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Probiotics and Periodontitis – A Literature review

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Abstract

Objective: This review was designed to explore the use of probiotics in prevention or treatment of periodontitis.

Methods: A search was performed using MEDLINE and bibliographies from previous reviews in order to identify any randomised controlled animal and human probiotic interventions in periodontitis.

Results: Five studies using probiotics in animal models of periodontitis and eight clinical studies using probiotics in patients with chronic periodontitis were analysed. The analysis of the animal models showed reduction in periodontal pathogens and bleeding on probing when probiotics were used in adjunction to mechanical debridement and significant increase in alveolar bone levels and bone density in the probiotic groups when compared with placebo. Some of the results of the clinical studies indicated decreased clinical parameters (gingival inflammation, bleeding on probing, plaque index) and decreased pro-inflammatory markers levels in saliva or gingival crevicular fluid in treated periodontitis patients when compared with controls or placebo. Other results included decreased periodontal pocket depth and clinical attachment loss for scaling and root planing plus probiotic treatment versus scaling and root planing alone or placebo and also reduction in *Porphyromonas gingivalis* numbers and the total viable count and proportion of obligate anaerobic bacteria.

Conclusions: Within the limitations of this review, the results are encouraging, supporting the notion that there is a place for probiotics in the treatment of periodontitis. Future independent studies are needed to investigate specific probiotic strains, doses, delivery methods, treatment schedules, mechanisms of action, safety and how to maintain the results of the probiotic interventions.

Keywords: probiotics, periodontitis, alveolar bone loss, lactobacilli, bifidobacteria, Lactobacillus rhamnosus GG

Introduction

Periodontitis is a common chronic inflammatory condition affecting the dentition of the adult population (Petersen, 2003). A key factor in the development of this disease is an increased bacterial challenge, specifically the presence of elevated numbers of certain potentially pathogenic commensal bacterial species resulting from altered environmental conditions arising from the host's inflammatory response (Bartold and Van Dyke, 2013).

Subgingival debridement, surgical interventions and in some cases selective use of antibiotics and antiseptics are current approaches used to reduce the pathogenic bacteria. Whilst these treatments result in a temporary reduction of the bacterial load and associated inflammation, they are often not sufficient to control the disease (Quirynen *et al*., 2002; Teughels *et al*., 2007a). Therefore, other adjunctive strategies need to be investigated. The administration of beneficial bacteria – probiotics – with antimicrobial and anti-inflammatory properties is one of several novel approaches being considered as an adjunct treatment for the management of periodontitis and may offer a low risk, inexpensive and easy-to-use treatment option.

Periodontitis

Periodontitis is a chronic inflammatory condition affecting both the hard and soft tissues surrounding the teeth, caused by a combination of specific bacteria and inflammatory host responses and resulting in the destruction of the connective tissue of the gingivae, periodontal ligament and alveolar bone (Petersen, 2003). It is one of the two most prevalent oral health burdens world-wide.

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A World Health Organization report from 2012 found 15-20% of middle-aged adults suffered from severe periodontal disease resulting in tooth loss (World Health Organization, 2012). Periodontitis is also considered a risk factor for cardiovascular disease, pulmonary disease, type II diabetes, rheumatoid arthritis and adverse pregnancy outcomes (López *et al.*, 2002; Bartold *et al.*, 2005; Blaizot *et al.*, 2009; Chee *et al.*, 2013).

The precise etiology of periodontitis is complex, multifactorial and not completely understood. Generally, it is believed to be a biofilm-induced disease with the host's immune system playing a central role (Flemmig, 1999; Darveau, 2010; Bartold and Van Dyke, 2013; Hajishengallis, 2014a; 2014b). The disease is associated with an imbalance in the host's local microbiome with elevated numbers and proportions of bacterial species designed as 'pathogens' and reduced proportions of bacteria associated with health (Socransky and Haffajee, 1992; Wade, 2011; Abusleme *et al.*, 2013).

Current treatments for periodontal disease, including subgingival debridement, surgical interventions and selective use of antibiotics and antiseptics, aim to reduce the pathogenic load (Quirynen *et al.*, 2002). Although these numbers of pathogens are reduced considerably, the shift is only temporary as re-colonization occurs within months (Magnusson *et al.*, 1984; Rhemrev *et al.*, 2006). The use of antibiotics as part of the treatment brings with it the important global issue of antibiotics resistance that has the potential to render many antibiotics useless. It also brings along a long list of possible side-effects, notably, antibiotic-associated diarrhea (Lynne, 2006).

Considering all of these factors, increasing the proportion of beneficial bacteria with inflammation modulating properties presents as an option to address the bacterial imbalance and may be considered as a preventive or treatment option in achieving periodontal health.

Probiotics

History, sources, definition

The microorganisms that live inside and on humans outnumber the body's cells tenfold with the majority of them being bacteria, with some archaea and eukaryotes also being present (Saier and Mansour, 2005). In periodontal health, communities of bacteria live in symbiosis with the host, playing a role in its immune function and health status. A disturbance in the microbial balance (a process labelled as 'dysbiosis') has been associated with several medical conditions (Goulet, 2015). Obesity, metabolic diseases, gastrointestinal diseases, autoimmune diseases, allergies and cancer have all been partly associated with an increased number of harmful bacteria and a decreased number of beneficial bacteria (Logan *et al.*, 2003).

