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Role of probiotics in periodontal health maintenance

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Abstract

Periodontitis is an inflammatory disease characterized by destruction of tooth-supporting tissues. Frequent recolonization of treated sites and emergence of antibiotic resistance necessitates new therapeutic approaches for its management. Probiotics have been extensively studied as an alternate treatment option in many diseases including periodontitis as well as for their overall health promoting effects. Present article will help readers understand the current concepts regarding probiotic use in periodontics along with a brief review of recent studies.

Keywords: periodontal diseases, periodontitis, probiotics, Lactobacillus, Streptococcus, inflammation.

Introduction

Periodontitis is a dysbiotic, unique clinical condition which is usually chronic inflammatory in nature and results from a complex, multispecies interaction between the subgingival microbes and the host response that develop in the periodontal tissues in response to the bacterial challenge. Periodontitis is not considered as an infection in classical terms because of ambiguity over any single or group of microbial species responsible for its initiation. Although the etiologic role of plaque bacteria is vastly researched, major determinant of disease susceptibility is the nature of the host immune response itself.

Taking the disease characteristics in account, two major treatment strategies have been devised against

periodontitis - elimination of pathogens and suppression of self-destructive host response. Conventional management involves supra and subgingival mechanical debridement concurrent with supervised oral hygiene maintenance, which results in significant decrease in the subgingival bacterial load.[1,2] However, this reduction is interim and recolonization of pocket occurs within short period of time with establishment of more virulent periodontal pathogens.[3] To deter this recolonization, systemic antibiotics and topical mouth washes are usually commissioned which provide synergistic effects to scaling and root planing. These adjuncts are found to have limited long term effectiveness. Also, grave concerns regarding antibiotic use and abuse leading to bacterial resistance to antibiotics have led to demand for newer and more noble treatment approaches for periodontitis.[4]

Probiotic therapy is one of emerging adjunctive treatment approaches in periodontics with considerable interest for researchers in recent years. It focuses on altering the biofilm composition, thereby qualitatively and quantitatively affecting the bacterial virulence using different but inter-related mechanisms and ultimately helping in decreasing the disease severity and progression.[5]

Probiotics

Word "probiotic" has greek origin and it simply means- for life.[6] Milk and its other derivative products find their mention in ancient texts as being sacred with miraculous healing properties. **Ilya Metchnikof (1908)** anticipated that few bacterial products of some species of residing microflora have deleterious effects on small intestine and an overall effect on human aging. For such conditions, he advocated for diet containing portions of lactobacilli fermented dairy products.

Lilley and Stillwell in 1965 first gave the term "probiotic" and defined it as ''Substances produced by micro-organisms which promote the growth of other micro-organisms''. Over time, multiple definitions have been proposed.[7-11] ISAPP meeting held in the year 2013 proposed the latest definition of probiotics as, "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host".

Probiotic strains which are currently marketed come from genera Lactobacillus and Bifidobacterium. Lactobacillus species include *L. acidophilus, L. reuteri, L. rhamnosus, L. johnsonii, L. paracasei, L. gasseri, L. casei* and others. Similarly, bifidobacterium probiotic strains include *B. infantis, B. bifidum, and B. longum*.[12] Apart from them, strains of Saccharomyces, Streptococcus, Aspergillus, Propionibacterium, non-pathogenic strain of *E.coli, Clostridium butyricum* and Enterococcus are the others having probiotics potential.[13, 14]

Currently, established probiotic effects are

(1) Ease of symptoms in diseases like rotavirus- induced or antibiotic- linked diarrhea as well as mitigation of distress during lactose intolerance.[15-18]

(2) Positive effect on microbial imbalance occurring in inflammatory gastro-intestinal conditions, including *H. pylori* infection.[19-24]

(3) Easing of passing stool in constipation or irritable colon.[25, 26]

(4) Prevention and symptomatic relief from allergies in infants and children.[27-29]

Probiotics And Periodontal Diseases

In case of periodontitis, apart from an immuno- susceptive host and pathogenic microbial presence, third etiological factor - reduction or absence of ''beneficial or good bacteria'' becomes the basis of adjunctive probiotic therapy. Theoretically, restoration of reduced population of beneficial bacteria and host modulation with the help of probiotics promises to be a feasible and viable treatment

option in the prevention and treatment of chronic periodontal conditions.

