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Probiotic therapy for periodontal and peri-implant health – silver bullet or sham?

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REVIEW ARTICLE

Abstract

Probiotics are thought to be beneficial microbes that influence health-related outcomes through host immunomodulation and modulation of the bacteriome. Its reported success in the treatment of gastrointestinal disorders has led to further research on its potential applicability within the dental field due to similarities such as a polymicrobial aetiology and disease associated microbial-shifts. Although the literature is replete with studies demonstrating its efficacy, the use of probiotics in dentistry continues to polarise opinion. Here, we explore the evidence for probiotics and its effect on periodontal and peri-implant health. MEDLINE, EMBASE, and CENTRAL were systemically searched from June 2010 to June 2020 based on a formulated search strategy. Of 1,956 potentially relevant articles, we selected 27 double-blinded randomised clinical trials in the areas of gingivitis, periodontitis, residual pockets during supportive periodontal therapy, and peri-implant diseases, and reviewed their efficacy in these clinical situations. We observed substantial variation in treatment results and protocols between studies. Overall, the evidence for probiotic therapy for periodontal and peri-implant health appears unconvincing. The scarcity of trials with adequate power and follow-up precludes any meaningful clinical recommendations. Thus, the routine use of probiotics for these purposes are currently unsubstantiated. Further multi-centre trials encompassing a standardised investigation on the most promising strains and administration methods, with longer observation times are required to confirm the benefits of probiotic therapy for these applications.

Keywords: *Lactobacillus*, *Bifidobacterium*, gingivitis, periodontitis, peri-implant disease

1. Introduction

With an estimated prevalence of 11%, severe periodontitis is the sixth most prevalent condition in the world (Kassebaum *et al.*, 2014). The condition is associated with progressive destruction involving loss of periodontal attachment and supporting bone. This presents clinically as tooth migration or drifting, hypermobility, and tooth loss; before reaching the terminal stage of masticatory dysfunction which may compromise nutrition and general health (Tonetti *et al.*, 2017). Periodontitis and its precursor gingivitis exert a negative impact on the quality of life of individuals, with greater disease severity having a greater impact (Ferreira *et al.*, 2017). The sequelae of periodontitis also extend beyond the oral cavity. A growing body of evidence supports a relationship between periodontitis-associated pathobionts, their resulting inflammation, and systemic diseases (Bui *et al.*, 2019). In addition, one study reported that severe tooth loss and severe periodontitis accounted for 88% of global productivity losses due to dental diseases for 2015, and this represents an increase from 81% ($117 billion US dollars) compared to 2010 data reported by the same group (Listl *et al.*, 2015; Righolt *et al.*, 2018).

The periodontium consists of specialised tissues that support teeth, and these comprise of the gingiva (gums), periodontal ligament, cementum, and alveolar bone. Microbial community shifts lead to dysbiosis of the intra-oral environment, resulting in clinically defined conditions such as gingivitis, periodontitis peri-implant mucositis, and

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peri-implantitis (Lasserre *et al.*, 2018). According to the 2017 World Workshop on the Classification of Periodontal Diseases and Conditions, gingivitis is defined as ≥10% bleeding sites with probing pocket depths ≤3 mm; and periodontitis is defined as loss of periodontal tissue support due to inflammation (Chapple *et al.*, 2018; Papapanou *et al.*, 2018). Peri-implant mucositis is associated with increased pocket probing depth and inflammation, whereas peri-implantitis represents progression resulting in alveolar bone loss (Berglundh *et al.*, 2018). Today, the paradigm that periodontal and peri-implant diseases are initiated by specific bacteria has shifted to a polymicrobial community model of dysbiosis, wherein there are shifts in the overall community structure rather than the presence of putative causative pathogens (Belibasakis and Manoil, 2020; Ng *et al.*, 2021). Conversion to a dysbiotic microbial community in periodontitis is the result of an environment modified by the inflammatory response (Bartold and Van Dyke, 2017, 2019; Hajishengallis, 2014). As the inflammatory host response plays a key role in disease pathogenesis, the use of host modulators may improve treatment outcomes (Donos *et al.*, 2019). In the medical field, probiotics have been demonstrated to be beneficial in the treatment of gastrointestinal disorders, such as irritable bowel syndrome and peptic ulcer disease (Dale *et al.*, 2019; Zhang *et al.*, 2015). In particular, its use as a monotherapy in eradicating *Helicobacter pylori* has been proposed as an alternative due to increasing concerns on antibiotic resistance (Losurdo *et al.*, 2018).

With its potential usefulness increasingly verified, probiotics have also been investigated in a wide field of stomatological conditions such as *Candida*-induced denture stomatitis, oral mucositis in patients undergoing chemotherapy, the prevention of dental caries, and oral malodour (Gungor *et al.*, 2015; Ishikawa *et al.*, 2015; Sharma *et al.*, 2016; Wu *et al.*, 2015). Evidence on the benefit on the prevention and treatment of periodontal disease has been equivocal, with independent large scale multi-centre studies still required to confirm its efficacy (Donos *et al.*, 2019; Yanine *et al.*, 2013). This review explores the evidence for probiotics and their efficacy in the management of gingivitis, periodontitis, supportive periodontal therapy, and peri-implant diseases. Understanding their mode of action, principles of use, and efficacy may aid clinicians in the decision to use them in clinical practice. Current limitations and research gaps are identified, and this may serve as a guide for future research.

2. Applying probiotics for the treatment of periodontal diseases

What are probiotics and how do they work?

