Review Article

Intelligent nutrition: Oral health promotion by probiotics

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ABSTRACT

Probiotic bacteria have been added to various foods because of their beneficial effects for human health, especially gut. Numerous studies have proved definite reliability of these viable bacteria in the treatment of gastrointestinal infections and diseases. The effect of probiotic in prevention and treatment of various oral disorders is also being studied. Although only a few clinical studies have been conducted so far, the results to date suggest that probiotics could be useful in preventing and treating oral infections, including dental caries, periodontal disease, and halitosis. This article summarizes the currently available data on the potential benefits of probiotics for oral health.

Key words: Nutrition, oral health, probiotics

Introduction

Probiotics are defined as living microorganisms, principally bacteria, that are safe for human consumption and, when ingested in sufficient quantities, have beneficial effects on human health, beyond basic nutrition. This definition has been approved by the United Nations Food and Agriculture Organization (FAO) and the World Health Organization (WHO).[1] The term "probiotics" was derived from a Greek word meaning, "for life."[2] The concept probably dates back to 1907, when Noble prize winner Eli Metchnikoff suggested that the long life of Bulgarian peasants resulted from their consumption of fermented milk products.[3] The term "probiotic" as opposed to antibiotic was initially proposed by Lilly and Stillwell in 1965. 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]

The vast majority of probiotic bacteria belong to the genera *Lactobacillus, Bifidobacterium, Propionibacterium,* and *Streptococcus*. Foods of human consumption such as fermented milk, cheese, fruit juice, and sausages mainly contain lactic acid bacteria as probiotic. Single or mixed cultures of live microorganisms are used in probiotic preparations. The effectiveness of probiotics have already been demonstrated by several clinical studies in the treatment of systemic and infectious diseases as infantile diarrhea, necrotizing ulcerocolitis, *Helicobacter pylori* infection, inflammatory bowel disease to cancer, female uro-genital infections, and surgical infections.[2] The introduction of these beneficial species into the GI tract has also proved to be a very attractive option to establish the microbial equilibrium that has been lost due to antibiotic usage, immunosuppressive therapy, and irradiation therapy.

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Properties of probiotics

Properties of an ideal probiotic preparation for oral use have been illustrated in Figure 1. For adequate amount of health benefit, a dose of five billion colony forming units a day (5×10^9 CFU/day) has been recommended, for at least five days. The microorganism, to be used clinically as a probiotic, both *in vitro* and *in vivo* studies must be conducted to demonstrate their mechanism of action, to allow prediction of its scope of applicability and its potential side-effects.[2] Importantly, they should also not carry transmissible antibiotic resistance genes.

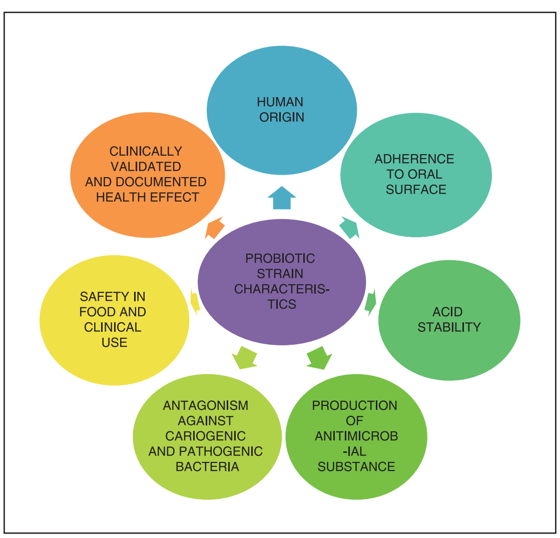
Mechanism of action of probiotics

Several mechanisms have been postulated regarding action of probiotics [Figure 2]. These bacteria produce several metabolites like free fatty acids, hydrogen peroxide, bacteriocin etc., which interfere with the growth of other pathogens. Dental caries involves the use of oral streptococci that are able to metabolize arginine or urea to ammonia.[5] A bacterium, *S. oligofermentans*, could be only isolated from caries-free human subjects, was found to metabolize lactic acid into hydrogen peroxide, thus inhibiting the growth of *S. mutans*.[6]