Russian bacteriologists started evaluating the efficacy of different bacterial species as probiotics for their probable use in periodontitis treatment.[29-31] Initial attempts for bacterial manipulation of oral microbiota were done by **Hillman and Shivers** using streptococcus spp. in 1985. Other Streptococci have also been studied for the potential use in periodontal diseases, like *Streptococcus oralis, Streptococcus rattus* and *Streptococcus uberis*. Lactobabillus strains used for same purpose includes *Lactobacillus salivarius, Lactobacillus rhamnosus, Lactobacillus brevis* and *Lactobacillus reuteri*.[12, 14, 32]

Mechanism of Action Of Probiotics

Literature suggests that oral probiotics may require some additional properties as compared to their gastro-intestinal counterparts, including more evolved hard and soft tissue adhesion and colonization properties to become part of the biofilm covering these surfaces. Also, carbohydrate fermentation by these bacteria would be undesirable as this can provide substrate to cariogenic bacteria. Principally, these pre-requisite might seem required, but evidence is lacking as present.

Periodontal effects of probiotics can be through:

(1) Host immunomodulation

(2) Production of antimicrobial proteins

(3) Competitive exclusion of periopathogens using different mechanisms.

(1) Host immunomodulation

Recognition of cellular components of probiotic bacteria or their metabolic by-products by immune responsive host cells such as epithelial cells helps in modulation of immune system.[33,34] Some of lactobacilli strains like *L. plantarum, L. brevis, L. rhamnosus* and *L. lactis* have been proven to have the ability to positively modify the balance of pro and anti-inflammatory cytokines produced and secreted by epithelial cells which can be observed in terms of levels of TNF-α, IL-1, IL-6 and reduced level of IL-8 in inflammatory conditions of the intestine.[35]

Probiotics have been proven to promote natural killer cell activity of neutrophils through signaling pathways by controlling expression of its phagocytosis receptors. To exemplify, macrophages have been observed to show higher phagocytic activity in presence of *L. casei* and *L. acidophilus*.[36]

Other mechanisms affecting the host response by probiotics include stimulated expression of cytoprotective proteins on cell surfaces of the host and suppression of cytokine-induced apoptosis.[37] Suppression nuclear factor kβ-pathway is also considered as one of the possible mechanisms but exact pathway is not clear till now.[38, 39]

(2) Production of antimicrobial proteins

Probiotic bacteria produce many biomolecules that can possess antimicrobial property such as lactic acid, bacteriocins & bacteriocin-like inhibitory substances and some reactive oxygen species.[34,40,41] Metabolic acids such as lactic acid has the ability to cross the bacterial cell envelope and cause cytoplasmic damage by causing acidification and thereby inhibiting bacterial proliferation. This inhibitory action is more pronounced as the availability of lactic acid increases.[42]

Evidence from various in-vitro and in-vivo studies demonstrate that synthesis of hydrogen peroxide by *S. sanguinis* can restrict growth of periodontopathogenic bacteria.[43-46]

Bacteriocins and Bacteriocin-like inhibitor substances are positively charged peptide ions having range of antimicrobial activities. *S. salivarius* produces class of bacteriocin termed as Salivaricin B which is effective against Prevotella and Micromonas spp. induced halitosis.[47] Also, bacteriocin from *Lactobacillus paracasei*

HL32 can fatally affect *P. gingivalis* by altering its cellular envelope.[48]

(3) Competitive exclusion of periopathogens using different mechanisms -:

It works through two different mechanisms:

a) Decreasing adhesion sites available for pathogenic bacteria or

b) Competition for same nutrients.