Probiotics are live microbes that confer a health benefit on the host when administered in adequate amounts (FAO, 2002). They may be part of functional foods, which are foods that reportedly promote human health and are historically based on live cultures or metabolites produced during fermentation (Stanton *et al.*, 2005). The main actions of probiotics are immunomodulation and microbiome modulation (Meurman, 2005). Medically, these beneficial microbes have demonstrated clinical benefits in the treatment of disorders and diseases such as rotavirus, inflammatory bowel disease, *Clostridium difficile* infection, eczema, and food allergies (Abraham and Quigley, 2017; Kechagia *et al.*, 2013; McFarland, 2006). However, probiotics used to modulate gut microbiota may not necessarily have the same application intra-orally. Reasons include their inability to colonise the mouth and compete with the resident oral microbiome for nutrients, or reduce the virulence expression of pathogens (Nissen *et al.*, 2014; Pham *et al.*, 2009).

The ideal properties necessary for a probiotic bacteria to be effective in the oral cavity include adherence to oral tissues, incorporation into a biofilm, production of antimicrobial substances, resistance to low pH values, and low acid production (Gungor *et al.*, 2015). However, significant diversity in adhesion capacity, influence on biofilm formation, and co-aggregation activity of different probiotic strains have been demonstrated (Gungor *et al.*, 2013; Jalasvuori *et al.*, 2012; Keller *et al.*, 2011). Thus, variation in these parameters according to specific strains and their response to environmental factors may account for strain-dependent biological effects. Current evidence suggests a limited effect on the protection against dental caries, but more promising outcomes on the preservation of gingival health (Jalasvuori *et al.*, 2012; Toiviainen *et al.*, 2015).

Probiotic species used in dentistry mostly belong to the genus *Lactobacillus* or *Bifidobacterium*, with not all of its species being endogenous to the oral cavity. Incorporation of beneficial bacteria has the potential to restore the ecological balance intra-orally, and proposed mechanisms of action include competitive exclusion, immune modulation, and production of antimicrobial substances (Stamatova and Meurman, 2009; Teughels *et al.*, 2011). While this has also been described as 'microbiome modulation' or 'guided pocket recolonisation' elsewhere (Teughels *et al.*, 2007; Zarco *et al.*, 2012), the phrase 'probiotic therapy' has been adopted for the purpose of this review.

Principles of probiotic therapy

Biofilms confer a protective effect on bacteria due to the presence of its protective extracellular matrix (Nadell *et al.*, 2015). On the other hand, reduction of indigenous microbes may improve colonisation and persistence of probiotics (Burton *et al.*, 2011). Therefore, it has been suggested that the disruption of biofilm should be performed before the administration of probiotics (Tekce *et al.*, 2015; Teughels

et al., 2013). It seems good practice that probiotic therapy should immediately begin upon completion of adequate debridement, although improved outcomes with probiotics as a monotherapy and three weeks after completion of debridment have been reported (Shimauchi *et al.*, 2008; Vicario *et al.*, 2013; Vivekananda *et al.*, 2010).

As some probiotic bacteria species may not be commensal in the oral cavity, probiotic therapy is not expected to permanently alter the oral microbiome, lasting for periods of two to three months after cessation if regularly consumed for at least three weeks (Tekce *et al.*, 2015; Wolf *et al.*, 1998). Probiotics should therefore be administered regularly for an appropriate duration and dose to be effective.

Antibiotics should not be administered concurently to prevent gene transfer of antibiotic resistance determinants present in probiotic bacteria (D'Aimmo *et al.*, 2007; Varankovich *et al.*, 2015). It has been suggested that probiotic bacteria be screened for antibiotic resistance, and where possible remove genetic resistance elements in the probiotic bacteria, as has been demonstrated with *Lactobacillus reuteri* DSM 17938 (Rosander *et al.*, 2008; Wong *et al.*, 2015).

3. Search methods for the identification of relevant studies and data extraction

The following electronic databases were used: MEDLINE (through Pubmed), EMBASE, and Cochrane Register of Controlled Trials (CENTRAL). A systematic search strategy was formulated to search for relevant literature for the subjects of gingivitis, periodontitis, residual pockets in supportive periodontal therapy, and peri-implant diseases (Figure 1). The relevant literature was searched over the last 10 years, from June 2010 to June 2020. Search results were imported into EndNote x8 (Thomson Reuters, New York City, NY, USA) and duplicates were removed. Titles and abstracts were independently screened by two reviewers (EN and JT). Full-text examination was carried out for studies with insufficient information from the titles or abstracts, and any disagreement between reviewers was resolved through discussion. Double-blinded randomised controlled trials in humans using probiotics in the above-mentioned clinical situations were included. No restrictions were placed on the type of probiotic or method of administration. The flowchart of the study selection process including excluded studies with reasons may be found in Supplementary Figure S1. For gingivitis, 457 records were identified. 25 were screened for full-text and six studies were included for review. For periodontitis, 818 records were identified. 30 were screened for full-text and 11 studies were included for review. For supportive periodontal therapy, 530 records were identified. Four were screened for full-text and three studies were included for review. For peri-implant disease, 151 records were identified. 10 were screened for full-text and seven studies were included for review. Data from individual studies was collated according to study name, study population, study design and evaluation period, intervention vs comparator, parameters measured, dose regimen, and outcomes. This was extracted and presented in tables by EN, and the accuracy of the data was verified independently by JT.

