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Probiotics for Management of Periodontal Disease: A Novel Therapeutic Strategy?

Dr. Sandeep Lawande
MDS, FICOI (USA), FICD, FPFA Assistant Professor, Department of Periodontics, Goa Dental College & Hospital, Bambolim, Goa, India – 403202

Abstract*—*Probiotics are live microrganisms administered in adequate amounts with beneficial health effects on the host. The use of probiotics is widespread in the management of systemic infections and disease. In recent years, there has been a growing interest in the use of probiotics in the field of Dentistry, particularly Periodontics. This article reviews the role of probiotics for management of periodontal diseases and explores its potential as a novel treatment strategy.
Keywords*—*probiotics, periodontal disease, lactobacillus, bifidobacterium

I. INTRODUCTION

The term 'probiotic' is derived from the Greek word, meaning "for life." [(1)] According to the currently adopted definition by FAO/WHO (The Food Agricultural Organization/World Health Organization), 'probiotics are living organisms, principally bacteria that are safe for human consumption and when ingested in sufficient quantities, have beneficial effects on human health, beyond the basic nutrition'. [(2)] Such non-pathogenic organisms (yeasts or bacteria, particularly lactic acid bacteria) are present in food, and can have a favourable impact on host health. Probiotics have been used for decades in fermented products, but potential use of probiotics as a nutritional medical therapy has not been formally acknowledged. [(3)]

The concept of probiotics dates back to 20th century when Ukranian bacteriologist and Nobel laureate Elie Metchnikoff laid down the scientific foundation of probiotics. He proposed that Bulgarian people had a longer longevity due to fermented milk containing viable bacteria. [(4, 5)]

The term 'probiotics', the antonym of the term 'antibiotics', was introduced in 1965 by Lilly & Stillwell as substances produced by microorganisms which promote the growth of other microorganisms. First probiotic species to be introduced in research was Lactobacillus acidophilus by Hull et al. in 1984; followed by Bifidobacterium bifidum by Holcombh et al. in 1991. [(4, 5)]

Probiotics, most commonly belong to the genera - Lactobacillus and Bifidobacterium. Lactobacillus species from which probiotic strains have been isolated include L. acidophilus, L. johnsonii, L. casei, L. rhamnosus, L. gasseri, and L. reuteri. Bifidobacterium strains include B. bifidum, B.longum, and B. infantis.[(6)] 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 key microorganisms in milk fermentation and food preservation and used as such from the dawn of mankind. 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.[(7)]

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. [(7, 8)]

Probiotics can improve patient condition in medical disorders such as diarrhea, gastroenteritis, short-bowel syndrome, and inflammatory intestinal diseases (Crohn's disease and ulcerative colitis), cancer, immunodepressive states, inadequate lactase digestion, pediatric allergies, growth retardation, hyperlipidemia, liver diseases, infections with Helicobacter pylori, genitourinary tract infections, and others; all such findings have been supported by several studies demonstrating improved results after using probiotics.[(5)]

Given the widespread emergence of bacterial resistance to antibiotics, the concept of probiotic therapy has been considered for application in oral health. Dental caries, periodontal disease and halitosis are among the oral disorders that have been targeted in recent years. [(9)] Specifically, limited information on the use of probiotics for periodontal disease management is currently available.

1.1 Aim of the study

The present study was conducted to update such information based on studies assessing probiotics in periodontal disease. A literature review search was performed for English-language articles using PubMed or Medline database with the following search terms: "probiotics" and "periodontal disease"; no restrictions were used for publication dates.

II. PROBIOTICS IN THE ORAL CAVITY

More than 700 species of oral microbiota have been detected in the human mouth and the resident microbiota of one individual may consist of 30-100 species. [10] An essential requirement for a microorganism to be an oral probiotic is its ability to adhere to and colonize surfaces in the oral cavity. Microorganisms generally considered as probiotics may not have oral cavity as their inherent habitat and, subsequently, their possibility to confer benefit on oral health is then questionable. [9] Studies suggest that lactobacilli as members of resident oral microflora could play an important role in the micro-ecological balance in the oral cavity. The studies further demonstrated that lactobacilli strains with probiotic properties may indeed be found in the oral cavity. Yet there is no evidence whether these lactobacilli strains were detected due to the frequent consumption of dairy products leading to temporary colonization only, or if the oral environment is their permanent habitat.[7,9]

2.1 Criteria for Probiotics

To be considered for use as probiotic following criteria needs to be fulfilled.[7, 11, 12]

1) It should 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 metabolising 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.