3.a). Hindering the adhesion of pathogenic bacteria

There are evidences available for competitive antagonistic bacterial strains like streptococcus species to cause interference in initiation or progression of disease process either by harboring themselves over the available surface and making it unavailable for pathogenic bacteria to occupy or actively restricting the adhering potential of periopathogens using different means.[49-52]

Release of biosurfactant molecules causing decrease in surface tension over the areas of adhesion is another mode of action for probiotics to prevent colonization. In one of the studies, surfactant generated by a *S. mitis* decreased the adhesion of several periodontal pathogens including *S. mutans*.[51]

some probiotic strains deteriorate salivary pellicle composition by detaching salivary agglutinin gp340, a protein compulsory for *S. mutans* adhesion which ultimately leads to decreased colonization potential of *S. mutans*.[52]

3.2 Competition for same nutrients

Periodontopathogens require specific nutrients for their optimal growth. For example, *P. intermedia* uses vitamin K and progesterone or estrogen for same purpose. Better adapted probiotic bacteria, if compete with pathogenic microbiota for these nutrients and outperform them, can drastically decrease periodontal disease initiation and progression. More studies are needed to confirm this feasible theoretical possibility a theory.[53,54]

(4). Other mechanisms of probiotic action

In order to augment and synergize the effectiveness, probiotics are usually prescribed in proportion based combinations. In addition, it is imperative to note that different formulations from strains of a single species can have different or antagonistic effects, which further calls for far more extensive research in this field.

Adverse Effects

Increased oral use of probiotics over the years as a dietary supplement has raised safety concerns because of its potential to interact with systemic circulation. But they are generally considered biocompatible with mild side effects.[57] Although very few, but serious complications like probiotics-related bacteremia, liver abscess, bacterial endocarditis has been reported in susceptible individuals having debilitating illness and immunosuppression. As per statistics, 1 per 1 million population consuming lactobacilli probiotics orally are at risk of developing associated bacteremia that responds well to antibiotic therapy.[58]

Evidence based risk factors for probiotics-associated sepsis have been categorized. Major risk factors comprise of immunodeficiency, premature infants and malignancy. Minor risk factors are -central venous catheterization, gastro-intestinal epithelial barrier damage, valvular defects of heart, simultaneous application of such antibiotics to which the probiotic is non-sensitive and administration of probiotics through jejunostomy tube. Literature cautions use of probiotics in patients with one major risk factor or more than one minor risk factor and in patients taking chemotherapeutic drugs and immunosuppressants. Lactobacilli probiotics are used with caution in subjects with lactose intolerance. Bifidobacteria, due to their non-pathogenicity, are not contraindicated in any specific clinical condition.[57]

Conclusion

Despite lack of concrete understanding about probiotic bacteria in terms of its survival and growth in subgingival niche, mechanisms of action, comparative efficacy of different probiotic strains in specific oral conditions and ideal means of their administration; there is increasing evidence that the use of probiotics can reduce periodontal inflammation in addition to improvement of periodontal health in general. With ever improving in-vitro and in-vivo biotechnology and genetic engineering techniques, better scientific understanding regarding above mentioned aspects of probiotics might further broaden the horizon of periodontal probiotics.

Recent Clinical Trials Evaluating Probiotic Effectiveness In Periodontal Disease

Study	Study design	Probiotic	Periodontal Assessment parameters	Results
Ishikawa et al.[59]	Parallel, open label	L. salivarius TI 2711	Bacterial numbers in saliva	Significant decrease in count of black pigmented anaerobic rods
Matsuoka et al.[60]	Double-blind, Placebo controlled	L. salivarius TI 2711	(1) Probing pocket depth (2) Bleeding on probing	Significant reduction in both parameters
Sugano et al.[61]	Double-blind, Placebo controlled	L. salivarius TI 2711	Subgingival bacterial population	Significant improvement in microbial parameters, but P. gingivalis count returned to pre-treatment 4 weeks after discontinuing probiotic.
Teughels et al.[49]		Mixture of pure S. salivarius, S.mitis and S. sanguinis		Study provides proof of concept for guided pocket recolonization (GPR) approach in the treatment of periodontitis.
Della Riccia et al.[62]	Randomized, double blind, paired comparison study	L. brevis	Clinical and inflammatory markers	Test group showed significant improvement in all clinical parameters as well as decreased level of inflammation-associated molecules
Shimauchi et al.[5]	Randomized, double blind,	L. salivarius WB21	Clinical parameters, Salivary Lactoferrin	Both the groups showed improved clinical parameters. Also, significantly