Beneficial bacteria are present in preserved food and beverages around the world: Korean *kimchi*, Indonesian tempeh, Indian chutney, Japanese miso, sauerkraut, kefir, yogurt and cheese. The preservation process called 'lacto-fermentation' is an anaerobic process in which lactic acid bacteria, predominantly lactobacilli, convert carbohydrates into lactic acid, which acts as a preservative (Turpin *et al.*, 2010). Consuming fermented foods is an ancient practice dating back as far as 5400 BC, whilst recommendations for gastrointestinal illness date back to 76 AD (Rawlings, 2013). The first scientist to lay down the foundations for the concept of beneficial bacteria was the Ukrainian born Nobel laureate bacteriologist Ilya Ilyich Mechnikov, known as "the father of modern immunology." He proposed a theory that aging is caused by toxic bacteria in the gut and attributed the longevity of peasants from the Balkan area to their consumption of large quantities of sour milk that contained lactobacilli (Mackowiak, 2013).

Other scientists continued Metchnikov's work and in 1965 the term "probiotics," meaning "for life," was introduced (Lilly and Stillwell, 1965). The current definition for probiotics is given by the World Health Organization, which defines probiotics as live microorganisms, most often bacteria (sometimes fungi), which, when consumed, confer beneficial effects to the host (World Health Organization, 2002).

Probiotics are bacterial strains usually isolated from human commensal microbiota and adequately characterized for strain identity, content, stability, and proven health effects. The most commonly used species of probiotics belong to the *Lactobacillus, Bifidobacterium, Escherichia, Enterococcus* and *Bacillus* genera and are all ubiquitous residents of the human skin, gastrointestinal tract, respiratory tract and vagina (Floch, 2014).

Lactobacilli are Gram-positive, rod-shaped, facultative anaerobes. Some of the most commonly known members that have been isolated and studied are *Lactobacillus acidophilus, L. reuteri, L. bulgaricus*, *L. rhamnosus*, *L. salivarius*, and *L. casei*. Bifidobacteria are Gram-positive, anaerobic bacteria, with some of the most commonly known members being *Bifidobacterium bifidum*, *B. breve*, *B. longum*, and *B. infantis* (Turroni *et al.*, 2014).

Functions and mechanisms

Probiotics fulfil many useful functions, thus having a major heath impact. They produce lactic acid with antibacterial effect, hydrogen peroxide with antiseptic effect, and anti-viral and anti-fungal agents that suppress pathogens. Probiotics are important for immune system development and regulation, maintenance of a healthy lining of the gastrointestinal tract, food digestion, synthesis of amino acids, proteins and different vitamins, absorption of calcium, iron and vitamin D (Ciorba, 2012; LeBlanc *et al.*, 2012; Jonathan and David, 2013). In order to exert all these effects, probiotics need to be able to survive the gastrointestinal passage resisting acid and bile and to preserve their stability during manufacturing and storage (Meurman, 2005).

Additional studies have shown that a combination of different probiotic species and/or strains (e.g. *Lactobacillus rhamnosus GG* and *Bifidobacterium lactis* Bb12) can enhance their effects in a synergetic manner (Juntunen *et al.*, 2001; Toiviainen *et al.*, 2015).

The precise mechanisms of how probiotics exert their effects are not known yet and may depend on a variety of factors: the condition being treated, the strain and the concentration of the probiotics used and the stage when they are introduced, the presence of prebiotics or enteric bacteria (Geier *et al.*, 2007).

The effects of probiotics can originate from three local or systemic main modes of action (Gueimonde and Salminen, 2006; Shira and Gorbach, 2006; Devine and Marsh, 2009):

1. Indirectly, probiotics compete with pathogens for essential nutrients; they can also restrict the pathogens' adhesion capabilities by changing the environmental pH.
2. Directly, probiotics are involved in the production of antimicrobial substances (lactic acid, hydrogen peroxide, bacteriocins) that can kill or inhibit the growth of periodontal pathogens.
3. Probiotics can act on the host by modulating the host's innate and adaptive immune response (reducing the production of pro-inflammatory cytokines: IL-6, IL-1β, TNFα and increasing production of anti-inflammatory cytokines: IL-10) and by improving the intestinal barrier integrity (Ciorba and Stenson, 2009).

It has not been established yet if colonization of the oral cavity by probiotics is necessary in order for them to exert their effects in the mouth, and the process of colonization of the oral cavity itself remains unclear, with studies using biased methods of detecting bacteria (Ravn *et al.*, 2012).

