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Review Article

Probiotics –A Miracle in Periodontal Therapy

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Abstract: Most common forms of infections are caused by oral diseases. The use of higher dose of antibiotics has resulted in the development of resistant subgingival microbiota in adult periodontitis patients. New methods such as probiotic approaches to eliminate pathogenic microbiota can be investigated. Probiotics are one of the newly introduced agents widely used for therapeutic action i.e. whole bacteria replacement therapy. This paper highlights the role of probiotics in periodontal therapy.
Keywords: Probiotics, Periodontal disease , Synbiotic , Bacteriotherapy , Lactobacilli, Bifidobacterium.

INTRODUCTION

Periodontal disease plays a major part of the burden of oral diseases. Predominantly gram negative anaerobic bacteria are considered to be pathogenic to dental supporting tissues. Periodontal diseases lead to destruction of periodontal ligament and the underlying alveolar bone [1]. Mechanical methods of subgingival debridement accomplished by thorough scaling & root planing, accompanied by oral hygiene procedures serve as a gold standard of periodontal therapy for decades [2]. Regarding elimination of pathogenic members of the oral cavity, a new method such as probiotic approach (Whole bacteria replacement therapy) can be investigated. Bacteriotherapy is an alternative and promising way to suppress infections by using harmless bacteria to destroy pathogenic micro-organisms [3]. Probiotics provides an effective alternative way which is economical & natural to combat periodontal diseases [4].

PROBIOTICS

The word 'probiotic', is derived from the Greek language, which means 'for life' and was first used by Kollath [5]. By definition, it is a "live microorganism that, when administered in adequate amounts, offer a health benefit to the host "(FAO/WHO in 2001).The concept of probiotics evolved at the turn of 20th century from a hypothesis first proposed by nobel prize winning Ukrainian bacteriologist laureate Elie Metchninoffin early years of 20th century working at the Pasteur institute in Paris, who laid down the scientific foundations of probiotics. The First probiotic species to be introduced in research was Lactobacillus acidophilus by Hull and followed by Bifidobacteriumbifidum by Holcombh *et al* [4].

Probiotics are broadly classified into 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 (GRAS) because they can reside in the human body, causing no harm, and on the other hand, they are the key micro-organisms in milk fermentation and food preservation. 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 [6].

Moreover, certain strains of *Aspergillus, Propionibacterium, Saccharomyces, Streptococcus, Enterococcus* & non-pathogenic strain of *E. coli, Clostridium butyricum*, are among others which have demonstrated probiotic properties [6].

Probiotics can improve patient condition in medical disorders such as diarrhea, gastroenteritis, short-bowel syndrome & inflammatory intestinal diseases (Crohn's disease & ulcerative colitis), cancer, immunodepressive states, inadequate lactase digestion, pediatric allergies, growth retardation, hyperlipedemia, liver diseases, Helicobacter pylori infection, genitourinary tract infections and others [6].

MECHANISM OF ACTION OF PROBIOTICS

1. **Barrier function :**
   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.

2. **Host cell Antimicrobial Peptides:**
   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.

3. **Probiotic antimicrobial factors:**
   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.

4. **Epithelial Adherence:**
   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.

5. **Immune modulation:**
   L. casei down-regulated 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 resulted in an anti-inflammatory effect that appeared to be mediated by the inhibition of the NF-κB pathway, particularly through stabilization of I-κBα.

6. **Interference with Quorum Sensing Signaling:**
   Bacteria communicate with each other as well as with their surrounding environment through chemical signalling molecules called auto-inducers. 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 [5].

PROBIOTICS AS FOOD PRODUCTS

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]

VEHICLES FOR DELIVERY

The different vehicles used to administer probiotics are:

Powder
Lozenge
Gel
Straw,tablet.
Cheese
Rinse solution
Capsule, liquid
Yogurt drink[4]

CLINICAL EVIDENCE OF PROBIOTICS ON PERIODONTAL HEALTH

Hillman and Socransky [7] reported that *Streptococcus oralis* and *Streptococcus uber* is inhibited the growth of pathogens both in the laboratory and animal models. 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.

L. acidophilus contained in a tablet named Acilact was first clinically tested by Pozharitskaia *et al* [8]and they found improved clinical parameters in periodontitis patients.

Grudiamov *et al* [9] 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.

Ishikawa et al. [10] in a parallel open label study, reported that daily intake of L. salivarius T1 2711 isolated from healthy humans in tablet form, 5times a day for 8 weeks, led to a decreased number of black-pigmented anaerobic rods .

According to Narva *et al* [11] 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.

Volozhin et al. [12] has shown that a collagenous periodontal dressing containing L.casei 37 can significantly reduce the number of periodontal pathogens and extend remission periods upto 10-12 months. This might be due to the inhibitory effect of probiotics on the growth of pathogens thus altering the composition of oral biofilm.

