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Review Article

Probiotics in Periodontics: A Review

Chhaya Mangla

Former Senior lecturer, Department of Periodontology, Adesh institute of dental sciences and research, Bathinda, Punjab, India

ABSTRACT:

Probiotics are counterparts of antibiotic thus are free from concerns for developing resistance, further they are body's own resident flora hence are most easily adapted to host. With fast evolving technology and integration of biophysics with molecular biology, designer probiotics poses huge opportunity to treat diseases in a natural and non invasive way. Periodontitis have established risk of various systemic diseases like diabetes, atherosclerosis, hyperlipidemia, chronic kidney diseases, and spontaneous preterm birth. Thus, a critical need to establish good periodontal health for attaining good systemic health is of utmost importance and probiotics are promising, safe, natural, and side effects-free option, which are required to be explored in depth for periodontal application. Advances and accomplishments attained give us the ability to employ these friendly bacteria (probiotics) as nano soldiers in combating periodontal diseases. Despite great promises, probiotics works are limited to gut. Periodontal works are sparse and need validation by large randomized trials. It can be said probiotics are still in "infancy" in terms of periodontal health benefits, but surely have opened door for a new paradigm of treating disease on a nano – molecular mode.

Key words: Probiotics, Prebiotics Periodontal disease, Lactobacillus, Bifidobacterium.

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Corresponding Author: Dr. Chhaya Mangla, Former Senior lecturer, Department of Periodontology, Adesh institute of dental sciences and research, Bathinda, Punjab, India

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INTRODUCTION

Currently, management of periodontal disease has progressed near an antibiotic/antimicrobial exemplary of illness or infection controlling. Treatment phase moves from hypothesis regarding management commencing particular bacteria extinction into changing bacterial ecosystem by good ones.¹ With the emergence of multi-resistant strains, antibiotic resistance has developed and has leads to seek other means of combating infectious diseases. Thus adjunctive therapy comes into importance for maintaining good oral flora. Probiotic bacteria, may favor periodontal health if able to establish them in oral biofilm and inhibit pathogen growth and metabolism. So, periodontitis could benefit from orally administered probiotics.² With increasing understanding that beneficial microbes are required for health, probiotics may become a

common therapeutic tool used by health-care practitioners in the not-too-distant future.³

HISTORICAL BACKGROUND

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 favorable 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 Ukrainian 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. 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 Holcomb et al. in 1991. (Table I) 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*. 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

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.⁴

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. 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. 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.⁴

Criteria for Probiotics To be considered for use as probiotic following criteria needs to be fulfilled.⁴

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 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.

MECHANISM OF ACTION

Probiotics can help to stop in addition cure health disorder by numerous tools: a) Directly communicating: It forms a network agreeably using disease-producing organisms, creating to be tougher to be intended to effect illness. b) Competitive elimination: Favourable micro-organisms openly participate by means of illness, increasing microscopic organism for nourishment or enterocyte bond locations. c) Alteration of host resistant response-It intermingles in addition reinforce the protection arrangement which aids in avoiding ailment. It motivates dendritic cells ensuing in manifestation of helper T cell (Th1) reaction, which controls immunity. Apoptosis so far additional suggested instrument. Probiotics is likewise identified to create antioxidants, it has the chance to stop plaque development by means of nullifying permitted electrons which are required for formation of calculus.⁵

COMMERCIALLY AVAILABLE PROBIOTICS FOR PERIODONTAL DISEASE MANAGEMENT

Few products containing probiotics (such as tablets, lozenges, chewing gums or tooth pastes) are currently available.⁴

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 2×10^8 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.

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.

Bifidumbacterin, Acilact , Vitonar (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.

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

This probiotic tablet contains 6.5x10⁸ 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.

Prodentis (BioGaia, Stockholm, Sweden)

This probiotic lozenge is a blend of two *Lactobacillus reuteri* strains containing a minimum of 1x 10⁸ 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.