Lactobacillus rhamnosus GG

One of the most studied probiotic microorganisms is *Lactobacillus rhamnosus GG* (LGG). It was originally isolated from healthy human intestines in 1983 (Gorbach, 1996). LGG survives the low pH of the stomach and the bile acids of the duodenum. It has pili facilitating adherence to the inner lining of the digestive system, thus colonizing the intestine (Tripathi *et al.*, 2012). One study investigating the colonisation of LGG in the oral cavity concluded that this is improbable in the majority of cases but possible in some (Yli-knuuttila *et al.*, 2006).

Lactobacillus rhamnosus GG has been extensively investigated in gastrointestinal studies and it is now used in dairy products in many countries. This probiotic does not ferment sucrose or lactose and has been shown to significantly reduce the risk of caries (Meurman *et al.*, 1995; Näse *et al.*, 2001). It has also been demonstrated to have anti-inflammatory properties *in vivo* (Lin *et al.*, 2009).

Considering its non-cariogenic and anti-inflammatory properties, LGG may prove to be a good candidate for future probiotic-periodontitis studies.

Probiotics in other fields of medicine

Traditionally, probiotics have been used in gastroenterology. Evidence-based reviews indicate that certain strains of probiotics contribute to the microbial balance of the gastrointestinal tract – supporting the immune system and reducing inflammation (Ciorba, 2012). Clinical trials have assessed the effects of probiotics in antibiotic-associated diarrhoea, gastroenteritis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, obesity, rheumatoid arthritis and allergies (Meurman, 2005; Vaghef-Mehrabany *et al.*, 2014). There are also laboratory studies that have shown promising results in treatment of childhood autism and colon cancer (Rafter, 2003; Critchfield *et al.*, 2011).

Probiotics and oral health

There have been many studies published investigating the potential health benefits of probiotics on systemic health, but investigations regarding their use in oral health are limited by comparison. These vary a lot in terms of probiotics strains used, concentrations, and vehicles for the application (cheese, lozenges, milk, kefir, ice cream, gum, drops, powder, and mouthwash; Teughels *et al.*, 2011).

Probiotics have been evaluated in caries control and have demonstrated the capacity to reduce *Streptococcus mutans* levels in saliva (Näse *et al.*, 2001). A recent meta-analysis indicated that probiotics could have a positive effect in caries prevention (Laleman *et al.*, 2014). There are also probiotic evaluations in oral conditions, e.g., candidiasis, chemotherapy-induced mucositis or halitosis (Stamatova and Meurman, 2009; Laleman and Teughels, 2015).

Probiotics and periodontitis

In periodontal disease, some studies investigated the role of probiotics in gingivitis and reported a significant decrease in terms of plaque and gingival indices, bleeding on probing and gingival inflammation in the probiotic groups (Laleman and Teughels, 2015).

A search was performed using MEDLINE in order to identify any randomised controlled animal and human probiotic intervention studies in periodontitis. The search considered those works published between 1980 and August 2015 and aimed at evaluating the effects of probiotics in periodontitis using the words "periodontal disease." "periodontitis" and "probiotics." Additional hand searches were performed and included bibliographies from previous reviews on the topic of oral probiotics (Stamatova and Meurman, 2009; Teughles *et al.*, 2011; Raff and Hunt, 2012; Dhingra, 2012; Laleman and Teughels, 2015). Only articles published in English were selected. Five studies using probiotics in animal models of periodontitis and eight clinical studies using probiotics in patients with chronic periodontitis were identified.

Probiotics in animal models of periodontitis

Table 1 highlights four animal studies where periodontal pockets were artificially created or a ligature-induced periodontitis model was used in either rats or beagle dogs.

Five millimetre periodontal bony defects were surgically created four months prior to the experiment in a split-mouth, double-blind, randomised trial in beagle dogs, (Teughels *et al.*, 2007b). Pellets containing a mixture of *Streptococcus salivarius, S. sanguinis* and *S. mitis* were applied to the root surface after scaling and root planing (i.e., to a suppressed oral microbiota). The authors concluded that the use of probiotics significantly delayed and reduced inflammation (bleeding on probing) in the probiotic group when compared with scaled and root planed pockets alone. There was also reduction in total anaerobic bacteria and delay in recolonization of pockets by the pathogens when compared with the control group, and the reduced levels were maintained 12 weeks after the treatment in the probiotic group but not the control group (Teughels *et al.*, 2007b; Teughels *et al.*, 2011). The limitations of the study were the absence of a placebo control group, the intersubject variation, the small sample size (eight dogs) and the intra-oral translocation.

Another study using the same model in eight beagle dogs found there was a significant increase in bone levels for the periodontal pockets treated with probiotics for 12 weeks in comparison with the control group (Nackaerts *et al.*, 2008). Bone density in the probiotic group also improved significantly. The previously mentioned limitations apply, together with the use of conventional radiographic films that introduces potential measurement accuracy errors.

In a randomised controlled study, 32 rats with ligature-induced experimental periodontal disease were administered *Bacillus subtilis* for 44 days (Messora *et al.*, 2013). The probiotic intervention generated reduced attachment loss and alveolar bone loss and protected the small intestine from reactive changes induced by ligature-induced periodontitis. There are a few shortcomings to this study. Like all ligature-induced periodontitis models, the mechanical lesions could aggravate the periodontal destruction (Molon *et al.*, 2013). In addition, the mode of probiotic administration, via drinking water, makes it difficult to quantify the amount ingested by each animal.

