Review Article

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Probiotics in Periodontal Therapy

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ABSTRACT

Background: Oral diseases are the most common type of infections occurring in humans. The development of bacterial resistance to the broad spectrum antibiotics has raised the possibility of a return to the pre-antibiotic dark ages. Time has approached to shift the paradigm of treatment from elimination of specific bacteria to alteration of bacterial ecology by probiotics. Probiotics are live micro-organisms that when administered in adequate amounts confer health benefits upon the host. A few conventional foods containing probiotics are yogurt, fermented and unfermented milk, soy beverages etc. Most often, they come from two groups of bacteria, *Lactobacillus or Bifidobacterium*. This article reviews all the aspects of probiotics used in periodontal therapy.

Keywords: Probiotics, Periodontitis, Lactobacilli, Bifidobacterium.

INTRODUCTION

Periodontal diseases contribute to the major part of the burden of oral diseases. Gram negative bacteria are considered as most harmful to dental supporting tissues. Periodontal diseases lead to destruction of periodontal ligament and the underlying alveolar bone.[1] Scaling and root planing (SRP) accompanied by oral hygiene procedures have served as a gold standard of periodontal therapy.[2] Surgical therapy for treatment of periodontal disease is another most common treatment modality apart form SRP. Taking into account the two major treatment strategies for periodontal disease viz, elimination of specific pathogens and suppression of destructive host response, the probiotic approach may add some value in achieving these treatment goals.

PROBIOTICS

The use of microorganism to promote health is very ancient and can even be traced back to the classical Roman literature where food fermented with microorganisms was used as a therapeutic agent. There is a long tradition, particularly in parts of Europe and Asia, of ingesting microbes or food products that affect the intestinal microbiota in ways that are believed to provide beneficial health effects, i.e. intake of probiotics and prebiotics.[3]

Ilya Metchnikov, Pasteur Institute, Paris, gave the concept of beneficial for health micro-organisms in early 20th century.[4] The term 'probiotic' was introduced in 1965 by Lilly & Stillwell as substances produced by microorganisms which promote the growth of other microorganisms.[5] The term "probiotics" is derived from the Greek word, meaning "for life."[6] The First probiotic species to be introduced in research was Lactobacillus acidophilus by Hull and followed by Bifidobacteriumbifidum by Holcombh *et al* [7]. It is currently used to name bacteria with beneficial effects for humans and animals.

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Probiotics mostly belong to two genus *Lactobacillus* and *Bifidobacterium.* The genus Lactobacillus includes *L. acidophilus, L. johnsonii, L. casei, L. rhamnosus, L. gasseri* & *L. reuteri*. Similarly, the Bifidobacterium strains include *B. bifidum, B. longum* & *B. infantis*. A probiotic may be made out of a single bacterial strain or it may be a consortium as well[2]. These bacteria are generally regarded as safe because they can reside in the human body without causing any harm, Lactobacilli found in raw milk and fermented dairy products such as cheese, yoghurt and fermented milk are ubiquitous in the diet and are found in the gastrointestinal tract soon after birth[8].

Furthermore, certain strains of *Aspergillus, Propionibacterium, Saccharomyces, Streptococcus, Enterococcus* and non-pathogenic strain of *E.coli, Clostridium butyricum,* are among others which have demonstrated probiotics properties.[9,10]

MECHANISM OF ACTION OF PROBIOTICS

Probiotics have been proposed to act through various mechanisms (*Koll Klais et al.* 2006):[11]

Direct interaction: Probiotics have the capability to interact directly with the disease-causing microbes, making it harder for them to cause the disease.

- Probiotics either by inducing host cells to produce peptides or by directly releasing peptides interfere with pathogens, and prevent epithelial invasion. Defensins (hBD protein) and cathelicidins are the antimicrobial peptides expressed constitutively by the intestinal epithelial cells and display antimicrobial activity against a wide variety of bacteria, fungi and some viruses. E.g: *E. coli* strain DSM 17252 G2 (one of the three Symbioflor 2 genotype strains) and several *Lactobacilli* species have shown to express certain defensins.

