placebo?

Search process: A broad literature search was performed using both electronic database and hand search in library. The important databases like COCHRANECENTRAL (1994-2015), MEDLINE (1950-2015), GOOGLE SCHOLAR (1987-2015), EMBASE (1990-2015) were used for online data search. Hand search was performed in the central library of the institute to identify the relevant articles. We reviewed cross references from relevant papers and abstracts of conferences related to the subject of the review.

Search strategies was based on the following terms:(1) probiotics, (2) periodontal diseases, (3) type of probiotics, and (4) randomized clinical trials (RCTs) or combination of these words according to Boolean search.

A comparison of different searches was to delete the repeated studies. Then abstracts of all available articles were examined. All studies, which appeared to meet the inclusion criteria, were obtained in the full text format and they go for validity assessment. Application of the Cochrane Collaboration tool[8] for evaluating the risk of bias was done. Then selected articles were grouped into high risk bias and low risk bias articles.

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 or with no treatment.
2. If test group is receiving SRP adjunct to probiotic, then control group should also receive same SRP as the treatment group.
3. Any type of probiotic with any type of administration method will be considered.
4. Articles published in English literature

Types of outcome measures:

- Outcome variables are probing pocket depth (PPD), measured in millimeters from the gingival margin to the depth of probe penetration,
- Clinical attachment level (CAL), measured in millimeters from the cement-enamel junction to the depth of probe penetration.
- Plaque index, gingival inflammation, and bleeding on probing (BOP) will be considered.
- There will be no restriction regarding the method for measuring any of the outcomes.
- Trials that reported any of these outcomes with a minimum follow-up of 4 weeks will be included.

RESULTS

The initial search resulted in 73 articles; however, 45 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 27 clinical trials, 12 were excluded because they did not fulfill all the selection criteria (Table 1). Our final review included 15 articles (Fig 1). Demographic details and General characteristics of included studies were described in table 2 & 3.

Among the articles included, nine studies administered Lactobacillus reuteri, and remaining studies administered strains of Lactobacillus salivarius, Lactobacillus casei, Lactobacillus brevis, Lactoacillus rhamnosus, Streptococcus salivarius, Streptococcus faecalis one in each.

Risk of bias of included studies: The included studies were subjected to critical analysis following the Cochrane Collaboration tool for evaluating the risk of bias, and we classified 9 articles as having a low risk of bias and 6 articles as having a high risk of bias. Table 4 shows the domain in which the trails were judged to have the high risk of bias.