In another ligature-induced periodontitis study, a 44-day experiment using the probiotic *B. subtilis* and restraint stress concluded that probiotics supplementation may reduce tissue breakdown in unstressed rats and that immunomodulatory effects of probiotics in intestinal and periodontal tissues were influenced by stress (Foureaux *et al.*, 2014). All the limitations of the Messora *et al.* (2013) study apply here as well.

The animal studies showed an effect of probiotics on oral microbiota and a limited effect on periodontal parameters. Due to the limited data available and all the limitations discussed above, it is premature to draw a conclusion on the recommended methodology (probiotic strain, concentration, duration of treatment and mode of administration).

Table 1. Animal probiotics studies included in this review

Study	Type of participants, number	Condition	Probiotic strains, vehicle, time	Results
Teughles *et al.,* 2007 (Teughels *et al.*, 2007b)	Beagle dogs, 8	Artificially created periodontal pockets	*Streptococcus salivarius, S. sanguinis, S. mitis*, pellets, 12 weeks	Reduction in periodontal pathogens and BOP when probiotics were used in adjunction to mechanical debridement
Nackaerts *et al.,* 2008	Beagle dogs, 8	Artificially created periodontal pockets	*S. salivarius, S. sanguinis, S. mitis*, pellets, 12 weeks	Significant increase in bone levels and bone density in probiotic group when compared with placebo
Messora *et al.,* 2013	Wistar rats, 32	Ligature-induced periodontitis	Product based on *Bacillus subtilis*, in water, 44 days	Mean values of AL and ABL were significantly higher in the induced periodontitis group compared with the treatment group
Foureaux *et al.,* 2014	Wistar rats, 64	Ligature-induced periodontitis associated with restraint stress	Product based on *B. subtilis*, in water, 44 days	Bone loss was prevented in the probiotic treated induced periodontitis unstressed group

BOP, bleeding on probing; AL, attachment loss; ABL, alveolar bone level

Probiotics in clinical studies in patients with chronic periodontitis

Studies using probiotics in patients with chronic periodontitis present a high degree of heterogeneity in the probiotic strains, dosages, vehicles of administration, modes of administration and duration. *Table 2* presents eight clinical studies with variations in terms of the severity of disease, sample size and administration of oral hygiene instructions.

L. brevis lozenges were used in a 2007 double-blind 4-day study in 21 male and female adults with no systemic diseases and with moderate to severe chronic periodontitis to assess anti-inflammatory effects of this probiotic (Riccia *et al.*, 2007). The authors concluded that all clinical parameters (gingival index (GI), plaque index (PI), calculus and temperature sensitivity) decreased in the probiotic group, in association with salivary levels of prostaglandin E_2 (PGE_2), matrix metalloproteinase (MMP) and interferon γ (INF-γ).

Table 2. Clinical probiotics-chronic periodontitis studies included in this review

Study	Type of participants, number, age	Probiotic strains, vehicle, time	Results
Riccia *et al.,* 2007	Adults, 29, 24-51	*Lactobacillus brevis,* lozenges, 4 days	Decreased clinical parameters in treated periodontitis patients when compared with controls (gingival inflammation, BOP, plaque, calculus, temperature sensitivity) Decreased levels of PGE_2, MMP and INF-γ in saliva samples of treated periodontitis patients
Shimauchi *et al.,* 2008	Adults, 66, 32-61	*L. salivarius*, tablets, 8 weeks	Current smokers in the probiotic group showed a significantly greater improvement of plaque index and probing pocket depth from baseline when compared with those in the placebo group
Vivekananda *et al.,* 2010	Adults, 30, 34-50	*L. reuteri,* lozenges, 42 days	PPD, CAL, GI, GBI and PPD significantly reduced in the SRP plus probiotic group compared with SRP alone or placebo
Teughles *et al.,* 2013	Adults, 30, older than 35	*L. reuteri*, lozenges, 12 weeks	Significantly more pocket depth reduction and attachment gain in the moderate and deep pockets and also reduction in *P. gingivalis* numbers in the test group when compared with controls
Vicario *et al.,* 2013	Adults, 20, 44-65	*L. reuteri,* tablets, 30 days	Improved short-term clinical outcomes (PI, BOP, and PPD) in non-smoking patients with initial-to-moderate chronic periodontitis
Szkaradkiewicz *et al.,* 2014	Adults, 38, 31-46	*L. reuteri,* tablets, 2 weeks	Significant improvement in SBI, periodontal probing depth and clinical attachment level and also decreased levels of pro-inflammatory cytokines TNF- α, IL-1β, IL-17 in treated patients when compared with the control group
Ince *et al.,* 2015	Adults, 30, 35-50	*L. reuteri*, lozenges, 3 weeks	Significant differences in PI, GI, BOP and PPD and significant mean values of attachment gain in favour of the test group compared with controls. Significant decreased levels of MMP-8 and increased levels of TIMP-1 were found in GCF for the test group up to day 180
Tekce *et al.,* 2015	Adults, 30, 35-50	*L. reuteri*, lozenges, 3 weeks	1 year follow-up study from the previous Ince *et al.*; 2015. PI, GI and BOP significantly lower in the test group compared with controls; difference in the total viable count and the proportion of obligate anaerobes were decreased in the test group up to day 180