Koll-Klais et al. [13] investigated the antimicrobial activity of oral streptococci against putative oral pathogens and showed that 69% percent of tested lactobacilli inhibited S. mutans, 88% A. actinomycetemcomitans, 82% P. gingivalis and 65% P. intermedia. The strongest antimicrobial activity was associated with Lactobacillus paracasei, L. plantarum, Lactobacillus rhamnosus, and Lactobacillus salivarius.

Krasse et al. [14] 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.

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. Kang et al. 15] attributed this to the ability of W.cibaria to co-aggregate with VSC producing organisms like F .nucleatum thus reducing the source of malodorous compounds.
Matsuka et al. [16] 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. [17] 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. [18] found that Lactobacillus salivarius, Lactobacillus gasseri and Lactobacillus fermentum are among the most prevalent species in the mouth, but significant difference in their number was found between groups of healthy patients and patients with periodontitis. He also suggested that Bifidobacterium inhibited some black pigmented anaerobes by competing for an essential growth factor vitamin K.

Application of selected beneficial bacteria, belonging to Streptococcus species as an adjunct to scaling and root planing inhibited the recolonization of periodontal pockets by periodontal pathogens. Teughels et al. [19] hypothesized that this concept of guided pocket recolonization (GPR) may be a valuable option in the management of periodontitis.

Shimauchi et al. [20] 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.

Shimazaki et al. [21] 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, whereas no significant associations were found with intakes of cheese, milk and other dairy foods.

Staab et al. [22] 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.

Van Essche et al. [23] reported that B. bacteriovorus, attack prey on and kill A. actinomycetemcomitans, thus suggesting a potential scope for the role of B.bacteriovorus in the prevention and treatment of periodontitis.

Twetman et al. [24] 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, and bleeding were significantly reduced.

Vivekananda MR *et al* [25] using Prodentis lozenges showed plaque inhibition, anti-inflammatory, and antimicrobial effects of Prodentis. The study proposed that probiotics could serve as a useful adjunct or alternative to periodontal treatment when SRP might be contraindicated.

PREBIOTICS

The term prebiotic was introduced by Gibson **[**29].They are non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already established in the colon,and thus in effect improve host health. It includes inulin, fructo-oligosaccharides, galacto-oligosaccharides and Lactulose [30]. They act beneficial to probiotics by "Synbiotic Concept".Synbiotic means mixture of probiotics and prebiotics beneficially affecting the host

by improving the survival of live microbial dietary supplements in gastrointestinal tract of host [27].

Probiotics are supplied along with prebiotic in the form of powder sachet, gelatine capsules, or suspension. "BION" commercially available in Indian market (combination of pre- and pro-biotic) 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 fructo-oligosaccharides, is prescribed as single dose daily before meals in the morning [28].

COMMERCIALLY AVAILABLE PROBIOTICS FOR PERIODONTAL DISEASE MANAGEMENT

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

I. Gum PerioBalance
II. PeriBiotic
III. Bifidumbacterin, Acilact , Vitanar
IV. Wakamate D
V. Prodentis[6]

SAFETY CONCERNS AND DOSAGE

Probiotics organisms are classified by FDA as generally regarded as safe (GRAS). Criteria of an ideal microorganism used as probiotics.

a) High cell viability, resistant to low ph and acids
b) Ability to persist
c) Adhesion to cancel the flushing effect
d) Able to interact or to send signals to immune cells
e) Should be of human origin
f) Should be non pathogenic
g) Resistance to processing
h) Must have capacity to influence local metabolic activity [28]

DESIGNER PROBIOTICS

The term "Patho-Biotechnology" was introduced by Sletor and Hill. It comprises of three basic approaches

I. Use of attenuated bacterial pathogens as vaccine
II. Isolation and purification of pathogen specific immunogenic protein for direct application
III. Equipping probiotics bacteria with genetic element necessary to overcome stress outside host, inside host and antagonise invading pathogens

Third approach is what is termed as "designer probiotics". This approach employs probiotics to be engineered to express receptor mimic structures on their surface. Few studies done are limited to gut, periodontal studies are lacking, but poses a great potential in this field to develop. Designer probiotics have been employed in treatment of HIV, also employs as a novel vaccine delivery vehicle. Improving the stress tolerance profile of probiotic cultures significantly improves tolerance to processing stress and prolongs survival during subsequent storage. This in turn contributes to a significantly larger proportion of the administered probiotics reaching the desired location (e.g., the gastrointestinal tract/periodontium) in a bioactive form [28].

CONCLUSION

Though various researchers have explored the role of probiotcs in periodontal therpy, still the usage of probiotics is in the infant stage. As new frontiers continue to be explored the challenge to basics of hygiene hypothesis will influence further development in field of probiotics. There is greater need to elucidate the role of oral beneficial bacteria, to identify and to conduct a proper large-scale studies on the usefulness of probiotics to maintain improve oral health.

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