Probiotic bacteria can specifically co-aggregate with the pathogenic bacteria. A recent study has demonstrated selective interaction of mutans streptococci with *L. paracasei* or *L. rhamnosus* facilitating their removal from the mouth without disruption of other oral flora.[7]

Probiotics can also use enzymatic mechanism to modify toxin receptors and block toxin-mediated pathology. Certain bacterial strains contain enzymes that prevent formation of harmful metabolites. *Lactobacillus brevis* could be attributed to the presence of Arginine Deiminase enzyme (AD), which prevented nitric oxide generation and hence can reduce inflammatory response of periodontal tissues. They prevent colonization of pathogens by competitive inhibition.[8] Hillman and colleagues introduced a non-acid-producing *S. mutans* strain that produces a bacteriocin, active against other *S. mutans* strains into the oral cavity to replace the naturally occurring cariogenic strains.[9]

Figure 1: Properties of an ideal probiotic preparation for oral use



Co-infection of rats with oral streptococci *S. salivarius* TOVE-R and *S. mutans* reduced dental caries incidence relative to the later organisms alone. This is likely due to the ability of TOVE-R to pre-empt the initial colonization of teeth surface and displace the cariogenic *S. mutans* that has already colonized the teeth surface.[10]

Studies have also shown that probiotic bacteria modulate immunoglobulin production (secretory IgA), which plays an important role in mucosal immunity, contributing to the barrier against pathogenic bacteria and viruses.[11,12] The increase in certain cytokines (TNF-α, IFN-γ, IL-10) has also been observed due to stimulation with probiotic bacteria.[13]

Hence, the probiotic bacteria in oral cavity, creates a biofilm, acting as a protective lining for oral tissues against oral diseases. Such a biofilm keeps bacterial pathogens off oral tissues by filling the space pathogens would invade in the absence of the biofilm, and competing with cariogenic bacteria and periodontal pathogens growth.

Probiotic approach in the management of dental caries

Dental plaque shows higher degree of organization. Within an established dental plaque, specific bacterial species are often found located adjacent to each other or mixed together to form unique structures that may confer adherence or growth advantages. Based on our current knowledge, it is reasonable to assume that the interactions between the oral microbial residents may influence the properties of the whole community. For example, in the presence of nearby base-producing bacteria, *S. mutans* in dental plaque may not be pathogenic. It is now recognized that dental caries results

Figure 2: Potential mechanism of action of probiotic bacteria in the oral cavity

AMTIMICROBIAL ACTIVITY	COLONIZATION RESISTANCE	IMMUNE EFFECT	INFLUENCE ENZYME ACTIVITY
• HYDROGEN PEROXIDE • BACTERIOCIN • LACTIC ACID • AMMONIA	• COMPETE FOR GROWTH FACTORS • COMPETE FOR NUTRIENTS • COMPETE FOR ADHESION SITES • COAGGREGATION	• CYTOKINES (TNF-α, IFN-γ, IL-10) • IgA • DECREASED MMP PRODUCTION • ADJUVENT EFFECT • STIMULATION OF PHAGOCYTES	• MODIFY TOXIN RECEPTORS • BLOCK TOXIN MEDIATED PATHOLOGY

not solely because of the presence of *S. mutans, rather*, it's the interaction of multiple acid-producing organisms such as *S. mutans* with other biofilm residents.[1] This dynamic balance of synergistic and antagonistic interactions with the neighboring bacteria has offered the probiotic strategies for dental caries treatment and prevention.