III. PROBIOTICS AND PERIODONTAL DISEASE

Periodontal diseases are classified into two major types – gingivitis and periodontitis. Gingivitis is characterized by inflammation of gingiva, whereas periodontitis is a progressive, destructive disease that affects all supporting tissues of teeth, including the alveolar bone. The main pathogenic agents associated with periodontitis are Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia and Aggregatibacter (formerly Actinomyces) actinomycetemcomitans. These bacteria have a variety of virulent characteristics allowing them to colonize the subgingival sites, escape the host defense system and cause tissue damage. [13]

3.1 Mechanisms of action of Probiotics

Probiotics can help prevent and treat disease through several mechanisms including direct interaction, competitive exclusion and modulation of host immune response. The treatment strategies conferred by probiotics against periodontal diseases are mainly anticipated to be either by inhibition of specific pathogens or by altering the host immune response through the following multiple factors: [7, 11, 12]

- **Inhibition of specific organisms**

- Inhibition of pathogen adhesion, colonization and biofilm formation
- Inhibition of pathogen growth by various substances such as organic acids, hydrogen peroxide and bacteriocins against oral pathogens.

- **Effects on host response**

- Inhibition of collagenases and reduction of inflammation associated molecules
- Induction of expression of cytoprotective proteins on host cell surfaces
- Modulation of pro-inflammatory pathways induced by pathogens
- Prevention of cytokine-induced apoptosis
- Modulation of host immune response

3.2 Clinical evidence of probiotic effectiveness in periodontal disease

Studies on probiotics and periodontal disease are particularly sparse and at present few clinical studies have evaluated the efficacy of probiotic species from a periodontal disease perspective. [7]

Streptococcus oralis and Streptococcus uberis have reported to inhibit 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. [14]

Krasse et al found that intake of L. reuteri for a period of 14 days led to the establishment of the strain in the oral cavity and significant reduction of plaque in patients with moderate to severe gingivitis. [15]

Staab et al 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.[16]

Riccia et al studied the anti-inflammatory effects of Lactobacillus brevis in a group of patients with chronic periodontitis. Anti-inflammatory effects of L. brevis could be attributed to its capacity to prevent the production of nitric oxide and, consequently the release of PGE2 and the activation of MMPs induced by nitric oxide. [17]

According to Narva et al, 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.[18]

Koll-Klais et al reported that resident lactobacilli flora inhibits the growth of P. gingivalis and Prevotella intermedia in 82% and 65%, respectively. [19] Ishikawa et al. observed in vitro inhibition of P. gingivalis, P. intermedia, and P. nigrescens by daily ingestion of L. salivarius in tablet form. [20]

Van Essche et al have 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. [21]

Hojo et al suggested that Bifidobacterium inhibited some black pigmented anaerobes by competing for an essential growth factor vitamin K. [22]

A study done by Vivekananda MR 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. [23]

Shimauchi et al 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. [24]

Volozhin et al 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. [25]

Grudianov et al reported that probiotics were effective in normalization of microbiota in periodontitis and gingivitis patients when compared with a control group. [26]

Shimazaki and colleagues, in an epidemiological study found that individuals, particularly nonsmokers, who regularly consumed yoghurt or beverages containing lactic acid exhibited lower probing depths and less loss of clinical attachment than individuals who consumed few of these dairy products. A similar effect was however not observed with milk or cheese. [27]

Twetman et al 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. [28]

3.3 Commercially available Probiotics for periodontal disease management

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

- **Gum PerioBalance** (marketed by Sunstar, Etoy, Switzerland)

This is probably the first probiotic specifically formulated to fight periodontal disease. It contains a patented combination of two strains of L.reuteri specially selected for their synergistic properties in fighting cariogenic bacteria and periodontopathogens. Each dose of lozenge contains at least 2 × 108 living cells of L. reuteri Prodentis. Users are advised to use a lozenge every day, either after a meal or in the evening after brushing their teeth, to allow the probiotics to spread throughout the oral cavity and attach to the various dental surfaces.[29]

- **PeriBiotic** (Designs for Health, Inc.,)

This toothpaste is an all-natural, fluoride-free oral hygiene supplement containing Dental-Lac, a functional Lactobacillus paracasei probiotics not found in any other toothpaste. [29]

- **Bifidumbacterin, Acilact , Vitanar** (marketed by Alfarm Ltd., Moscow, Russia)

This probiotics preparation of a complex of five live lyophilized lactic acid bacteria, is claimed to improve both clinical and microbiologic parameters in gingivitis and mild periodontitis patients. After routine

mechanical debridement, 2 tablets to be dissolved in the mouth, three times a day for 20-30 days for improved outcome. [26]

- **Wakamate D** (Wakamoto Pharmaceutical Co., Tokyo, Japan)

This probiotic tablet contains $6.5x10^8$ colony forming units (CFU) per tablet of Lactobacillus salivarius WB21 and xylitol (280 mg/ tablet) was originally prepared to contribute for the intestinal microbial balance by providing acid tolerant L. salivarius WB21.[24]

- **Prodentis** (BioGaia, Stockholm, Sweden)

This probiotic lozenge is a blend of two Lactobacillus reuteri strains containing a minimum of $1x\ 10^8$ colony forming units (CFU) for each of the strains DSM 17938 and ATCC PTA 5289. [23]

Additional studies are however required to evaluate the long-term effects of using these commercially available products.