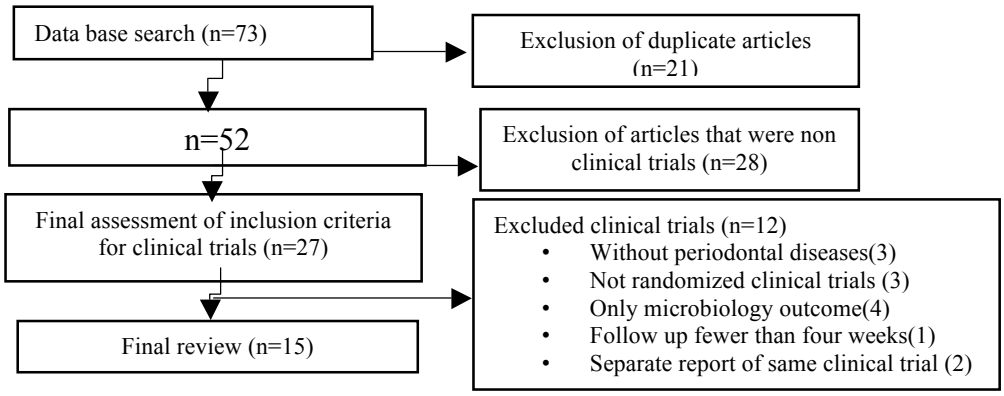

Figure 1: Flow chart of methodology

Table 1 Articles excluded from the study

Author	Title of article	Reason for exclusion
Caglar E etal. 2007[9]	A probiotic lozenge administered medical device and its effect on salivary mutana streptococci and lactobacilli	Only had to do with a study of caries
Della Ricca DN etal.2007[10]	Anti-inflammatory effects of lactobacillus brevis(CD2) on periodontal disease	No between group comparison for the clinical outcomes
Mayanagi G etal.2009[11]	Probiotic effects of orally administered lactobacillus salivarius WB12 containing tablets on periodotopathic bacteria: a double blinded, placebo controlled, randomized clinical trail	This is a separate microbiological repot of study included
Tsubura S etal.2009[12]	The effect if bacillus subtilis mouth rinsing in patients with periodontitis	Not a randomized study
Zahradnik RT etal.2009[13]	Preliminary assessment of safety and effectiveness in humans of probiora a probiotic mouthwash	Outcome measures were not satisfying inclusion criteria
Harini PM etal.2010[14]	Efficacy of a probiotic and chlorhexdine mouth rinses: A short term clinical study.	Follow up for fewer than 4 weeks
Tahmourespour A etal.2011[15]	The effect of a probiotic strain (lactobacillus acidophilus) on the plaque formation of oral streptococci	Outcome measures were related to dental caries.
Marttinen A etal.2012[16]	Short term consumption of probiotic lactobacilli has no effect on acid production of supra gingival plaque	Not a randomized study Outcome measures were not satisfying inclusion criteria
Dhawan R etal.2013[17]	Role of probiotics on oral health: A randomized, double-blind, placebo controlled study	It is the duplicate study of other study that was included
Ericson D etal. 2013[18]	Salivary IgA response to probiotic bacteria and mutans streptococci after the use of chewing gum containing lactobacillus reuteri	Outcome measures were not satisfying inclusion criteria
Maekawa T etal.2014[19]	Topical treatment with probiotic Lactobacillus brevis CD2 inhibits experimental periodontal inflammation and bone loss	In-vitro study
Terai T etal.2015[20]	Screening of probiotic candidates in human oral bacteria for the prevention of dental disease	Not a randomized clinical trail

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

Study	No.	Men	Women	Age	Clinical characteristics
Shimauchi H etal. 2008[21]	66	57	9	32-61	Systematically healthy individuals with periodontitis
Staab B etal. 2009[22]	50	25	25	24±1.9	Systematically healthy individuals with gingivitis
Twetman S etal. 2009[23]	42	26	16	24	Systematically healthy individuals with moderate levels of gingivitis
Vivekananda MR etal.2010[24]	30	19	11	34-50	Systematically healthy individuals with chronic periodontitis
Iniesta M etal.2012[25]	40	8	32	20-24	Systematically healthy patients with gingivitis
Bruton JP etal.2013[26]	83	33	50	5-10	Systemically healthy patients with dental caries and gingivitis
Dawan S etal. 2013[27]	40	10	30	21	Systematically healthy individuals suffering with chronic gingivitis
Hallstrome H etal. 2013[28]	18	0	18	38	Systematically healthy patients and they induced gingivitis
Karuppaiah RM etal.2013[29]	208			14-17	Systematically healthy patients with gingivitis
Piyush M etal.2013[30]	30	14	16	14-35	Systematically healthy individuals with probing depth and loss of clinical attachment level
Teughels W etal.2013[31]	30	15	15	40-48	Systemically healthy individuals with moderate to severe periodontitis
Vicario M etal. 2013[32]	19	12	7	43-65	Systematically healthy individuals with initial to moderate chronic periodontitis
Ince G etal.2015[33]	30	17	13	35-50	Systematically healthy individuals with chronic periodontitis
Tekce M etal.2015[34]	40				Systematically healthy individuals with chronic periodontitis
Toiviainen A etal. 2015[35]	62	7	55	24	Systematically healthy patients without gingivitis or periodontitis