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 recolonization 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.⁶

The following probiotic drugs are available in the Indian market:³

- ViBact capsules/sachets (USV),
- Binifit capsules/sachets (Ranbaxy),
- Becelac PB capsules (Dr. Reddy's Labs),
- Vizyl capsules/sachets (Unichem),
- Econova capsules (Glenmark),
- Biors sachets (Tablets India Ltd.) and
- Gutpro capsules/sachets (JBCPL),
- Ecoflora capsules (Tablets India Ltd.).

PREBIOTICS

Prebiotics have been proved to be an aid to complement probiotics in the treatment of oral diseases. Prebiotics are non-digestible dietary supplements. Their function is to enhance the growth and activity of beneficial organisms and simultaneously suppress the growth and activity of potentially deleterious bacteria. In this way prebiotics modify the balance of the intestinal micro-flora. The characteristic feature of prebiotic ingestion is mainly to change microbial population density . Some of the

commonly known prebiotics are Lactose, Inulin, Fructo oligosaccharides, Galacto oligosaccharides and Xylo oligosaccharides. Prebiotics are naturally found plenty in certain fruits like bananas, asparagus, garlic, tomato and onion wheat .The characteristic features of ideal prebiotics are as that they are neither to be hydrolysed nor absorbed by mammalian enzymes or tissues. They are selectively enriched with a limited number of beneficial bacteria. The most important characteristic feature is that prebiotics can alter the intestinal micro-flora and its activities. Prebiotics can also change luminal or systemic aspects of the host defense system.⁷

Relationship between Prebiotics and Probiotics

Prebiotics when combined with probiotics have many advantages. Basically, prebiotics selectively stimulate the growth of probiotics, which is dose and strain dependent. Prebiotics serve as a selective growth substrate for the probiotics strain during fermentation, during the period of storage, or during its passage through the gut. These two combinations implant live microbial dietary supplements and create a congenial environment for their survival in gut flora. Thereby this environment in gut flora improves healthy microbial balance. So, the combination of prebiotics and probiotics may have additive and synergistic effect in providing better oral health conditions.⁷ Paster et al in an attempt to determine bacterial diversity in the human subgingival plaque by using culture-independent molecular methods have estimated that the total species diversity in the oral cavity ranges between 500 and 600 species. This number was further extended by Kazor et al, who detected 200 additional unknown species on the dorsum of the tongue, making the number of species in the mouth to reach 700. *Lactobacilli* make approximately 1% of the cultivable oral microflora. Definite *S. mutans* count reduction after a 2-week consumption of yoghurt containing *L. reuteri*. A temporary reduction in *S. mutans* was observed during the period of yogurt intake and few days after cessation of consumption, indicating the necessity of continual administration of the probiotic in order to achieve an effect. Studies showed in a placebo-controlled randomized double-blind intervention study that the administration of probiotics *lactobacilli* (LGG) to kindergarten children in Helsinki, Finland, resulted in reduction of their caries risk and initial caries development. Certain conditions are required to remove cariogenic bacteria from the surface of the teeth to fight against dental caries. First, probiotic bacteria must be able to stick to the tooth surface where cariogenic bacteria reside. Secondly they must become a part of the biofilm that develops on teeth. Finally they must compete with cariogenic bacteria. All this process helps display a probiotic effect against carries by drastic reduction of the levels of cariogenic bacterial growth.^{8,9}

PROBIOTICS AND PERIODONTAL DISEASES

Gingivitis and periodontitis are the most common diseases with microbial etiology affecting the periodontium. Periodontitis is characterized by a progressive destruction of the supporting structures of the teeth. It is the result of inflammatory responses to dental plaque in a susceptible host. Bacteria may also directly cause tissue damage due to virulence factors, such as toxins and enzymes. The inflammatory response including an increased flow of gingival crevicular fluid (GCF) and a rise in pH favor the Gram-negative, proteolytic species thus leading to an ecological shift as suggested by the ecological plaque hypothesis (Marsh, 2003).^{10,11} Prevention and treatment of periodontal diseases mainly focuses on the reduction of bacterial load. Conventional treatment modalities include surgical and non-surgical management which emphasizes on mechanical debridement, often accompanied by antibiotics. Due to the emergence of antibiotic resistance and frequent re-colonization of treated sites with pathogenic bacteria, probiotics have emerged in the field of periodontics. Probiotics is based on the concept of bacterial interference whereby one microorganism can prevent and or delay the growth and colonization of another member of the same or different ecosystem.³