PGE_2, prostaglandin E_2; MMP, metalloproteinase; TIMP-1, tissue inhibitor of metalloproteinase; INF-γ, interferon γ; PI, plaque index; BOP, bleeding on probing; PPD, pocket probing depth; CAL, clinical attachment loss; GI, gingival index; GBI, gingival bleeding index; SRP, scaling and root planing; SBI, sulcus bleeding index

The inflammatory effects of *L. brevis* were attributed to its capacity to prevent the production of nitric oxide and hence the release of PGE_2 and the activation of MMPs (Riccia *et al.*, 2007). No placebo group was used in this study, no data were provided on the periodontal disease, and data for bleeding on probing (BOP) were unclear.

L. salivarius tablets were administered three times daily for eight weeks in a double-blind, placebo-controlled, randomised clinical study that included 66 adult patients with mild to moderate chronic periodontitis (Shimauchi *et al.*, 2008). The authors found significantly decreased PI, GI and pocket depth in probiotic treated smokers when compared with placebo. No significant difference was detected in BOP between the probiotic and the placebo groups. The study also looked at salivary lactoferrin levels as a measure for the host's immune response and found that these were decreased significantly in the test group smokers. The study does not report on the lactoferrin levels of the non-smokers group alone. The Hawthorne effect regarding altered oral hygiene regimens due to observation was taken into account. The patients who volunteered were workers at the company that manufactured the probiotic tablets and funded the study (Shimauchi *et al.*, 2008).

The use of *L. reuteri* lozenges in 30 adult patients with mild to moderate chronic periodontitis combined with scaling and root planing (SRP) significantly reduced GI, clinical attachment loss (CAL), gingival bleeding index (GBI) and periodontal pocket depth (PPD) and was more effective than either treatment alone (Vivekananda *et al.*, 2010). Patients receiving only probiotics without SRP also showed significant clinical improvement when compared with placebo. The administration of probiotics started 21 days after SRP, twice a day for three weeks. The authors of this double-blind, randomised, placebo-controlled clinical trial presented probiotics as an adjunct or alternative to periodontal treatment when SRP might be contraindicated. The private laboratory making the probiotic funded the test products and the publication of the study (Vivekananda *et al.*, 2010).

L. reuteri lozenges were also used for 12 weeks in a randomised, placebo-controlled clinical trial in 30 adults with moderate to severe previously untreated chronic periodontitis (Teughels *et al.*, 2013). The group found that there was more pocket depth reduction and attachment gain, together with reduction in *Porphyromonas gingivalis* numbers in the probiotic group when compared with controls, concluding that *L. reuteri* can be a useful adjunct to SRP. The private laboratory that manufactured the probiotic partially supported this study (Teughels *et al.*, 2013).

Two strains of *L. reuteri* tablets were used for 30 days in a double-blind, placebo-controlled, randomised clinical trial in non-smoking patients with initial to moderate chronic periodontitis (Vicario *et al.*, 2013). The probiotics used significantly improved short-term clinical outcomes (BOP, PI and PPD). No mechanical intervention was performed. The subject size used in this study was quite small (20 patients) and the study period short. No statistically significant changes could be shown in the control group (Vicario *et al.*, 2013).

In 2014, an experiment using *L. reuteri* tablets for two weeks in 38 adult patients with moderate chronic periodontitis found significant improvement ($p < 0.05$) in sulcus bleeding index (SBI), PPD and CAL in treated patients when compared with controls (Szkaradkiewicz *et al.*, 2014). The gingival crevicular fluid (GCF) levels of pro-inflammatory cytokines TNF-α, IL-1β and IL-17 were decreased in the treated group (Szkaradkiewicz *et al.*, 2014).

The effects of *L. reuteri* on clinical and biochemical parameters, adjunctive to initial periodontal therapy, were evaluated in a randomised, parallel, controlled, double-masked clinical trial of 30 adult patients with initial to moderate chronic periodontitis over a one-year period (İnce *et al.*, 2015; Tekce *et al.*, 2015). Significant differences were found in PI, GI, BOP and PPD in favour of the test group, together with significant mean values of attachment gain. The GCF levels of proteolytic enzyme metalloproteinase MMP-8 and the tissue inhibitor of metalloproteinase TIMP-1 were measured and followed for 360 days, with significantly decreased levels of MMP-8 and increased levels of TIMP-1 detected up to day 180. Both forms of MMPs (active and latent) were measured and the active forms seemed to be found at sites with progressive periodontitis. The total viable count and the proportion of obligates anaerobes were also decreased up to day 180. The study was supported by a private laboratory. However, the authors of the study declared that the company was not involved in the data management (İnce *et al.*, 2015; Tekce *et al.*, 2015).

