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PROBIOTICS IN PERIODONTICS: CURRENT CONCEPT AND FUTURE PROSPECTS

Periodontics

Dr. Farha Nasim	Second year postgraduate student, Department of Periodontics, Guru Nanak Institute of Dental Sciences and Research, 157/F, Nilgunj Road, Panihati, Kolkata-700114.
Dr. Surupa Dutta*	Final year postgraduate student, Department of Periodontics, Guru Nanak Institute of Dental Sciences and Research, 157/F, Nilgunj Road, Panihati, Kolkata-700114. *Corresponding Author
Prof.(Dr.) Manoj Kumar Singh	Professor, Department of Periodontics, Guru Nanak Institute of Dental Sciences and Research, 157/F, Nilgunj Road, Panihati, Kolkata-700114.
Prof.(Dr.) Abhijit Chakraborty	Professor and Head of the Department, Department of Periodontics, Guru Nanak Institute of Dental Sciences and Research, 157/F, Nilgunj Road, Panihati, Kolkata-700114.
Dr. Debarghya Pal	Second year postgraduate student, Department of Periodontics, Guru Nanak Institute of Dental Sciences and Research, 157/F, Nilgunj Road, Panihati, Kolkata-700114.
Dr. Debarshi Jana	Young Scientist (DST), Department of Gynecology and Obstetrics, Institute of Post-Graduate Medical Education and Research, A.J.C. Bose Road, Kolkata-700020, West Bengal, India

ABSTRACT

Periodontal disease involves complex interplay between the pathogens and the host. Probiotic therapy, being natural with no adverse-effects, carries great potential in improving the clinical signs of periodontal disease by reducing the bacterial load and modulating host immune response. Here an approach has been made to highlight the efficacy of probiotics for treating periodontal disease based on the existing status of knowledge.

KEYWORDS

Probiotics, Periodontal disease, Bacterio-therapy

INTRODUCTION

Periodontal disease involves a complex interplay between the pathogenic bacteria and the host leading to destruction of the periodontium.[1] The current view on the etiology of plaque-related periodontal inflammation considers three factors that determines the susceptibility of disease: a susceptible host; the presence of pathogenic species; and the reduction or absence of so-called beneficial bacteria.[2] This complexity of periodontitis emphasizes the necessity of a treatment that is highly customized to the specific needs of the patient. Over the years, a number of surgical and non-surgical therapies have been implicated in the treatment of periodontal diseases, of which the non-surgical mechanical debridement therapy is considered to be the 'gold standard' for treatment.[3] However, certain limitations of mechanical debridement such as long-term maintainability of deep periodontal pockets, risk of disease recurrence and skill of the operator has prompted the use of adjunctive therapies like antibiotics and antiseptics, laser and photodynamic therapy to improve the outcome of mechanical periodontal therapy (SRP). But, these provided only short-term benefits based on the elimination of the pathogens. Also with the long-term use of antibiotics there has been increase in the antibiotic resistant microorganisms causing recolonization of the treated sites and it may also be associated with unwanted side effects.[4] These shortcomings granted the search for other alternative therapy. The changing treatment paradigm from nonspecific to specific approach aims at reducing the bacterial load as well as modifying the biofilm composition by shifting from pathogenic plaque to a biofilm of 'beneficial bacteria' by administration of probiotics. Probiotic is an innovative approach in the field of dentistry because it not only suppresses the emergence of pathogens but they might also protect us through the promotion of a beneficial host response.[5]

As defined by World Health Organization (WHO) probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host".[6] They help in repopulating the beneficial bacteria, which can kill pathogenic bacteria and fight against infection. The most commonly used and studied probiotics are lactic acid bacteria, in particular Lactobacillus spp. and Bifidobacterium spp. While other microorganisms includes yeast and moulds e.g., *Saccharomyces cerevisiae, Aspergillus niger, Aspergillus oryzae, Sochromyces boulardii*.[7]

Evolution of probiotics

It was introduced by the German scientist Werner Kollath in 1953 to describe "active substances that are essential for a healthy development of life."[8] However the history of probiotic is old and is closely related to the use of fermented food for its beneficial effects. The modern history of probiotics started since the beginning of 1900s with the pioneering studies of Nobel laureate Elie Metchnikoff, when he identified the association between the health and longevity of Bulgarian peasants to the consumption of yoghurt containing large quantities of Lactobacillus species.