Table 3: General characteristics of the included studies

Study	Probiotic type and pharmaceutical form	Placebo controlled	Experimental group	Control group	N	Results	Follow up time
Shimauchi etal.2008[21]	Tablet of lactobacillus salivariusWB21 ($6.7^{*}10^{8}$CFU/tab) and xylitol(280mg/tab).	Yes	34	32	66	-Probing pocket depth -gingival index -plaque index -bleeding on probing -changes in salivary lactoferrin levels -side effects	8weeks
Stabb B etal.2009[22]	Probiotic milk with lactobacillus casei(dose of 65 ml)	No	25	25	50	-papillary bleeding index -plaque index -interproximal plaque index -activity of elastase and myeloperoxidase in gingival crevicular fluid	8weeks
Twetman S etal.2009[23]	Chewing gums of lactobacillus reuteri($1^{*}10^{8}$CFU/gum	Yes	29	13	42	-bleeding on probing -concentration of inflammatory mediators in gingival circular fluid	4weeks
Vivakananda MR etal .2010[24]	Tablet of prodentis with lactobacillus reuteri	Yes	15	15	30	-probing pocket depth -plaque index -gingival index -gingival bleeding index -variation in quantity of pathogens	42days
Iniesta M etal.2012[25]	Tablet of lactobacillus reuteri($2^{*}10^{8}$CFU/tab).	Yes	20	20	40	-plaque index -gingival index -saliva and subgingival for CFU of total anaerobic microbiota	8weeks
BurtonJPetal.2013[26]	Lozenges contained streptococcus salivarius M18($3.6^{*}10^{9}$CFU)	Yes	25	25	50	-gingival index -oral hygiene index -streptococcus mutans counts	3months
Dhawan Setal.2013[27]	Capsule contained lLactobacillus sporogens 100 million, Streptococcus faecalis T-110JPC 60 million,Clostridium butyrium TO-A 4 million, Bacillus mesentricus TO-A JPC 2 million.	Yes	20	20	40	-plaque index -gingival index -streptococcus mutans count	4weeks
Hallstrome Hetal.2013[28]	Lozenges containing 2 strains of lactobacillus reuteri(ATCC55730 and ATCC PTA5289;$1^{*}10^{8}$CFUof each strain	Yes	9	9	18	-plaque index -gingival index -bleeding on probing -inflammatory biomarkers in gingival cervicular fluid -microbiological profile of supragingival plaque	5weeks
Karuppaiah RM etal. 2013[29]	Probiotic curd with lactobacillus strain	Yes	104	104	208	-gingival index -plaque index	8weeks
Piyush sahaMetal. 2013[30]	Lozenges of probiotic contained10^{8}CFU per gram of lactobacillus brevis and tablets of the antibiotic, doxycycline(100mg).	Yes			30	-plaque index -gingival index -probing pocket depth -clinical attachment loss	2months

Table 4: Studies having high risk of bias

Improper randomization	2 Studies (Toiviainen A et al.2015[35], Twetman Setal.2009[23])
Improper blinding	1 Study(Burton JP etal.2013[26])
Improper blinding and Improper randomization	2 Studies(Karuppaiah RM etal.2013[29], Stab Betal.2009[22])
Improper randomization, Improper blinding and Improper reporting of incomplete outcomes	1 Study(Piyush M etal.2013[30])

Effects of probiotics:

Probing pocket depth(PPD): Seven trails evaluated this outcome.

Six of seven trials reported clinically significant differences in probing pocket depth values after using probiotics.[24,30,31,32,33,34] Among six studies 3 studies[24,31,34] have shown that probiotic along scaling and root planning had higher beneficiary effect, other 3 studies[30,32,33] have used only probiotic without scaling and root planning. One study21showed no difference in probing pocket depth. **Plaque index (PI):** 13 trails evaluated this outcome among 13 trials eight trials[24,27,29,30,33,34,35] reported significant reduction in plaque scores after using probiotics. Five trials[21,22,25,28,31] reported no significant change in plaque scores. **Gingival inflammation:** Eleven trails evaluated this outcome, among which six trials[24,27,30,33,34,35] reported change in gingival inflammation after the use of probiotic. Five trails[21,25,26,28,29] reported no change in gingival inflammation after the use of probiotic as intervention. **Bleeding on probing:** Seven trails evaluated this outcome, among which four trials[23,32,33,34] reported reduction in bleeding on probing after using probiotics. Three trials[21,28,31] reported no significant change. **Clinical attachment levels:** Three trails[24,30,31] measured this outcome with no significant difference for clinical attachment levels. There by it was concluded that there was no benefit for clinical attachment levels after use of probiotic levels.