The high degree of heterogeneity of the human studies (different strains and concentrations, small sample size, different duration of treatment, durability of response, mode of administration and the role of environmental factors such as the pH of the delivery area) makes it difficult to draw a robust conclusion. Despite all these limitations, it seems that probiotics can still have an impact on the oral microbiota and a limited effect on periodontal parameters. This now needs to be investigated further.

Probiotic therapy is generally considered to be safe and complications rare (Ciorba, 2012) with a closer exploration needed in critically ill or immunocompromised patients (Verna and Lucak, 2010).

Conclusions and recommendations for future research

Periodontitis is an inflammatory disease that has proven very difficult to treat. The results of the animal and clinical periodontitis studies included in this short literature review support the notion that there is a place for probiotics in the treatment of periodontitis and that probiotics may offer a low-risk, inexpensive, easy to use prevention or treatment option for the management of periodontal disease. In the future, more independent studies are needed to look into specific probiotic strains, doses, delivery methods, treatment schedule, mechanisms of action, safety and how to maintain the results of the probiotic interventions.

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References

Abusleme L, Dupuy A, Dutzan N, *et al.* The subgingival microbiome in health and periodontitis and its relationship with community biomass and inflammation. *The ISME Journal* 2013; **7**:1016-1025.

Bartold PM, Marshall RI and Haynes DR. Periodontitis and rheumatoid arthritis: a review. *Journal of Periodontology* 2005; **76**:2066-2074.

Bartold PM and Van Dyke TE. Periodontitis: a host-mediated disruption of microbial homeostasis. Unlearning learned concepts. *Periodontology 2000* 2013; **62**:203-217.

Blaizot A, Vergnes JN, Nuwwareh S, Amar J and Sixou M. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. *International Dental Journal* 2009; **59**:197-209.

Chee B, Park B and Bartold PM. Periodontitis and type II diabetes: a two-way relationship. *International Journal of Evidence-Based Healthcare* 2013; **11**:317-329.

Ciorba MA. A gastroenterologist's guide to probiotics. *Clinical Gastroenterology and Hepatology* 2012; **10**:960-968.

Ciorba MA and Stenson WF. Probiotic therapy in radiation-induced intestinal injury and repair. (Report). *Annals of the New York Academy of Sciences* 2009; **165**:190-193.

Critchfield JW, van Hemert S, Ash M, Mulder L and Ashwood P. The potential role of probiotics in the management of childhood autism spectrum disorders. *Gastroenterology Research and Practice* 2011; **2011**:1-8.

Darveau PR. Periodontitis: a polymicrobial disruption of host homeostasis. *Nature Reviews Microbiology* 2010; **8**:481-488.

Devine DA and Marsh PD. Prospects for the development of probiotics and prebiotics for oral applications. *Journal of Oral Microbiology* 2009; **1**:1-11.

Dhingra K. Methodological issues in randomized trials assessing probiotics for periodontal treatment. *Journal of Periodontal Research* 2012; **47**:15-26.

Flemmig TF. Periodontitis. *Annals of Periodontolgyy* 1999; **4:**32-38.

Floch MH. Recommendations for probiotic use in humans-a 2014 update. *Pharmaceuticals (Basel, Switzerland)* 2014; **7**:999-1007.

Foureaux RC, Messora MR, de Oliveira LFF, *et al.* Effects of probiotic therapy on metabolic and inflammatory parameters of rats with ligature-induced periodontitis associated with restraint stress. *Journal of Periodontology* 2014; **85**:975-983.

Geier MS, Butler RN and Howarth GS. Inflammatory bowel disease: Current insights into pathogenesis and new therapeutic options; probiotics, prebiotics and synbiotics. *International Journal of Food Microbiology* 2007; **115**:1-11.

Gorbach SL. The discovery of *Lactobacillus GG*. *Nutrition Today* 1996; **31**:3S-5S.

Goulet O. Potential role of the intestinal microbiota in programming health and disease. *Nutrition Reviews* 2015; **73**:32-40.

Gueimonde M and Salminen S. New methods for selecting and evaluating probiotics. *Digestive and Liver Disease* 2006; **38**:S242-S247.

Hajishengallis G. Immunomicrobial pathogenesis of periodontitis: keystones, pathobionts, and host response. *Trends in Immunology* 2014; **35**:3-11.

Hajishengallis G. The inflammophilic character of the periodontitis-associated microbiota. *Molecular Oral Microbiology* 2014; **29**:248-257.

İnce G, Gürsoy H, İpçi ŞD, Cakar G, Emekli-Alturfan E and Yılmaz S. Clinical and biochemical evaluation of lozenges containing *Lactobacillus reuteri* as an adjunct to non-surgical periodontal therapy in chronic periodontitis. *Journal of Periodontology* 2015; **86**:746-754.

Jonathan RB and David A. Commensal bacteria at the interface of host metabolism and the immune system. *Nature Immunology* 2013; **14**:676-684.

Juntunen M, Kirjavainen PV, Ouwehand AC, Salminen SJ and Isolauri E. Adherence of probiotic bacteria to human intestinal mucus in healthy infants and during rotavirus infection. *Clinical and Vaccine Immunology* 2001; **8**:293-296.