In 2002 FAO/WHO formulated the current definition and subsequently put forward guidelines regarding the evaluation and safety of probiotics in various food products.[9]

Proposed mechanism of action of probiotic

The probable mechanism of action of probiotics have been outlined in the figure 1

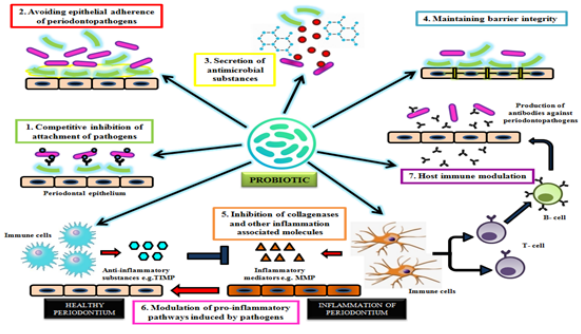

Fig.1: Mechanism of action of probiotic

1. Competitive inhibition of attachment of pathogens

Probiotic effectively inhibits the colonisation of the pathogenic microorganisms over the host tissue surfaces by either hindering the adhesion of pathogenic bacteria by their ability to co-aggregate with the microorganisms or by competing with them for the same

nutrients.[10]

One such example is competition for iron by L. acidophilus and L. delbrueckii which bind to ferric hydroxide at their cells surfaces, rendering it unavailable to pathogenic microorganisms.[11]

2. Avoiding epithelial adherence

Several strains of *Lactobacillus* and *Bifidobacterium* compete with the invading pathogens for binding to adhesion sites and displace the pathogens from the host cells or even by secretion of lectin-like bacteriocins.[7]

Other modes of anti-adhesiveness expressed by probiotics could be degradation of carbohydrate receptors by secreted proteins, establishing a biofilm, through receptor analogues and production of biosurfactants.[10]

Another mechanism by which probiotic species prevent pathogenic microorganisms' adherence is by their ability to co-aggregate with the bacteria. Lactobacillus rhamnosus is seen to co-aggregate with Fusobacterium nucleatum, and thus blocks the colonisation of other pathogenic microorganisms.[12]

3. Secretion of antimicrobial substances

Probiotic species exhibit strong inhibitory effects against invading pathogens by the production of antimicrobial compounds, including organic acids, hydrogen peroxide, carbomide peroxide, diacetyl, low molecular weight antimicrobial substances, bacteriocins, and adhesion inhibitors.[13]

Organic acids (particularly acetic acid and lactic acid), dissociates into the cytoplasm causing intracellular acidification, thus exhibiting a strong cytotoxic effect especially against Gram-negative bacteria.[14]
Weissella cibaria possesses the ability to inhibit Volatile sulphur compounds (VSC) production which is responsible for halitosis, by co-aggregating with F. nucleatum responsible for VSC production.[15]
Bacteriocins produced by the microorganisms specifically Bifidobacteria species cause destruction of target cells by pore formation and/or inhibition of cell wall synthesis. Streptococcus salivarius produces bacteriocins, which inhibit bacteria producing VSC.[16]
Lactobacillus also exhibit antifungal properties by production antifungal substances and short-chain fatty acids that.[14] Teichoic acid present in the cell wall of L. plantarum is also known to possesses anti-inflammatory property.[17]