4. Gingivitis

Gingivitis is a reversible condition that develops following the accumulation of biofilm. Implicit in this transformation is the presence of inflammation, which alters the biofilm from a health-promoting symbiotic state to one of incipient dybiosis (Meyle and Chapple, 2015). Reinstitution of oral hygiene results in clinical health over a period of 3-10 days, with the re-establishment of the original bacterial flora (Loe *et al.*, 1965). The use of probiotics may be beneficial for cases with severe gingivitis that may take a longer time to resolve. In this review, six double-blinded randomised controlled trials which investigated the effect of probiotics on established adult gingivitis subjects were included (Table 1). Studies using an experimental gingivitis model were excluded, as this situation is not comparable to persistent gingival inflammation in a natural setting (Deinzer *et al.*, 2007). Clinical parameters (plaque and gingival index most commonly, bleeding on probing, pocket probing depth), microbiological parameters, and cytokines in gingival crevicular fluid were assessed.

Three studies (Alkaya *et al.*, 2017; Iniesta *et al.*, 2012; Montero *et al.*, 2017) found no significant clinical differences and three studies (Jagadeesh *et al.*, 2017; Keller *et al.*, 2018; Schlagenhauf *et al.*, 2016) observed significant reductions in bleeding on probing and gingival index when probiotics were used. Professional prophylaxis was performed before probiotic administration in three studies (Alkaya *et al.*, 2017; Iniesta *et al.*, 2012; Montero *et al.*, 2017), while only oral hygiene instructions were given for the remaining three studies (Jagadeesh *et al.*, 2017; Keller *et al.*, 2018; Schlagenhauf *et al.*, 2016). Adjunctive probiotics only had a statistical benefit in the studies where professional prophylaxis was not performed. Subjects with a diagnosis of moderate gingivitis or worse could benefit from greater resolution of inflammation when probiotics were used (Jagadeesh *et al.*, 2017; Keller *et al.*, 2018), although another study observed no significant differences in bleeding on probing or gingival index when comparing groups with varying severities of gingivitis (Alkaya *et al.*, 2017). A few studies investigated microbiological and biochemical parameters. Two studies assessed microbiological parameters with a quantitative PCR (Iniesta *et al.*, 2012; Montero *et al.*, 2017) and one used a microbiome approach (Keller *et al.*, 2018). Minimal differences were noted between test and control groups, with the exception of

Gingivitis
#1 ("Probiotics"[MeSH Terms])
#2 ("Lactobacillus"[MeSH Terms])
#3 ("Bifidobacterium"[MeSH Terms])
#4 ("Probiotic agent"[tw] OR "Probiotic tablet"[tw] OR "Probiotic lozenge"[tw] OR "Probiotic mouthwash"[tw] OR "Probiotic"[tw] OR "Probiotics"[tw] OR "Replacement therapy"[tw] OR "Bacterial interference"[tw] OR "Bacteriotherapy"[tw])
#5 (#1 OR #2 OR #3 OR #4)
#6 ("Gingivitis"[MeSH Terms])
#7 ("Gingival haemorrhage"[MeSH Terms])
#8 ("Gingivitis"[tw] OR "Gingival inflammation"[tw] OR "Gingival bleeding"[tw])
#9 (#6 OR #7 OR #8)
#10 (#6 AND #9)

Periodontitis
#1 ("Probiotics"[MeSH Terms])
#2 ("Lactobacillus"[MeSH Terms])
#3 ("Bifidobacterium"[MeSH Terms])
#4 ("Probiotic agent"[tw] OR "Probiotic tablet"[tw] OR "Probiotic lozenge"[tw] OR "Probiotic mouthwash"[tw] OR "Probiotic"[tw]
#5 (#1 OR #2 OR #3 OR #4)
#6 ("Periodontitis"[MeSH Terms])
#7 ("Periodontal diseases"[MeSH Terms])
#8 ("Periodontal pocket"[MeSH Terms])
#9 (#6 OR #7 OR #8)
#10 (#4 AND #9)

Supportive periodontal therapy
#1 ("Probiotics"[MeSH Terms])
#2 ("Lactobacillus"[MeSH Terms])
#3 ("Bifidobacterium"[MeSH Terms])
#4 ("Probiotic agent"[tw] OR "Probiotic tablet"[tw] OR "Probiotic lozenge"[tw] OR "Probiotic mouthwash"[tw] OR "Probiotic"[tw] OR "Probiotics"[tw] OR "Replacement therapy"[tw] OR "Bacterial interference"[tw] OR "Bacteriotherapy"[tw])
#5 (#1 OR #2 OR #3 OR #4)
#6 ("preventive dentistry"[tw] OR "dental prophylaxis"[tw] OR "oral prophylaxis"[tw] OR "dental scaling"[tw] OR "supportive periodontal care"[tw] OR "SPT"[tw] OR "Recall maintenance"[tw] OR "Supportive therapy"[tw] OR "Recall maintenance"[tw])
#7 (#5 AND #6)

Peri-implant disease
#1 ("Probiotics"[MeSH Terms])
#2 ("Lactobacillus"[MeSH Terms])
#3 ("Bifidobacterium"[MeSH Terms])
#5 ("Probiotic agent"[tw] OR "Probiotic tablet"[tw] OR "Probiotic lozenge"[tw] OR "Probiotic mouthwash"[tw] OR "Probiotic"[tw] OR "Probiotics"[tw] OR "Replacement therapy"[tw] OR "Bacterial interference"[tw] OR "Bacteriotherapy"[tw])
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 ("Peri-implantitis"[MeSH Terms])
#8 ("Dental implants"[MeSH Terms])
#9 ("Dental implantation, endosseous"[MeSH Terms])
#10 ("Peri-implant disease*"[tw] OR "Peri-implant infection*"[tw] OR "Implantitis"[tw] OR "Peri-implant mucositis"[tw] OR "Perimucositis"[tw] OR "Peri-implant"[tw] OR "implant*"[tw])
#11 (#7 OR #8 OR #9 OR #10)
#10 (#6 AND #11)

Figure 1. Detailed search strategy identifying relevant gingivitis, periodontitis, supportive periodontal therapy, and peri-implant disease studies.