Laleman I, Detailleur V, Slot D, Slomka V, Quirynen M and Teughels W. Probiotics reduce mutans streptococci counts in humans: A systematic review and meta-analysis. *Clinical Oral Investigations* 2014; **18**:1539-1552.

Laleman I and Teughels W. Probiotics in the dental practice: A review. *Quintessence International* 2015; **46:**255-264.

LeBlanc JG, Milani C, de Giori GS, Sesma F, van Sinderen D and Ventura M. Bacteria as vitamin suppliers to their host: A gut microbiota perspective. *Current Opinion in Biotechnology* 2012; **24:**160-168.

Lin PW, Myers LES, Ray L, *et al.* *Lactobacillus rhamnosus* blocks inflammatory signaling *in vivo* via reactive oxygen species generation. *Free Radical Biology and Medicine* 2009; **47**:1205-1211.

Logan AC, Venket Rao A and Irani D. Chronic fatigue syndrome: Lactic acid bacteria may be of therapeutic value. *Medical Hypotheses* 2003; **60**:915-923.

López, NJ, Smith, PC and Gutierrez J. Periodontal therapy may reduce the risk of preterm low birth weight in women with periodontal disease: a randomized controlled trial. *Journal of Periodontology* 2002; **73**:911-924.

Lilly DM and Stillwell RH. Probiotics: Growth-promoting factors produced by microorganisms. *Science* 1965; **147**:747-748.

Lynne VM. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of *Clostridium difficile* disease. *The American Journal of Gastroenterology* 2006; **101**:812-822.

Mackowiak PA. Recycling Metchnikoff: Probiotics, the intestinal microbiome and the quest for long life. *Frontiers in Public Health* 2013; **1**:1-3.

Magnusson I, Lindhe J, Yoneyama T and Liljenberg B. Recolonization of a subgingival microbiota following scaling in deep pockets. *Journal of Clinical Periodontology* 1984; **11**:193-207.

Messora MR, Oliveira LF, Foureaux RC, *et al*. Probiotic therapy reduces periodontal tissue destruction and improves the intestinal morphology in rats with ligature-induced periodontitis. *Journal of Periodontology* 2013; **84**:1818-1826.

Meurman JH. Probiotics: do they have a role in oral medicine and dentistry?. *European Journal of Oral Sciences* 2005; **113**:188-196.

Meurman JH, Antila H, Korhonen A and Salminen S. Effect of *Lactobacillus rhamnosus* strain GG (ATCC 53103) on the growth of *Streptococcus sobrinus in vitro*. *European Journal of Oral Sciences* 1995; **103**:253-258.

Molon RS, Avila ED and Cirelli JA. Host responses induced by different animal models of periodontal disease: a literature review. *Journal of Invetsigative and Clinical Dentistry* 2013; **4:**211-218.

Nackaerts O, Jacobs R, Quirynen M, Rober M, Sun Y and Teughels W. Replacement therapy for periodontitis: Pilot radiographic evaluation in a dog model. *Journal of Clinical Periodontology* 2008; **35**:1048-1052.

Näse L, Hatakka K, Savilahti E, *et al*. Effect of long-term consumption of a probiotic bacterium, *Lactobacillus rhamnosus GG*, in milk on dental caries and caries risk in children. *Caries Research* 2001; **35**:412-420.

Petersen P. The World Oral Health Report 2003: Continuous improvement of oral health in the 21st century - the approach of the WHO Global Oral Health Programme. *Community Dentist. Oral Epidemiology* 2003; **31**:3-23.

Quirynen M, Teughels W, Soete MD and Steenberghe DV. Topical antiseptics and antibiotics in the initial therapy of chronic adult periodontitis: Microbiological aspects. *Periodontology 2000* 2002; **28**:72-90.

Raff A and Hunt LC. Probiotics for periodontal health: A review of the literature. *Journal of Dental Hygiene* 2012; **86**:71-81.

Rafter J. Probiotics and colon cancer. *Best Practice & Research Clinical Gastroenterology* 2003; **17**:849-859.

Ravn I, Dige I, Meyer RL and Nyvad B. Colonization of the oral cavity by probiotic bacteria. *Caries Research* 2012; **46**:107-112.

Rawlings D. *Fermented Foods for Health*, Beverly: Fair Winds Press, 2013; 5-8.

Rhemrev GE, Timmerman MF, Veldkamp I, Van Winkelhoff AJ and Van der Velden U. Immediate effect of instrumentation on the subgingival microflora in deep inflamed pockets under strict plaque control. *Journal of Clinical Periodontology* 2006; **33**:42-48.

Riccia DND, Bizzini F, Perilli MG, *et al*. Anti-inflammatory effects of *Lactobacillus brevis* (CD2) on periodontal disease. *Oral Diseases* 2007; **13**:376-385.

Saier JMH and Mansour NM. Probiotics and prebiotics in human health. *Journal of Molecular Microbiology and Biotechnology* 2005; **10**:22-25.