- Probiotics have been shown to suppress pathogen growth through the release of a variety of antimicrobial factors like defensins, bacteriocins, hydrogen peroxide, nitric oxide, and short chain fatty acids (SCFA),such as lactic and acetic acids, which reduce the pH of the lumen.

Competitive exclusion:

- The beneficial microbes directly compete with the disease by developing microbes for nutrition. Probiotic bacteria compete with invading pathogens for binding sites to epithelial cells and the overlying mucus layer in a strain specific manner. It acts directly or indirectly by producing protein that blocks adherence.

Interference with Quorum Sensing

Bacteria communicate with each other as well as with their surrounding environment through chemical signalling molecules called autoinducers. This phenomenon is called quorum sensing.The use of this cell-to-cell signaling mechanism facilitates the enteric microbes allowing them to successfully colonize and start infection in their host. E.g: *Lactobacillus acidophilus* secretes a molecule that inhibits the quorum sensing signalling or directly interact with bacterial transcription of E. coli O157 gene, involved in colonization and thus, bacterial toxicity is opposed.

Modulation of host immune response:

The interaction of probiotics and strengthening of the immune system.

- *L. casei* down-regulates the transcription of a number of genes encoding pro-inflammatory effectors such as cytokines and chemokines and adherence molecules induced by invasive S. flexneri. This results in an anti-inflammatory effect that appeared to be mediated by the inhibition of the NF-κB pathway, particularly through stabilization of I-κBα.

- Probiotics are capable of influencing epithelial barrier function either by decreasing apoptosis of intestinal cells or increased mucin production. E.g: Lactobacillus rhamnosus GG prevents cytokine-induced apoptosis by inhibiting tumor necrosis factor (TNF) and also prevents inflammation and programmed cell death of the lining intestinal epithelial cells. It exerts mitogenic effects and enhances mucosal regeneration.

Methods of Administration:

The different methods used to administer probiotics are:[7]

- Powder
- Lozenge
- Gel
- Straw, Tablet.
- Cheese
- Rinse solution
- Capsule, Liquid
- Yogurt drink

In terms of microbial preparation and functional food, probiotics are provided in products in four ways:

1. Culture concentrate added to beverage (e.g: Fruit juices)
2. Innoculated into probiotic fibers
3. Innoculated into milk based food (Dairy products,Yoghurt, biodrink, kefir)
4. As dietary supplements (Non-dairy products such as tablets, gelatin, capsule)[2]

PROPERTIES OF PROBIOTICS

To be considered for use as probiotic following criteria needs to be fulfilled.[1,12]

1. It should be capable of exerting a beneficial effect on the host animal, e.g. increased growth or resistance to disease.
2. It should be of human origin.
3. It should have high cell viability.
4. It should be non-pathogenic and non-toxic.
5. It should be able to interact or to send signals to immune cells.
6. It should have capacity to influence local metabolic activity
7. It should be capable of surviving and metabolizing in the gut environment e.g. resistance to low pH and organic acids.
8. It should be stable and capable of remaining viable for periods under storage and field conditions.

PROBIOTICS IN GENERAL MEDICINE

Probiotics are available in foods and dietary supplements. Examples of foods containing probiotics are yogurt, milk and soy beverages. In probiotic foods and supplements, the bacteria may have been present originally or added during preparation. Probiotics have proven to be effective in the treatment of several systemic and infectious diseases such as acute diarrhoea, Crohn's disease, cancer, immunodepressive states, inadequate lactase digestion, hyperlipidemia, liver diseases, infections with Helicobacter pylori, genitourinary tract infections and others.[13]

PROBIOTICS IN ORAL HEALTH

Prevention of caries

Clinical studies have indicated that lactobacilli and bifidobacteria have some promise for prevention of caries. Lactobacillus gasseri ingested in dairy products reduced salivary Mutans streptococcal counts in adults and protected against caries in children.[14-15] Lactobacillus reuteri when ingested in the form of yoghurt[16] tablet,[17] chewing gum[18] or as a lozenge,[19] significantly reduced the count of M. streptococci in saliva. Short-term consumption of yoghurt[20] or ice cream[21] containing bifidobacterium species resulted in a significant reduction in salivary mutans streptococci, but not in lactobacilli.