Table 1. General characteristics of randomised placebo-controlled clinical trials in gingivitis subjects.[1]

Study	Study population	Study design and evaluation period	Professional prophylaxis, OHI, intervention	Parameters measured	Outcome
Alkaya *et al.* (2017)	40 non-smoking, systematically healthy patients with generalised gingivitis, mean age 25 years	Double-blinded, RCT, 8 weeks	Yes, OHI given. *Bacillus subtilis, Bacillus megaterium, Bacillus pumulus* as a toothpaste, mouthrinse, and toothbrush cleaner. Twice a day for eight weeks	Plaque and gingivitis index, PPD, BOP	No statistical difference between placebo and probiotic groups
Jagadeesh *et al.* (2017)	30 systemically healthy moderate-severe gingivitis subjects	Double-blinded, RCT, 3 weeks	No, OHI not given. *Bacillus coagulans* chewable tablets, three times a day for three months	BOP, gingival index, plaque index, glutathione peroxidase activity	Probiotics was associated with significant reduction in inflammation (reduced BOP, gingival index, glutathione peroxidase activity)
Iniesta *et al.* (2012)	40 mild-moderate gingivitis subjects, age 20-24	Double-blinded RCT, 4 weeks	Yes, OHI not given. *Lactobacillus reuteri* lozenges, once a day for four weeks	Plaque index, gingival index, microbiological	Reduction in *Porphyromonas gingivalis* in subgingival plaque at four weeks but not eight weeks. No clinical differences
Keller *et al.* (2018)	47 moderate gingivitis subjects, mean age 26 years	Double-blinded RCT, 10 weeks	No, OHI not given. *Lactobacillus rhamnosus, Lactobacillus curvatus* tablets. Twice a day for four weeks	BOP, plaque index, GCF flow, cytokines, microbiome analysis	Significant reduction in BOP and GCF, no other differences
Montero *et al.* (2017)	59 mild-moderate gingivitis subjects, mean age 32 years	Double-blinded RCT, 6 weeks	Yes, OHI given. *Lactobacillus plantarum, Lactobacillus brevis, Pediococcus acidilactici* lozenges, twice a day for six weeks	Gingival index, microbiological	No significant difference in gingival index, only *Tannerella forsythia* reduced in the test group
Schlagenhauf *et al.* (2016)	45 healthy women, mild-moderate pregnancy gingivitis, mean age 31 years	Double-blinded RCT, 7 weeks	No, OHI not given. *Lactobacillus reuteri* lozenges, twice a day for seven weeks	Gingival index, plaque index, TNF-α	Significantly lower mean gingival and plaque index, no difference for TNF-α at re-evaluation

[1] RCT = randomised controlled trial; PPD = probing pocket depth; GCF = gingival crevicular fluid; BOP = bleeding on probing; OHI = oral hygiene instructions; TNF = tumour necrosis factor.

a reduction in two periodontitis-associated pathobionts (*Porphyromonas gingivalis* and *Tannerella forsythia*) in subgingival plaque. Three studies analysed changes in inflammation with biochemical markers. While some reported significant resolution of inflammation (Jagadeesh *et al.*, 2017), others reported no differences (Keller *et al.*, 2018; Schlagenhauf *et al.*, 2016).

The included studies indicate that clinical improvement was inconsistent, and only studies not performing professional prophylaxis observed significant benefits. Furthermore, the observed clinical improvement correlated with a reduction in parameters of inflammation, such as bleeding on probing, gingival index, glutathione peroxidase activity, and gingival crevicular fluid flow, but did not show a correlation with

plaque index. Limited evidence suggests that severe forms of gingivitis could benefit from adjunctive probiotics.

5. Periodontitis

Although non-surgical periodontal therapy is effective, some periodontal sites may not improve significantly even after treatment (Hughes *et al.*, 2006; Preshaw *et al.*, 2013). This is partly due to anatomically inaccessible areas on the root surface and re-colonisation from non-dental sites, such as tonsillar crypts, dorsum of the tongue, and saliva into the periodontal pocket. Hence, probiotics may be a valid option in improving non-surgical outcomes. This review identified 11 studies that investigated the effects of probiotics as an adjunct to scaling and root planing in the management of periodontitis (Table 2). Patients were either untreated chronic periodontitis patients (Laleman *et al.*, 2015; Morales *et al.*, 2016, 2018; Penala *et al.*, 2016; Teughels *et al.*, 2011) or had not undergone periodontal treatment at least six months prior to the start of the study (Ince *et al.*, 2015; Invernici *et al.*, 2018; Pelekos *et al.*, 2019; Soares *et al.*, 2019; Tekce *et al.*, 2015; Vivekananda *et al.*, 2010).