Interference in quorum sensing

Probiotic species are shown to interfere with quorum sensing. Lactobacillus acidophilus secretes a molecule that inhibits the cell signalling involved in quorum sensing or prevents bacterial colonization by directly interacting with gene transcription.[18]

4. Maintaining barrier integrity

Probiotic species stabilize the cellular cytoskeleton and preserve the epithelium barrier integrity by the release of metabolic products such as short chain fatty acids, which enhance the epithelial barrier integrity by regulating the expression and assembly of transmembrane proteins**.** Another mechanism is the overproduction of mucin which forms a physicochemical barrier protecting the epithelial cells against chemical and mechanical damage as well as limits microbial adherence and invasion.[19]

5. Inhibition of collagenases and reduction of inflammation associated molecules

Probiotic species can effectively reduce the levels inflammatory molecules, such as prostaglandin E2 and interferon-γ, and also inhibit the activity of matrix metalloproteinase in saliva thus reducing periodontal inflammation.[20]

6. Modulation of pro-inflammatory pathways induced by pathogens

Probiotic have the ability to regulate the balance of pro-inflammatory and anti-inflammatory cytokines. The pro-inflammatory cytokines TNF-α, IL-1β and IL-8 are reduced through action on NF-κβ pathways. Decreased production of IL-1β causes decreased production of other pro-inflammatory cytokines like IL-6, while there is increased production of anti-inflammatory cytokines such as IL-10.[21]

7. Host immune modulation

Probiotics may influence the innate and acquired immune system. Probiotics stimulate dendritic cells resulting in expression of Th1 or Th2, further modulating the immunity.[26]

Increased phagocytic capacity of macrophages has been reported, causing increased production of free oxygen radicals and lysozomal enzymes which is destructive to microorganisms.[10]

Probiotics are also known to regulate the expression of phagocytosis receptors in the neutrophils of healthy individuals and enhance the activity of natural killer cell.[22]

Probiotic also manifest immune modulation by the increased production of immunoglobulins (IgA), enhanced activity of macrophages and lymphocytes, and stimulation of interferon production.[7]

Clinical evidences supporting the effectiveness of probiotic

Table 1: Probiotic species and their health effect in the oral cavity (results from clinical trials)

Study	Probiotic	Vehicle	Clinical effects
Pozharitskaia et al.	five live lyophilized lactic acid bacteria.	Tablet Acilact	showed improved clinical and microbiological parameters in gingivitis and mild periodontitis patients and shift in local microflora towards gram-positive cocci and lactobacilli.[23]
Grudianov et al.	a mixture of probiotic strains.	Tablet	reduced microbiota and improved clinical parameters of gingivitis and periodontitis than control group.[24]
Ishikawa et al.	L. salivarius-containing	Tablet	reduced salivary counts of the black pigmented anaerobes (P. gingivalis, P. intermedia and Prevotella nigrescens).[25]
Narva et al.	Lactobacillus helveticus	Fermented milk	Lactobacillus helveticus contains small peptides that stimulate osteoblasts to promote bone formation, thus proposing important role in repair of periodontal bone destruction.[26]
Krasse et al.	Lactobacillus reuteri formulations	Tablet	Reduction in plaque and gingivitis scores and plaque in patients with moderate to severe gingivitis. L. reuteri secretes bacteriocins namely reuterin and reutericyclin, that inhibit the growth of a wide variety of pathogens.[27]
Shimauchi et al.	Lactobacillus salivarius WB21	Freeze-dried Tablet	improved periodontal status both in smokers and non-smokers. Salivary lactoferrin level was also significantly decreased in the test group smokers.[28]
Riccia et al.	Lactobacillus brevis	Lozenges	Anti-inflammatory effects with significant reduction in salivary levels of PGE2 and MMPs attributed to the ability of L. brevis to prevent the production of nitric oxide consequently.[20]
Twetman et al.	Lactobacillus reuteri	Chewing gum	showed significant reduction in gingival bleeding and decreased pro-inflammatory cytokines in gingival crevicular fluid (GCF) in the probiotic group.[21]