3.4 Guided Pocket Recolonization (GPR)

Recently, Teughels et al reported that the subgingival application of a bacterial mixture including Streptococcus sanguinis, Streptococcus salivarius (S. salivarius), and Streptococcus mitis after scaling and root planing significantly suppressed the re-colonization of Porphyromonas gulae (canine P. gingivalis) and P.intermedia in a beagle dog model. This novel approach of Guided Pocket Recolonization may provide a valuable addition or alternative to the armamentarium of treatment options for periodontitis. [30]

3.5 Effectiveness of Probiotics in Halitosis

Halitosis or oral malodour refers to the foul and unpleasant odour emanating from the oral cavity. Volatile sulphur compounds (VSC) are responsible for halitosis. Bacteria responsible for VSC production are Fusobacterium nucleatum, Porphyromonas gingivalis, Prevotella intermedia, and Treponema denticola. [31]

Kazor et al reported that L. salivarius was the most predominant species detected in healthy subjects, whereas it was detected in only one of the subjects with halitosis at very low levels. [32]

Weissella cibaria, a probiotics strain has been shown to inhibit VSC production under both in vitro and in vivo conditions. This is likely to be because of its ability to co-aggregate with VSC producing species like F. nucleatum, thus reducing the source for malodorous compounds in oral cavity and also by producing hydrogen peroxide which inhibit F.nucleatum as reported by Kang et al. [33]

Streptococcus salivarius produces bacteriocins which inhibit bacteria producing VSC. It was shown that lozenges and gum containing Streptococcus salivarius decrease VSC in halitosis patients. The use of gum or lozenges containing S. salivarius K12 (BLIS Technologies Ltd., Dunedin, New Zealand) reduced levels of volatile sulphur compounds among patients diagnosed with halitosis. S. salivarius K12 taken in a lozenge after a mouthwash could reduce oral VSC levels in 85% of the test groups according to study by Burton et al. [34]

3.5 Effectiveness of Probiotics in Yeast infections

Hatakka et al observed 32% reduction in counts of Candida albicans in the elderly population after 16 weeks of probiotics cheese intake. [35]

Elahi et al assessed the pattern of colonization of Lactobacillus acidophilus and Lactobacillus fermentum and demonstrated a rapid decline in Candida albicans after the intake of probiotics strains in mice. Continuous consumption of probiotics led to almost undetectable numbers of fungi in the oral cavity, maintaining the protective effect for a prolonged period after cessation of application. [36]

3.6 Safety aspects of Probiotics

Increased probiotic supplementation of different food products during the recent years has raised safety concerns. When probiotics are applied orally, at least a part of them will be ingested and can interact with a patient's systemic health. When ingested orally, probiotics are generally considered safe and well tolerated with bloating and flatulence occurring frequently [8].

The increased probiotic consumption inevitably leads to increased concentrations of these species in the host organism. Although rare, cases of probiotics-related bacteraemia, lactobacillus endocarditis and liver abscess secondary to L. rhamnosus have been reported in the literature and such cases have responded well to appropriate antibiotic therapy. [8, 9]

Recently, major and minor risk factors for probiotics-associated sepsis have been identified. Major risk factors include immunosuppression (including a debilitated state or malignancy) and prematurity in infants. Minor risk factors are the presence of a central venous catheter, impairment of the intestinal epithelial barrier (such as with diarrhoeal illness), cardiac valvular disease (Lactobacillus probiotics only), concurrent

administration with broad-spectrum antibiotics to which the probiotic is resistant and administration of probiotics via a jejunostomy tube (this method of delivery could increase the number of viable probiotics organisms reaching the intestine by bypassing the acidic contents of the stomach). Therefore, it is recommended that probiotics should be used cautiously in patients with one major risk factor or more than one minor risk factor (Boyle et al). [37]

Although administration of probiotics generally can be considered safe, each strain of probiotics has specific properties that should be considered before its use in any patient. In addition, a particular concern when evaluating probiotic effects on periodontal disease relates to the means of administration of these bacteria. Generally probiotics are delivered in dairy products (mainly fermented milks), as food supplements in tablet forms or in soft drinks. However these routes of administration cannot provide prolonged contact with oral tissues, facilitating probiotic adhesion to saliva coated surfaces. A lozenge form or chewing gum tablet or gum might better serve the needs for periodontal health prophylaxis. Controlled clinical trials and long term studies are required to investigate the concentration of probiotics bacteria in the specific means of administration. [8, 9, 37]

IV. CONCLUSION

Recent advances in technology have led to a constant drive to develop novel strategies for the treatment of periodontal diseases. The probiotics concept essentially entails the introduction of specific viable microbial species in order to confer health benefits upon a host by functioning via different mechanisms. The literature review shows that use of oral probiotics is associated with improvement in periodontal health. However, the effects of probiotics on periodontal health and its maintenance including means of administration, dosage and safety aspects are not clear. Numerous randomized clinical studies will be required to clearly establish the potential of probiotics in the prevention and treatment of periodontal diseases. There is no doubt that with further significant progress, probiotics may have an important role to play in the near future within the periodontal arena.

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