Adjunctive probiotics to non-surgical periodontal therapy may be associated with statistically significant clinical improvements, as reported by seven studies. Among these studies, one observed significantly more probing depth reduction for moderate and deep sites (Teughels *et al.*, 2013), three studies only assessed mean probing depth values (Penala *et al.*, 2016; Soares *et al.*, 2019; Vivekananda *et al.*, 2010), and three studies found significance for both mean changes and moderate to deep sites (Ince *et al.*, 2015; Invernici *et al.*, 2018; Tekce *et al.*, 2015). Most studies investigating the role of probiotics on the microbiota have evaluated the proportions of specific periodontitis-associated pathobionts in the subgingival biofilm. Seven studies evaluated microbiological findings (Invernici *et al.*, 2018; Laleman *et al.*, 2015; Morales *et al.*, 2018; Penala *et al.*, 2016; Tekce *et al.*, 2015; Teughels *et al.*, 2013; Vivekananda *et al.*, 2010), and five studies demonstrated a significantly greater reduction in at least one periodontitis-associated pathobiont or total anaerobe counts. However, two studies reported no significant differences in microbiological parameters when comparing probiotics with a placebo (Morales *et al.*, 2018; Vivekananda *et al.*, 2010). The immunomodulatory activity of adjunctive probiotics was also investigated by two studies. Comparing gingival crevicular fluid cytokine levels at baseline to the end of probiotic administration, higher levels of the anti-inflammatory cytokine interleukin (IL)-10 and lower levels of the pro-inflammatory cytokines IL-1β and IL-8 levels were observed (Invernici *et al.*, 2018). Similarly, another study showed that treatment with probiotics led to a greater decrease in gingival crevicular fluid volume and matrix metalloproteinase-8 (MMP-8) concentrations, with a concomitant greater increase in tissue inhibitor of metalloproteinases-1 (TIMP-1) (Ince *et al.*, 2015).

At a glance, limited evidence suggests the potential of probiotic therapy in achieving further probing pocket depth reductions. This observation should be interpreted with caution in light of the findings of a recent meta-analysis, which observed the mean difference in probing pocket depth reduction between probiotics and placebo to be insignificant and of limited clinical relevance (Donos *et al.*, 2019). Biochemical markers suggest immunomodulation and a protective effect against periodontal breakdown, and this was consistent with clinical improvements in the respective studies. As microbiological parameters inconsistently correlated with clinical results, the production of antimicrobial compounds or enhancement of colonisation resistance by probiotics as a mode of action may not play a major role clinically. Further, the recent S3 Level Clinical Practice Guideline for the treatment of Stage I-III periodontitis states that no conclusions can as yet be drawn on the effectiveness of probiotics as adjuncts to subgingival instrummentation, leading to the suggestion not to use probiotics as an adjunct in this respect (recommendation 2.7) (Sanz *et al.*, 2020). The parameters taken under consideration for making this recommendation were the substantial heterogeneity in both the effect of the treatment and the different probiotic formulations, and the lack of multi-centred studies.

6. Residual pockets in supportive periodontal therapy

The benefits of supportive periodontal therapy (SPT) in maintaining periodontal stability and minimising tooth loss are well-documented (Axelsson *et al.*, 2004; Ng *et al.*, 2011). However, despite improvements after periodontal treatment and a well-organised supportive therapy, recurrent infection and progression can still occur (Matuliene *et al.*, 2008; Tonetti *et al.*, 1998). As residual pockets ≥5 mm after non-surgical therapy represent a risk factor for further disease progression and tooth loss, the aim of periodontal treatment should be closure or elimination of these sites (Graziani *et al.*, 2018). Three studies were included for this section (Table 3).

In a study using *L. reuteri* lozenges for three months as an intervention, significant clinical improvements (improvement in pocket probing depth, bleeding on probing, and probing attachment level) were reported and these effects persisted even after a wash out period of three months (Grusovin *et al.*, 2019). Further, the percentage of sites with ≥5 mm probing pocket depths improved in the probiotic group, although this difference was not significant when compared to a placebo. Another study observed a significant mean pocket probing depth reduction in favour of probiotics, and a more pronounced effect was noted for initially

Table 2. General characteristics of randomised placebo-controlled clinical trials in periodontitis subjects.[1]

Study	Study population	Study design and evaluation period	Intervention	Parameters measured	Outcome
Pelekos *et al.* (2019)	41 chronic periodontitis patients	Double-blinded, RCT, 6 months	SRP + probiotic *Lactobacillus reuteri* lozenges, twice a day for one month	PPD, CAL, BOP, PI	No additional benefits compared to non-surgical therapy alone
Soares *et al.* (2019)	60 Stage III and IV, grade B and C periodontitis subjects	Double-blinded RCT, 12-weeks	SRP + probiotic *L. reuteri, Lactobacillus salivarius, Lactobacillus acidophilus* sachet, once daily for three months	PPD, CAL, BOP, PI, GBI, halitosis parameters (Tanita device and organoleptic method)	Probiotics improved clinical and halitosis parameters more than placebo, and this was statistically significant
Morales *et al.* (2018)	47 chronic periodontitis patients	Double-blinded RCT, 9 months	SRP + probiotic *Lactobacillus rhamnosus* SP1 sachet, once a day for three months	PPD, supragingival plaque accumulation, BOP, CAL, subgingival plaque samples	Adjunctive use of probiotic and azithromycin did not have superior clinical or microbiological results
Invernici *et al.* (2018)	41 generalised chronic periodontitis patients	Double-blinded RCT, 3 months	SRP + probiotic *Bifidobacterium lactis* HN019 lozenges, twice daily for one month	PI, BOP, PPD, CAL, GR, GCF, subgingival plaque samples	Adjunctive probiotic significantly promotes additional clinical, microbiological, and immunological benefits
Penala *et al.* (2016)	32 chronic periodontitis patients	Double-blinded RCT, 3-months	SRP + probiotic *L. salivarius, L. reuteri*, subgingival delivery and probiotic mouthwash, twice daily for two weeks	PI, MGI, ORG, bleeding index, PPD, CAL, BANA, halitosis (organoleptic scores)	Adjunctive probiotics had significantly greater PPD reduction in moderate pockets and reduced oral malodour parameters. Significant reduction in BANA at one month
Morales *et al.* (2016)	28 chronic periodontitis patients	Double-blinded RCT, 12 months	SRP + probiotic *L. rhamnosus* SP1 sachet, once a day for three months	Plaque accumulation, BOP, PPDs, CAL	Reductions in percentage of sites and number of teeth with PPD ≥5 mm were greater in probiotic group, but not statistically significant
Tekce *et al.* (2015)	40 chronic periodontitis patients	Double-blinded RCT, 360 days	SRP + probiotic *L. reuteri* lozenges, twice a day for three weeks	PI, GI, BOP, PPD, subgingival plaque samples	Probiotics significantly improved treatment outcomes and delayed re-colonisation. Significantly decreased proportions of obligate anaerobes.
Laleman *et al.* (2015)	48 moderate-severe chronic periodontitis patients	Double-blinded RCT, 24 weeks	SRP + probiotic *Streptococcus oralis* KJ3*, Streptococcus uberis* KJ2*, Streptococcus rattus* JH145 lozenges, twice a day for 12 weeks	PPD, BOP, CAL, GI, PI, micro-biological sampling (supra-gingival and subgingival plaque, saliva, tongue)	No differences compared to placebo except for PI
Ince *et al.* (2015)	30 chronic periodontitis patients	Double-blinded RCT, 360 days	SRP + probiotic *L. reuteri* lozenges, twice a day for three weeks	PI, GI, BOP, PPD, attachment gain, GCF (MMP-8, TIMP-1)	Significantly improved clinical parameters up to day 360 and GCF biomarkers up to day 180
Teughels *et al.* (2013)	30 chronic periodontitis patients, moderate-severe	Double-blinded RCT, 12 weeks	SRP + probiotic *L. reuteri* lozenges, twice a day for 12 weeks	PPD, recession, BOP, plaque percentage, microbiological sampling (saliva, supragingival and subgingival plaque)	Significant improvement in PPD, CAL, plaque scores, no significant differences in microbiological outcomes between treatment groups other than *Porphyromonas gingivalis*
Vivekananda *et al.* (2010)	30 chronic periodontitis patients	Double-blinded RCT, split-mouth, 42 days	SRP + probiotic *L. reuteri* lozenges, twice a day for three weeks	PPD, CAL, PI, GI, GBI, microbiological samples	Significant improvement in all clinical parameters. No significant effects on microbiological parameters