DISSCUSSION

There are many well documented health benefits of probiotics, including relieving of inflammation and prevention of certain infections and allergies. Thus 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 studies included in this review demonstrated large variability in the type of probiotic used, the probiotic concentration, pharmaceutical form and the clinical characteristics at the patients in which they were tested. Furthermore many studies were financed by laboratories involved in the production of probiotics, which raises concerns regarding the confidence in the apparent treatment benefits. It should be noted that two of the trails recruited patients with no signs of gingivitis or periodontitis Stabb B et al (2009) evaluated the effects of probiotic drink milk after inducing gingivitis by interrupting mechanical plaque control for 96 hours. Hallstrome H etal (2013) evaluated the effects of probiotic lozenges after inducing gingivitis by using a customized acrylic mouth guard covering first premolar to second molar and applied during tooth brushing, in this way patients refrained from cleaning four of their lateral teeth during the experimental periods. We acknowledge that this is a clinical scenario unlikely to be real; however, these studies fulfilled the selection criteria and answered the clinical question of interest and thus they were included.

Among the seven studies which evaluated probing pocket depth. Three studies not only evaluated the effects of probiotic tablets versus placebo, but also included scaling and root planning as intervention and they reported better results when compared to studies evaluated the effects of probiotics alone. So if probiotics used adjunct to SRP there will be more beneficial effect. Plaque index evaluated by thirteen trails among them only five trails reported significant results. But among these five trails, two trails were funded by private laboratories one trail induced gingivitis experimentally. Follow up periods were also varying for these five trails. Strain of probiotic used was also varying. Thus the effect of probiotic on plaque was questionable. Significant change in bleeding on probing was reported by four trails. Among these four trails three trails were funded by private laboratories, there was a variation in the follow up period, two trails were conducted for 360 days; other two studies were done for four weeks. But since the four studies used same strain of probiotic, clinical characteristics of patients were similar the clinically beneficial effect of probiotic on bleeding on probing can be accepted. Only three trails evaluated clinical attachment loss with no significant change. This is because once clinical attachment loss occurs (recession) need perio plastic surgery to restore it. Among 15 studies, Lactobacillus genus was used by 14 studies among these 8 studies used Lactobacillus reuteri species. One study[26] used Streptococcus salivarius but that study showed non-significant change in outcomes. Among bacteria used as probiotic one of the most important groups is the genus Lactobacillus. These organisms are naturally present in the healthy human gut, and can be found in foods like yogurt and sauerkraut. Among different strains in Lactobacillus, Lactobacillus reuteri is commonly found in some cultured vegetables, in the intestinal tracts of animals, in meat and dairy products, and in natural environment. Because L.reuteri as a species commonly found in food, the environment and within us it is generally safe. It is best known for its ability against pathogen microbes, it also produces carbon dioxide, ethanol, acetic acid and lactic acid from glucose and so is considered to be obligately heterofermentive and many strains of Lactobacillus have been recovered from faeces showing the ability to withstand stomach acid and bile acids in the digestive tract.[36] So, this may be the reason most of studies used Lactobacillus as probiotic.

CONCLUSSION

Despite certain limitations, probiotics had a beneficial effect on reducing probing pocket depth, gingival inflammation, bleeding on probing when compared with placebo. There was no effect on clinical attachment loss. Lactobacillus was the most commonly used probiotic genus, in which L.reuteri strain had most beneficial effects.

Scope for future studies:

The results of this systematic review confirm that more studies are necessary to evaluate the efficacy of probiotics

with correct methodological design, without private funding 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.

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