Shimauchi H, Mayanagi G, Nakaya S, *et al*. Improvement of periodontal condition by probiotics with *Lactobacillus salivarius* WB21: a randomized, double-blind, placebo-controlled study. *Journal of Clinical Periodontology* 2008; **35**:897-905.

Shira D and Gorbach SL. Probiotics: Their role in the treatment and prevention of disease. *Expert Review of Anti-Infective Therapy* 2006; **4**:261-275.

Socransky SS and Haffajee AD. The bacterial etiology of destructive periodontal disease: Current concepts. *Journal of Periodontology* 1992; **63**:322-331.

Stamatova I and Meurman JH. Probiotics and periodontal disease. *Periodontology 2000* 2009; **51**:141-151.

Szkaradkiewicz AK, Stopa J and Karpinski TM. Effect of oral administration involving a probiotic strain of *Lactobacillus reuteri* on pro-inflammatory cytokine response in patients with chronic periodontitis. *Archivum Immunologiae et Therapiae Experimentalis* 2014; **62**:495-500.

Tekce M, Ince G, Gursoy H, *et al*. Clinical and microbiological effects of probiotic lozenges in the treatment of chronic periodontitis: A 1-year follow-up study. *Journal of Clinical Periodontology* 2015; **42**:363-372.

Teughels W, Durukan A, Ozcelik O, Pauwels M, Quirynen M and Haytac MC. Clinical and microbiological effects of *Lactobacillus reuteri* probiotics in the treatment of chronic periodontitis: a randomized placebo-controlled study. *Journal of Clinical Periodontology* 2013; **40**:1025-1035.

Teughels W, Kinder Haake S, Sliepen I, *et al*. Bacteria interfere with *A. actinomycetemcomitans* colonization. *Journal of Dental Research* 2007; **86**:611-616.

Teughels W, Loozen G and Quirynen M. Do probiotics offer opportunities to manipulate the periodontal oral microbiota? *Journal of Clinical Periodontology* 2011; **38**:159-177.

Teughels W, Newman MG, Coucke W, *et al.* Guiding periodontal pocket recolonization: A proof of concept. *Journal of Dental Research* 2007; **86**:1078-1082.

Toiviainen A, Jalasvuori H, Lahti E, *et al.* Impact of orally administered lozenges with *Lactobacillus rhamnosus GG* and *Bifidobacterium animalis subsp. lactis BB-12* on the number of salivary mutans streptococci, amount of plaque, gingival inflammation and the oral microbiome in healthy adults. *Clinical Oral Investigations* 2015; **19**:77-83.

Tripathi P, Dupres V, Beaussart A, *et al.* Deciphering the nanometer-scale organization and assembly of *Lactobacillus rhamnosus GG* pili using atomic force microscopy. *Journal of Surfaces and Colloids* 2012; **28**:2211-2216.

Turpin W, Humblot C, Thomas M and Guyot JP. Lactobacilli as multifaceted probiotics with poorly disclosed molecular mechanisms. *International Journal of Food Microbiology* 2010; **143**:87-102.

Turroni F, Ventura M, Buttó L, *et al.* Molecular dialogue between the human gut microbiota and the host: a *Lactobacillus* and *Bifidobacterium* perspective. *Cellular and Molecular Life Sciences* 2014; **71**:183-203.

Vaghef-Mehrabany E, Alipour B, Homayouni-Rad A, Sharif SK, Asghari-Jafarabadi M and Zavvari S. Probiotic supplementation improves inflammatory status in patients with rheumatoid arthritis. *Nutrition* 2014; **30**:430-435.

Verna EC and Lucak S. Use of probiotics in gastrointestinal disorders: What to recommend? *Therapeutic Advances in Gastroenterology* 2010; **3**:317-319.

Vicario M, Santos A, Violant D, Nart J and Giner L. Clinical changes in periodontal subjects with the probiotic *Lactobacillus reuteri Prodentis*: A preliminary randomized clinical trial. *Acta Odontologica Scandinavica* 2013; **71**:813-819.

Vivekananda MR, Vandana KL and Bhat KG. Effect of the probiotic *Lactobacilli reuteri (Prodentis)* in the management of periodontal disease: a preliminary randomized clinical trial. *Journal of Oral Microbiology* 2010; **2**:1-9.

Wade W. Has the use of molecular methods for the characterization of the human oral microbiome changed our understanding of the role of bacteria in the pathogenesis of periodontal disease?. *Journal of Clinical Periodontology* 2011; **38:**7-16.

World Health Organization. Fact Sheet Number 318. April 2012. *http://www.who.int/mediacentre/factsheets/fs318/en/* 2012; [accessed 11/12/2015].

World Heath Organization. Joint FAO/WHO Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food. *ftp://ftp.fao.org/es/esn/food/wgreport2.pdf* 2002; [accessed 11/12/2015].

Yli-knuuttila H, Snäll J, Kari K and Meurman JH. Colonization of *Lactobacillus rhamnosus GG* in the oral cavity. *Oral Microbiology and Immunology* 2006; **21**:129-131.