	placebo controlled trial			decreased salivary lactoferrin level in the smokers included in the test group
Mayanagi et al.[63]	Randomized, double blind, placebo controlled	L. salivarius	Microbiological parameters	Reduced count of red complex bacteria and A. Actinomycetemcomitans in the subgingival plaque at 4 weeks. Also, Significant reduction of T. forsythia at both 4 and 8 weeks.
Vivekanananda et al.[64]	Double blind,randomized, split mouth design, placebo controlled	L. reuteri DSM17938 with L. reuteri ATCC PTA5289	Clinical and microbiological parameters	Significant improvement in clinical as well as in microbial parameters in groups treated with probiotics.
Suzuki et al.[65]	Double blind,randomized, placebo controlled	L. salivarius WB21	Clinical parameters, stimulated salivary volume, Salivary pH, Microbiological parameters	Improved clinical as well as microbial parameters.
Iniesta et al.[66]	placebo-controlled, parallel	L. reuteri ATCC 55730 ATCCPTA 5289	Inflammatory clinical and microbiological parameters	Decreased count of periodontopathogens in probiotic group without much difference in plaque and gingival indices.
Hallstrom et al.[67]	double-blind randomized placebo-controlled cross-over design	L. reuteri ATCC 55730 ATCCPTA 5289	Clinical parameters and biomarkers	No significant differences in clinical as well as biological markers.

Teughels et al.[68]	Randomized, double blind, placebo controlled	L. reuteri DSM17938 with L. reuteri ATCC PTA5289	Clinical and Microbiological parameters	Probiotic group showed probing pocket depth reduction, clinical attachment gain and reduction in overall pathogenic bacterial count.
Vicario et al.[69]	randomized, parallel, double blind, placebo controlled	L. reuteri ATCC 55730 with L. reuteri ATCC PTA5289	Clinical parameters	Significant improvement in clinical parameters.
Shah et al.[70]	Randomized controlled trial	L. brevis	Clinical and microbiologial parameters	Increase in Lactobacilli counts in saliva after probiotic consumption.
Tekce et al.[71]	Randomized, double blind, placebo controlled	L. reuteri	Clinical and microbiological parameters	Significant reduction in clinical parameters in the probiotic group. Reduction in the obligate anaerobe counts
Ince et al.[72]	Randomized, double blind, placebo controlled	L. reuteri	Clinical and biochemical parameters	Clinical parameters significantly improved in the probiotic group. Significant mean attachment gain in probiotic group. Decreased GCF MMP-8 levels and increased TIMP-1 levels.
Laleman et al.[73]	Randomized, double blind, placebo controlled	Mixture of S. oralis, S. uberis and S. rattus.	Clinical and microbiological parameters	Improvements in P. intermedia count and plaque index in probiotic group.
Toiviainen et al.[74.]		L. rhamnosus and B. subtilis	Plaque and gingival index	PI, GI lowered in probiotic group

Lee et al.[75]		L. brevis CD2	PI, GI BOP	No significant difference in PI, GI. BOP reduced in probiotic group
Morales et al.[76]	Randomized, double blind, placebo controlled, parallel study	Lactobacillus rhamnosus SP1	Clinical parameters	Significant reduction in probing pocket depth at sites with PPD ≥ 6mm.

PPD = Probing pocket depth, **REC** = Gingival recession, **GI** = Gingival index, **PI** = Plaque index, **BOP** = Bleeding on probing, **CAL** = Clinical attachment level, **GBI**=Gingival bleeding index