EVIDENCE SUPPORTING THE USE OF PROBIOTICS IN GINGIVITIS

Krasse *et al.* (2006)¹², Riccia *et al.* (2007)¹³, and Shimauchi *et al.* (2008)¹⁴ reported statistically significant decreases in gingival index when probiotic group was compared with baseline values. In contrast, the study by Staab *et al.* (2009)¹⁵ probiotic group showed a statistically significant increase in gingival index. Krasse *et al.* assessed the beneficial effect of *Lactobacilli reuteri* against gingivitis, at a dosage of 2×10^8 CFU/day for 2 weeks. *L. reuteri* can act by the following three mechanisms: • *L. reuteri* is known for the secretion of two bacteriocins, reuterin and reutericyclin, that inhibit the growth of a wide variety of pathogens. • *L. reuteri* has a strong capacity to adhere to host tissues, thereby competing with pathogenic bacteria and • The recognized anti-inflammatory effects of *L. reuteri* on the intestinal mucosa, leading to inhibition of secretion of proinflammatory cytokines, could be the foundation for a direct or indirect beneficial effect of this bacterium on patients with periodontal disease. In the study by Twetman *et al.* (2009)¹⁶, the authors observed that as soon as the probiotic (Chewing gum containing two strains of *L. reuteri*: ATCC 55730 and ATCC PTA 5289, 1×10^8 CFU/gum, to be chewed for 10 min daily for 2 weeks) intake was stopped, the percentage of sites that showed bleeding upon probing increased again.

EVIDENCE SUPPORTING THE USE OF PROBIOTICS IN PERIODONTITIS

Among healthy individuals, the prevalence of lactobacilli (particularly *Lactobacillus gasseri*, *Lactobacillus salivarius* and *Lactobacillus fermentum*) and *Bifido bacterium* species were greater than in patients with chronic periodontitis. Studies suggest that lactobacilli residing in the oral cavity could play a role in oral ecological balance. During the fermentation of 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. Shimauchi *et al.* (2008)¹⁴ analyzed salivary lactoferrin levels. The study showed that during the course of the study, for both the placebo as well as the probiotic (6.7×10^8 CFU of *L. salivarius* tablets three times daily for 8 weeks) group, salivary lactoferrin levels decreased significantly from baseline values. In the study done by Teughels *et al.* (2007)¹⁷, where no oral hygiene was performed, multiple applications of *S. salivarius*, *Streptococcus mitis* and *S. sanguinis* resulted insignificant microbiological changes in sub-gingival plaque. In comparison with scaling and root planning alone, multiple sub-gingival applications of *S. salivarius*, *S. mitis* and *S. sanguinis* after root planning, resulted in significant additional microbiological reductions in anaerobic bacteria, in *Porphyromonas gulae*, in black pigmented bacteria and in *P. intermedia*, 12 weeks after root planning and without any form of oral hygiene. A statistically significant lower bleeding upon probing was observed for pockets that received multiple applications of probiotics, when compared with pockets, where scaling and root planning was done alone (30% vs. 45%, respectively). In this 12-week study, no oral hygiene was provided to the dogs. Mayanagi *et al.* (2009)¹⁸ reported that the periodontal pathogenic bacteria in the probiotic group (the test group received 2.01×10^9 CFU/day of *L. salivarius* WB21 and xylitol in tablets for 8 weeks) were significantly decreased in sub-gingival plaque after 4 weeks of probiotic usage and tended to be lower after 8 weeks when compared with the placebo group. The authors calculated that the odds ratio for a reduction of *Tannerella forsythia* in the probiotic group was significantly increased over the course of the study compared with the placebo group. When combining the microbiological effects for *L. salivarius* TI 2711 (tablet form) on untreated periodontitis patients, it has been shown that this probiotic could reduce the salivary black pigmented bacteria levels showed that this probiotic could reduce the salivary black pigmented bacteria levels. Additionally, when compared with a placebo treatment, additional sub-gingival reductions in *P. gingivalis* levels could be achieved. A species-specific antimicrobial activity was also observed by Koll-Klais *et al.* (2005)¹⁹, with facultative hetero fermentative lactobacilli being the strongest inhibitors of *A. actinomycetemcomitans*,