PROBIOTICS IN PERIODONTAL DISEASE

Plaque initiates periodontal disease, and probiotics have proved to inhibit plaque formation. The mode of action is by lowering the salivary PH, so that bacteria associated with plaque formation cannot form plaque. Probiotics are also known to produce antioxidants, which in turn prevent plaque formation by neutralizing the free electrons which are needed for the mineralization of plaque.[1]

GINGIVITIS

Studies have been conducted for the effectiveness of probiotics in the treatment of gingivitis. Certain studies have revealed that probiotics not only significantly reduced plaque accumulation but also showed a significant reduction in the gingival index scores. Probiotics act by neutralizing the pH hence preventing the formation of organized dental plaque. The antioxidants produced by the probiotics further prevent plaque accumulation by the neutralization of free electrons which are essential for the mineral formation.

Probiotic strains reduce the presence of cytokines in gingival crevicular fluid and decrease bleeding on probing Noel Kelsch and Gregory Kutzman found that the use of dental probiotic had a profound effect on the oral health of patients, showing a 47% reduction in plaque accumulation. The scientists observed decreased levels of plaque index and a lower incidence of gingivitis. The probiotic L. reuteri prodentis has been shown to inhibit plaque and have anti-inflammatory and anti-microbial effects that could make it useful in maintenance of healthy teeth and gums.[22] *Krasse et al.* observed a decrease in amount of bacterial plaque as well as a reduction in the gingival index following the use of chewing gums incorporated with Lactobacillus reuteri for a period of 14 days.[22] A probiotic mouth rinse containing Weissella. Cibaria was found to produce 20% reduction in plaque score as well as inhibition of VSC production both in vitro and in vivo.

Probiotic mouthwashes have been demonstrated to cause a significant reduction in plaque formation and gingivitis in 6-8 years old children *(Harini and Anegundi 2010).*[23] Oral probiotics used in combination with xylitol are highly beneficial after gum treatments. These are of great benefit when used at bedtime by increasing the salivary flow.[24]

A study conducted to test the effect of probiotics in patients with chronic gingivitis, found that lozenges containing the microbes decreased the oral bacteria 90% more than the traditional treatments.[25]

PERIODONTITIS

Hillman and Socransky (1985)[26] reported that *Streptococcus oralis* and *Streptococcus uber* inhibits the growth of pathogens They are indicators of healthy periodontium. When these bacteria are absent from sites in the periodontal tissues, those sites become more prone to periodontal disease. *Teghels et al.* (2007)[13] was the first to assess the role of commensal microflora in the modulation of periodontal pocket recolonization. They conducted a study based on the repeated applications of *Streptococcus sanguinis*, *Streptococcus mitis,* and *Streptococcus salivarius* after root planning and observed a significant reduction of anaerobic species and black pigmented bacteria. It was further hypothesized that this concept of guided pocket recolonization (GPR) may be a valuable option in the management of periodontitis.

Lactobacilli associated with periodontal health were found to inhibit the growth of certain periodontal pathogens. The inhibitory activity of lactobacilli against periodontal pathogens was found to be related to their production of acid, not hydrogen peroxide or bacteriocin.[3] Studies have shown that ingested lactobacilli colonized only transiently and disappeared soon after the colonization of the probiotic ended.[19-21] The colonization of the gut by probiotics may have beneficial systemic effects enabling these organisms to provide protection against diseases at distant sites.[27] For example, It was proposed that they may reduce the levels of these pathogens on the tongue which constitutes a major reservoir for colonization of plaque and hence, indirectly reduce the colonisation of subgingival plaque by periodontal pathogens[3], as supragingival and subgingival plaque are intimately connected, and any changes in supragingival plaque will influence the future composition of subgingival plaque.