Vivekananda et al.	Lactobacillus reuteri	'Prodentis' Lozenges	improvements in the plaque scores and gingival inflammation with reduced pocket depth, increased attachment levels and significant reduction of periodontopathogens, considering that this therapy could serve as a useful adjunct or alternative to periodontal treatment.[29]
Shah et al.	Inersan® (a combination of the Lactobacillus brevis with doxycycline)	Lozenge	improved clinical and microbiologic parameters in the treatment of aggressive periodontitis.[30]
Volozhin et al.	L. Casei 37	Periodontal dressing	decrease in number and frequency of Bacteroids, Actinomyces and Str. intermedius in periodontal pockets and also Fungus (Candida albicans) with remission upto 10-12 months.[31]
Zahradnik et al.	Strep. Oralis KJ3sm, Strep. Uberis KJ2sm, and Strep. Rattus JH145	PROBIORA3 mouthwash	Decrease the levels of dental pathogens in saliva and periodontal pathogens in subgingival plaque.[32]

For potential probiotic action in the oral cavity the routes of administration should be such which provides prolonged contact with oral tissues and facilitating probiotic adhesion to saliva-coated surfaces. A lozenge, chewable tablet, chewing gum or even oral rinse might better serve the needs for periodontal health prophylaxis.

Probiotic-prebiotic

In 1995, Gibson and Roberfroid defined prebiotic as a "non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health".[33]

A combination of synergistically acting probiotics and prebiotics is termed as "synbiotics", where the prebiotic selectively favours probiotic bacteria for their growth and survival together with enhancing their mechanism of action.[33]

Natural sources	Artificial sources
Artichokes	lactulose
Asparagus	galactooligosaccharides
Garlic	fructooligosaccharides
onions	maltooligosaccharides
green vegetables	cyclodextrins
legumes	xylitol
berries	
bananas	
oats, barley, and wheat	

The improved efficacy of probiotic-prebiotic combination is limited to the gut. Though, there are no studies supporting the role of prebiotics in enhancing probiotic activity in the oral cavity, however, the prebiotic concept might still be advocated in the dental field if consumption of prebiotic carbohydrates would perhaps stimulate the probiotic strains to remain for longer period in the mouth.

Safety concerns

Although probiotic micro-organisms are classified by FDA as generally regarded as safe (GRAS), the issue of safety is of utmost concern, due to the increased probiotic supplementation of different food products, especially during the past few years.

Since they are live micro-organisms, there is a reasonable chance that these preparations might cause bacteraemia, particularly in critically ill and severely immune-compromised patients. It is for this reason that probiotics are contraindicated in patients with cardiac valvular disease, artificial heart valves as well as central venous catheters. It is also contraindicated in patients having hypersensitivity to lactose or milk products and with concurrent administration with broad-spectrum antibiotics, to which the probiotic is resistant.

L. rhamnosus is one such strain which has shown an increased risk of bacteraemia and endocarditis in animal studies and inhuman case reports.[34]

Conclusion and recommendation for future research

The earlier concept of bacterio-therapy which lost interest with the emergence of antibiotic therapy, is gaining momentum in current treatment scenarios. It is now recognized as one of the alternative approaches in the non-surgical periodontal treatment arena, as it plays an important role in combating the issues with overuse of antibiotics and antimicrobial resistance.[4]

Over the last few years a number of clinical studies have been conducted in the field of dentistry showing promising results. Though the periodontal studies are sparse and it needs more validation and reliability through more large scale multicentre clinical trials to understand the ability of probiotic bacteria to survive and grow, the therapeutic effect when used for treatment or when added to food, to fix the doses and schedules and vehicles of probiotics administration as well as the utility of probiotic-prebiotic combination. But it surely has opened the door for a new paradigm in treating periodontal disease.

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