[1] BANA = N-benzoyl-DL-arginine-napthylamide; BOP = bleeding on probing; CAL = clinical attachment level; GCF = gingival crevicular fluid; GI = gingival index; GBI = gingival bleeding index; GR = gingival recession; MGI =modified gingival index; MMP-8 = matrix metalloproteinase-8; ORG = organoleptic score; PI = plaque index; PPD = probing pocket depth; RCT = randomised controlled trial; SRP = scaling and root planing, TIMP-1 = tissue inhibitor of metalloproteinases-1.

Table 3. Studies investigating the adjunctive use of probiotics in residual pockets during supportive periodontal therapy.[1]

Study	Study population	Study design and evaluation period	Intervention	Parameters measured	Outcome
Iwasaki *et al.* (2016)	36 SPT subjects	Double-blinded RCT, 4 months	Re-instrumentation, heat-killed *Lactobacillus plantarum* L-137 capsules, daily for three months	Gingival index, plaque index, BOP, PPD	Significantly greater reduction in PPD, more pronounced in teeth/sites with PPD ≥4 mm
Grusovin *et al.* (2019)	20 SPT subjects, Stage III/IV grade C	Double-blinded RCT, 12 months	Re-instrumentation, *Lactobacillus reuteri* lozenges, twice a day for three months	Tooth survival, PPD, PAL, BOP	Statistical improvement in PPD, PAL, BOP with probiotics
Laleman *et al.* (2020)	39 SPT subjects, Stage III/IV grade B	Double-blinded, RCT, 6 months	Re-instrumentation + *L. reuteri* drops, *L. reuteri* lozenges, twice a day for three months	PPD, CAL, full mouth plaque and bleeding scores, microbiological	Adjunctive probiotic lozenges significantly improved PPD reduction, with no impact on periodontal pathogens

[1] RCT = randomised controlled trial; PPD = probing pocket depth; GCF = gingival crevicular fluid; BOP = bleeding on probing; PAL = probing attachment level.

deeper pockets (Laleman *et al.*, 2020). Notably, the clinical improvement was not accompanied by significant microbiological changes, suggesting that the primary beneficial effect of probiotics may not be bacteriome modulation. However, despite the improvement in moderate to deep pockets, the authors noted that many residual sites could still be classified as being in need of surgery. Heat-killed *Lactobacillus plantarum* L-137 (HK L-137) has also been used in patients undergoing supportive periodontal therapy to achieve further reduction of residual (≥4 mm) probing depths (Iwasaki *et al.*, 2016).

These studies highlight that although adjunctive probiotics could be effective in achieving further pocket reduction, this treatment approach cannot replace surgery entirely. They may have a role in limiting the extent of surgery required, or achieving stability in populations not suitable or reluctant for surgery. However, the aetiology of a residual pocket should be considered and sites that do not respond to a second session of non-surgical treatment may require surgical intervention (Tomasi *et al.*, 2008).

7. Peri-implant diseases

The prevalence of peri-implant disease has been reported by two studies to occur at a rate of 41.6-48% for peri-implant mucositis, and 14-16% for peri-implantitis (Roos-Jansaker *et al.*, 2006; Schwarz *et al.*, 2017). Although sharing the aetiology of biofilm accumulation, peri-implant soft tissues develop a stronger inflammatory response than natural teeth and do not return to baseline even after three weeks of resumed plaque control (Salvi *et al.*, 2012). Further, treatment of peri-implant mucositis does not always result in complete resolution in all cases (Heitz-Mayfield *et al.*, 2011). Therefore, it would be advantageous if probiotics can enhance resolution in at least peri-implant mucositis.