Volozhin et al. (2003)[28] showed that a collagenous periodontal dressing containing L.casei can significantly reduce the number of periodontal pathogens. This might be due to the inhibitory effect of probiotics on the growth of pathogens thus altering the composition of oral biofilm. Further, according to Narva et al. (2004),[29] during the fermentation process in milk, Lactobacillus helveticus produces short peptides that act on osteoblasts and increase their activity in bone formation. These bioactive peptides could thereby contribute in reducing bone resorption associated with periodontitis.

Ishikawa et al (2003)[30] observed in vitro inhibition of *Porphyromonas gingivalis*, *Prevotella intermedium*, and *Prevotella nigrescens* by daily ingestion of *L. salivarius* in tablet form. Similarly, *Koll-Klais et al* (2005)[11] isolated *L. gasseri* strains from periodontally healthy subjects and found them efficient at inhibiting the growth of *Aggregatibacter actinomycetemcommitans.*

In another study, *Shimauchi et al.* (2008)[31] demonstrated that the oral administration of a

tablet containing *L.salivarius* WB21 decreased plaque index significantly and pocket probing depth markedly in smokers and reduced salivary lactoferrin at the end of 8-week trial. They concluded that a probiotic intervention could be a useful tool for the treatment of inflammation and the clinical symptoms of periodontitis. *Shimazaki et al.* (2008)[32] in an epidemiological study found that an increased intake of lactic acid/fermented foods was associated significantly with lesser mean pocket depth and attachment loss.

Staab et al. (2009)[33] observed reduction in activity of MMP-3 and elastase enzymes in subjects with plaque-induced gingivitis after consuming probiotic milk containing *Lactobacillus casei* species for a period of 8 weeks. *Twetman et al.* (2009)[34] used L. reuteri-containing chewing gum in 42 healthy patients and assessed its effects on crevicular fluid volume, cytokine(interleukin-1β, interleukin-6, interleukin-10, and TNF-α) levels, and bleeding on probing. Crevicular fluid volume, as well as TNF-α and interleukin-8 levels, andbleeding were significantly reduced.

Acilact a Russian probiotic preparation of *L. acidophilus* in a tablet form, has claimed to improve both clinical and microbiological parameters in periodontitis patients. *Acilact* was first clinically tested by *Pozharitskaia et al* (1994)[35] and they found improved clinical parameters in periodontitis patients. *Grudiamov et al* (2002)[36] reported that the use of probiotics when given orally as tablets Azilact and bifidumbacterin showed normalization of microbiota and reduction of signs of gingivitis and Periodontitis.

Matsuka et al. (2006)[37] reported a decrease in bleeding on probing and a decrease in P.gingivalis count in subjects who consumed tablets containing *Lactobacillus salivaris* T1 2711. *Riccia et al.* (2007)[27] analyzed the anti-inflammatory effects of *Lactobacillus brevis* extracts on periodontitis patients and investigated the involved mechanisms in vitro on activated macrophages. The treatment led to the total disappearance or amelioration of all analyzed clinical parameters in all patients and suggested that the anti-inflammatory effects of *L. brevis* could be attributed to the presence of Arginine deiminase which prevented nitric oxide generation.

Hojo et al. (2007)[38] suggested that *bifidobacterium* inhibit some black pigmented anaerobes by competing for an essential growth factor vitamin K. Increasing evidence points to the fact that probiotics in the gut are not able to become a part of the resident gastrointestinal microbiota and they disappear through the faeces very soon after the probiotic ingestion ends. They also found *L. gasseri* as well as *L. salivarius* and *L. fermentum* to be more prevalent in healthy sites but not exclusive to health. Counts of bifidobacteria were particularly high in a group of well-maintained experiodontitis subjects, indicating perhaps that these bacteria are better able to colonize sites that have undergone plaque removal. Thus, it is possible that prebiotic therapy promotes the growth of certain bifidobacteria and lactobacilli, which may enhance periodontal health.