P. gingivalis and *P. intermedia*. S taab *et al.* (2009)¹⁵, investigated the effects of a commercially available probiotic milk containing *L. casei* Shirota on gingival health. The test group drank a probiotic drink once a day for 8 weeks; the control group did not receive any product to drink. They also analyzed, the amount of interproximal plaque and plaque index, the papillary bleeding index and polymorphonuclear elastase, myeloperoxidase and matrix metalloproteinase-3 in GCF. At the end of this 8-week study, elastase activity and matrix metalloproteinase-3 was significantly lower in the probiotic group when compared with the control group. In the 4-day study of Riccia *et al.* (2007)¹³, using a *Lactobacillus brevis* (CD2) lozenge once daily, on untreated periodontitis patients, significant decreases were seen in nitrite/nitrate, prostaglandin E2, matrix metalloproteinase and interferon-gamma levels in saliva of the probiotic group at the end of the study. Nackaerts *et al.* (2008)²⁰ analyzed radiologically the alveolar bone around the teeth that received the positive control treatment and the alveolar bone around the teeth that received root planning and repeated sub-gingival application of the bacterial mixture. These authors observed that the bone density within periodontal pocket treated with beneficial bacteria improved significantly after 12 weeks, while this improvement was not statistically significant for the positive control pockets.

PROBIOTICS IN PREVENTION OF HALITOSIS

Halitosis has many causes (including consumption of particular foods, metabolic disorders, respiratory tract infections), but in most cases it is associated with an imbalance of the commensal microflora of the oral cavity. More specifically, halitosis results from the action of anaerobic bacteria that degrade salivary and food proteins to generate amino acids, which are in turn transformed into volatile sulphur compounds, including hydrogen sulphide and methyl mercaptan and dimethyl sulphide.²¹

There have also been clinical and laboratory studies of probiotics in their potential for preventing halitosis. Kazor *et al.* (2003)²² showed that certain bacterial species, including *Atopobium parvulum*, *Eubacterium sulci* and *Solobacterium moorei*, predominate on the dorsal surface of the tongue among people with halitosis. Conversely, another species, *Streptococcus salivarius*, was detected most frequently among people without halitosis and is therefore considered a commensal probiotic of the oral cavity. *S. salivarius* is known to produce bacteriocins, which could contribute to reducing the number of bacteria that produce volatile sulphur compounds.²³

S. salivarius K12 produces salivaricin, a lantibiotic with inhibitory activity towards most *Streptococcus pyogenes*. This strain has been commercially promoted as a probiotic that is reported to be protective against throat infections and oral malodour.²⁴ The importance of strain selection for probiotic use is illustrated by the fact that

some *S. salivarius* strains differ from K12 in some important activities; one strain increased production of malodorous products by facilitating *P. gingivalis* metabolism of salivary mucins and another up-regulated IL-8 secretion by oral epithelial cells in contrast to the down-regulation observed in response to K12.^{25,26}

SAFETY ISSUES

From the safety point of view, the putative probiotic microorganisms should not be pathogenic, should not have an ability to transfer antibiotic resistance genes. 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.⁴

Recently, major and minor risk factors for probiotics-associated sepsis have been identified. Major risk factors include immunosuppression 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. 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.*)²⁷. Probiotics can alter the immune response to vaccines. There is evidence that some specific probiotics can alter monocyte and natural killer cell function in the blood. Evidence is also accumulating that taking some specific probiotics can boost antibody responses to oral and systemically administered vaccines. This area needs further investigation.³

CONCLUSION

Bearing in mind the present serious methodological evaluations besides precise limited research, broad consideration of the wide-ranging biological alterations prompted by this subject is indispensable toward measure their extended period values for wellbeing of oral cavity besides illness. Methodical lessons and randomized controlled trials remain desirable towards discovering out the finest probiotic/prebiotic strains and worth of their management in diverse oral wellbeing situations.

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