This review identified seven studies assessing the effects of probiotics as an adjunct to biofilm disruption in the treatment of peri-implant mucositis and peri-implantitis (Table 4). Six studies included peri-implant mucositis subjects, and all of these studies performed biofilm disruption prior to administration of probiotics. Approaches to biofilm disruption included polishing, photodynamic therapy, ultrasonic instruments, or titanium curettes. Most studies used *L. reuteri* while one study used a combination of *L. plantarum* and *Lactobacillus brevis* (Mongardini *et al.*, 2017). In addition to probiotic lozenges or tablets, two studies delivered the probiotic subgingivally after biofilm disruption (Hallstrom *et al.*, 2016; Laleman *et al.*, 2020; Mongardini *et al.*, 2017).

In the treatment of peri-implant mucositis, adjunctive use of probiotics was associated with significant clinical improvements in half of the included studies. These improvements comprised of reductions in plaque index, pocket probing depth, bleeding on probing, and gingival crevicular volume (Alqahtani *et al.*, 2019; Flichy-Fernandez *et al.*, 2015; Galofre *et al.*, 2018). However, the effect of probiotics had a limited effect on the subgingival microbiota

Table 4. Characteristics of included studies investigating the adjunctive effects of probiotics in peri-implant disease.[1]

Study	Study population	Study design and evaluation period	Intervention	Parameters measured (implant level)	Outcome
Flichy-Fernandez *et al.* (2015)	22 subjects with healthy implants, 12 with peri-implant mucositis	Double-blinded cross-over study (6-month wash out), 7 months	Biofilm disruption (polishing), *Lactobacillus reuteri* lozenge, daily for one month	Plaque index, gingival index, PPD, bio-chemical (GCF volume, IL-1β, IL-6, IL-8)	Significantly Improved clinical parameters and decreased cytokine levels in both groups with probiotics
Hallstrom *et al.* (2016)	49 subjects with peri-implant mucositis	Double-blinded RCT, 6.5 months	Biofilm disruption (titanium curettes), *L. reuteri* droplet after debridement, lozenges, twice a day for three months	PPD, plaque index, BOP, microbiological, biochemical	Probiotics did not provide additional benefits for any parameter measured
Mongardini *et al.* (2017)	20 subjects with experimentally induced peri-implant mucositis	Double-blinded crossover study (4-week wash out), 6 weeks	Biofilm disruption (prophylaxis, PDT), subgingival application of probiotic *Lactobacillus. plantarum* and *Lactobacillus brevis,* lozenge, daily for 14 days	Plaque index, BOP	Professional prophylaxis + PDT was effective in reducing number of BOP positive sites, probiotics had no added effect
Galofre *et al.* (2018)	22 subjects with peri-implant mucositis and 22 with peri-implantitis	Triple-blinded RCT, 3 months	Biofilm disruption (ultrasonic and titanium curettes), *L. reuteri* lozenge, daily for one month	PPD, plaque index, BOP, microbiological	Probiotic lozenges significantly improved clinical outcomes although the effect on microbes was limited
Alqahtani *et al.* (2019)	40 smokers and 40 non-smokers with peri-implant mucositis	Double-blinded RCT, 6 months	Biofilm disruption (ultrasonic), *L. reuteri* lozenges, twice a day for 3 weeks	PPD, plaque index, BOP	Adjunctive probiotics significantly reduced BOP in the non-smoker group at 3 but not 6 months
Pena *et al.* (2019)	50 subjects with peri-implant mucositis	Triple-blinded RCT, 3 months	Mechanical debridement (ultrasonic), 0.12% chlorhexidine rinse 2 weeks, *L. reuteri* tablet, daily for one month	Plaque index, BOP, microbiological	Administration of probiotic did not provide additional clinical or microbiological benefits
Laleman *et al.* (2020)	19 subjects with peri-implantitis	Double-blinded RCT, 6 months	Biofilm disruption (ultrasonic and titanium curettes, air polishing), *L. reuteri* drops after debridement and lozenges, twice a day for three months	BOP, PPD, plaque index, sulcular bleeding index, microbiological	No adjunctive effects with the use of probiotics on clinical or microbiological parameters

[1] RCT = randomised controlled trial; PPD = probing pocket depth; GCF = gingival crevicular fluid; BOP = bleeding on probing; PDT = photodynamic therapy; IL = interleukin.

(Galofre *et al.*, 2018; Hallstrom *et al.*, 2016; Pena *et al.*, 2019). Two studies reported biochemical parameters, with one study reporting a decrease in pro-inflammatory cytokines (Flichy-Fernandez *et al.*, 2015) and another reporting no significant intergroup differences (Hallstrom *et al.*, 2016). These observations corresponded with the clinical findings in the earlier mentioned studies. Hence, probiotics could be used as an adjunct in the treatment of peri-implant mucositis and its prevention, although the strength of evidence is equivocal.

The adjunctive effect of probiotics in the management of peri-implantitis was investigated by two studies. One study observed improvements in bleeding on probing and probing pocket depth, but no improvement in microbial parameters (Galofre *et al.*, 2018). Another study showed that probiotics had no adjunctive effects on both clinical or microbiological parameters (Laleman *et al.*, 2020). These two studies provide limited evidence suggesting that adjunctive probiotics are not indicated in the management of peri-implantitis, although they may result in short term improvements of inflammation.