Van Essche et al (2009)[39] have reported Bdellovibrio bacteriovorus' action on *A. actinomycetemcommitans,* and suggested that it could potentially prevent and treat periodontitis. More recently, *Vivekananda MR et al.* (2010)[40] using Prodentis lozenges, showed its plaque inhibition, anti-inflammatory, and antimicrobial effects. They proposed that probiotics could serve as a useful alternative to periodontal treatment when SRP might be contraindicated. *In vitro* studies have also proven that probiotic components can maintain their viability when exposed to saliva, which mediated their adherence to oral surfaces. Strong species dependent and strain dependent activities against periodontal pathogens have been observed.

Halitosis

Halitosis is a condition of oral malodor which can be attributed to the disturbed microflora equilibriu. Kang *et al.*[41] found the inhibitory effect of *Fusobacterium nucleatum.* The proposed mechanism in volatile sulphur compounds (VSC) production is the formation of hydrogen peroxide by *Weissella cibaria* that effects the reproduction of *F. nucleatum*.

It was noted that *S. salivarius* was significantly present in the mouths of volunteers with the best breath.[42] The use of chewable lozenges containing *S. salivarius* K 12 reduced levels of VSC among patients with halitosis(Burton *et al* 2005).[43-44] Though probiotics are being marketed

for both mouth and gut associated halitosis, their efficacy highly demands more clinical studies.[42]

Designer Probiotic

This approach employs probiotics to be engineered to express receptor mimic structures on their surface. The aim is to equip the probiotics bacteria with the appropriate and necessary genetic element to overcome stress inside and outside host. Improving the stress tolerance profile of probiotic cultures significantly prolongs their survival during subsequent storage, which in turn leads to a larger proportion of the probiotics reaching the desired location. They have been employed as vaccine delivery vehicle and in the treatment of HIV.[9]

COMMERCIALLY AVAILABLE PROBIOTICS FOR PERIODONTAL DISEASE MANAGEMENT

Few products containing probiotics (such as tablets, lozenges, chewing gums or tooth pastes) are currently available:[8]

I. Gum PerioBalance
II. PeriBiotic
III. Bifidumbacterin, Acilact , Vitanar
IV. Wakamate D
V. Prodentis

PREBIOTICS

The term prebiotic was introduced by Gibson.[45] They are non-digestible food ingredients that affect the host by selectively stimulating the growth and activity of bacterial species already established in the colon, thereby, improving host health. They include inulin, fructo-oligosaccharides, galacto-oligosaccharides and Lactulose.[46] They act in conjunction with probiotics by Synbiotic Concept, i.e, their mixture of affects the host by improving the survival of live microbial dietary supplements in gastrointestinal tract of host.[47] Probiotics are supplied along with prebiotic in the form of powder sachet, gelatine capsules, or suspension. For example, BION, which is commercially available combination of pre- and pro-biotic in Indian market, has 0.48 billon spores of Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium bifidum, Streptococus thermophilus, and 0.10 billon spores of Saccharomyces boulardii along with 300 mg of fructooligosaccharides. It is prescribed as single dose daily before meals in the morning.[9]

SAFETY ASPECTS OF PROBIOTICS

Increased probiotic supplementation has raised safety concerns. When probiotics are applied orally, a part of them is ingested which can interact with a patient's systemic health. Probiotics are generally considered safe and well tolerated. Bloating and flatulence have been frequently reported.[9] Increased consumption of probiotics leads to increased concentrations of these species in the host organism, rarely, causing cases of probiotics-related bacteraemia. Lactobacillus endocarditis and liver abscess secondary to L. rhamnosus have been reported. Major risk factors reported include immunosuppression and prematurity in infants.[10]

CONCLUSION

Probiotics represent a new area of research in medical science, offering therapeutic advantages systemically and a new hope in periodontal therapy. Also, they may help in combating issues with overuse of antibiotics and antimicrobial resistance. More clinical trials need to be carried out to assess their method of administration and dosages for different therapeutic uses, and attaining the required effect where it is needed, i.e., systemically or in oral cavity. Studies conducted in animals, and human studies have not been sufficient to assess their impact on periodontal disease, especially. Much more scientific developments and research is needed to have a better understanding of these bacteria in order to broaden their potential applications.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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