8. Conclusions

Clinical implications

Although several randomised controlled trials have been conducted, significant variation in treatment results, heterogenous methodology, small study numbers, and insufficient observation times pose an interpretational challenge. Notably, studies observing clinical benefits with adjunctive probiotic therapy consistently report a lack of significant microbiological changes concomitant with clinical improvement, suggesting that the immunomodulatory effect on the host rather than direct modulation of the microbiome is more important. Indeed, many probiotic effects are mediated through immune regulation, and probiotic bacteria have been shown to enhance humoral immune responses, stimulate non-specific host resistance to pathogens, and aid in their immune elimination (Isolauri *et al.*, 2001). It is also clear that current evidence is insufficient to make any clinical recommendations.

Limitations and concerns

Probiotics are administered in the form of mouth rinses, satchets, tablets, or lozenges. We observed that tablets or lozenges for dissolution in the mouth are more commonly used in randomised controlled trials. One concern in the manufacturing process is that compression during tableting and interaction with other ingredients that increase water activity may reduce the overall viability of the probiotics in the tablet (Dianawati *et al.*, 2016; Muller *et al.*, 2014). Hence, the amount of viable probiotic in products should be evaluated. The accessibility of probiotics to subgingival biofilm could also be a limitation (Becirovic *et al.*, 2018). For these reasons, the amount of viable probiotic that colonises the intended area and the quantity required for the probiotic to be effective remain unknown.

Another observation from included randomised controlled trials is the heterogenous administration protocol for probiotics. The optimal dosing period, minimum effective dose, and most effective vehicle are still undetermined. Further, studies report benefits largely based on clinical findings alone, and it is thus unclear if the probiotic succeeded in colonising the site.

While there have been no adverse effects reported in systemically healthy patients with periodontal disease (Laleman *et al.*, 2015; Morales *et al.*, 2016, 2018; Teughels *et al.*, 2013), the safety profile has not been sufficiently evaluated in immunocompromised patients, or in patients suffering from systemic diseases. It should be cautioned that the administration of viable probiotic bacteria has resulted in harmful effects in individuals with organ failure, systemic compromise, or mucosal barrier dysfunction (Besselink *et al.*, 2009). Other areas of concern are the transfer of antibiotic resistance genes to other organisms in the bacterial community, and the presence of unlabeled microorganisms in retail products (Sanders *et al.*, 2010). Probiotics are usually regulated as food supplements, thus their regulation is not as stringent as pharmaceutical drugs which have specific disease-related health claims (De Simone, 2019).

Future direction and research

Current evidence from clinical trials is inconsistent. The effect of probiotics on clinical, periodontal, and biochemical parameters differs depending on the strains used and endpoints analysed. Heterogeneity between strains and the administration protocol also mean that the beneficial effects of one strain cannot be generalised. Future studies should standardise study design, reported parameters, and utilise appropriate forms of administration. The effect of bacteriome modulation is also not well-defined, and this could be due to limitations of techniques in the pre-microbiome era. The development of next-generation sequencing approaches such as 16S RNA analysis may provide better evidence on how probiotic therapy can modulate the dysbiotic oral microbial community towards health. The optimal strain for the treatment of these different periodontal conditions also remains to be identified. Dose-ranging studies are also required to determine the appropriate dosing regimen as commercially available products may not contain the correct strains or doses.

Recently, an *in vitro* study demonstrated that both heat-killed *L. reuteri* cells or its cell-free supernatant had similar

antibacterial activity against *P. gingivalis* as live cells, leading the authors to conclude that the antimicrobial and immunomodulatory effects do not depend on cell viability (Geraldo *et al.*, 2020). It is suggested that non-viable probiotics may retain immunomodulatory effects via immune system recognition of specific bacterial components (Adams, 2010). The term 'paraprobiotic' has previously been proposed for this application, indicating the use of inactivated microbial cells to confer a health benefit on the consumer (Taverniti and Guglielmetti, 2011). In support of this concept, other probiotics, such as heat-killed *L. plantarum* are also able to maintain their immunomodulatory activity, as demonstrated by enhanced Th1-type immune responses in mice (Murosaki *et al.*, 1998). In a study of healthy adults, the same group demonstrated improved acquired immunity with daily intake of heat-killed *L. plantarum* (Hirose *et al.*, 2006). Bacterial cell-free probiotics may also exert biogenic effects, and these are due to metabolically active products produced by probiotic bacteria, independent of bacterial colonisation and cell viability (Ohshima *et al.*, 2019). The utilisation of microbial metabolites has also been termed 'postbiotics' (Ren *et al.*, 2018). While the antimicrobial activity of *L. reuteri* has typically been attributed to the production of organic acids, hydrogen peroxide, or bacteriocins (Kang *et al.*, 2011), there has been growing research on the contribution of biogenic substances. In agreement with the study by Geraldo et al, supernatants derived from a *L. reuteri* strain missing genes encoding antibacterial compounds have also demonstrated inhibitory activity on the growth and biofilm formation of oral pathogenic bacteria (Yang *et al.*, 2021). Further, by the application of specific enzymes, the authors were able to demonstrate that the antibacterial substances produced originated from carbohydrates or fatty acid metabolites. Therefore, the application of non-viable strains or their active metabolites could lead to the development of safer and more stable products and eliminate the difficulty of biofilm colonisation.

In conclusion, this study focused on the efficacy of oral probiotics in the management of periodontal and peri-implant conditions. From a clinical standpoint, the studies reviewed do not provide convincing evidence for the routine use of probiotic therapy for these applications. Current limitations and research gaps are identified, and this may serve as a guide for further quality research in this burgeoning field.

Supplementary material

Supplementary material can be found online at https://doi.org/10.3920/BM2020.0182.

Figure S1. Flowcharts of the study process.

Conflict of interest

The authors declare that they have no competing interests. No funding was received for this work.

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