Hence, to have a beneficial effect in limiting or preventing dental caries, a probiotic must be able to adhere to dental surfaces and integrate into the bacterial communities making up the dental biofilm. It must also compete with and antagonize the cariogenic bacteria and thus prevent their proliferation. A recent study showed that some specific Lactobacillus strain has the capacity to adhere and form a biofilm on HA surface, hence replacing the more cariogenic pathogens.[15] Haukioja and colleagues investigated in vitro the effect of probiotic bacteria used in commercial products in the adherence of two oral streptococci, Streptococcus mutans and Streptococcus gordonii. The results of their research showed that probiotic bacteria that bound to saliva-coated hydroxyapatite reduced the adhesion of *S. mutans*, but the inhibitory effect on the adherence of *S. gordonii* was weaker.[16] Hence, these studies clearly suggest that commercial probiotic products competitively prevents the adhesion of the pathogenic bacteria to the dental surfaces. However, adhesion of common probiotic strains of Lactobacillus and Bifidobacterium in the oral cavity greatly varies, resulting in the difference in their survival and achieving the probiotic effect.[17]

Several studies have also shown that consumption of products containing probiotics bacteria could reduce the number of mutans streptococci in saliva, hence providing protection against dental caries.[18-28] However, these results are highly inconclusive as the same strain of probiotic has shown dissimilar effects[29,30] [Table 1]. Importantly, these clinical trials are also of short duration, and number of individuals participating in the study is also less. Lodi and colleagues (2010) in their study has presented that fermented milk containing probiotic decreased the pH of dental biofilm and promoted demineralization of the enamel.[31] Whereas others have suggested in their *in vitro* studies that, final pH in the medium is an important factor for growth inhibition, either directly or due to the production of bacteriocins at low pH. The antimicrobial activity of *Lactobacillus* spp. against *S. mutans* is pH-dependent and lower the final pH, higher the inhibition.[32]

Other bacteria have also shown probiotic effect against dental caries. ProBiora3, an oral probiotic mouthwash product consisting of a mixture of *Strep. uberis* strain KJ2smTM, *Strep. oralis* strain KJ3smTM, and *Strep. rattus* strain JH145TM, has been shown to be safe and effective in reducing salivary levels of mutans streptococci, preserving dental health in young orally healthy adults.[33]

Probiotic approach in the management of periodontal disease

The main pathogenic agents associated with periodontitis are *P. gingivalis*, *Treponema denticola*, *Tannerella forsythia,* and *Aggregatibacter actinomycetemcomitans*. Studies have reported the capacity of lactobacillus to inhibit the growth of these pathogens. Probiotic strains used include *L. reuteri* strains, *L. brevis* [CD2], *L. casei Shirota*, *L. salivarius* B21, and *Bacillus subtilis*.[34] Effect of probiotic tablets on gingivitis and different grades of periodontitis has been studied where probiotic treatment resulted in better normalization than control groups. Krasse and colleague assessed the beneficial effects of *L. reuteri* against gingivitis. After 14 days of ingestion of probiotic-incorporated chewing gum, there was a reduction in plaque index, and concluded that this probiotic was effective to reduce gingivitis and bacterial plaque deposition in patients with moderate to severe gingivitis.[33]

Table 1: Summary of studies showing interference of probiotic bacteria with *S. mutans* growth

Reference	Type of study	Probiotic strain used, Dose, Vehicle	Outcome
Näse *et al*.[18]	RCT, DB	*L. rhamnosus* GG milk	Decrease counts of MS in saliva, reduced caries
Ahola *et al*.[19]	RCT, DB	*L. rhamnosus* cheese 5 x 15 g/day for 3 weeks	Decreased counts of yeast and MS in saliva
Nikawa *et al*.[20]	RCT, cross-over	*L. reuteri* yoghurt	Decrease counts of MS in saliva
Caglar *et al*.[22]	placebo-controlled study design	*L. reuteri* via straw and tablet	Decrease counts of MS in saliva via both straw and tablets containing probiotic
Caglar *et al*.[23]	RCT	*L. reuteri* gums (3 times/day after meal for 3 weeks) with or without xylitol and xylitol alone	Daily chewing on gums containing probiotic or xylitol reduced the levels of salivary MS in saliva. No synergistic effect in probiotic + xylitol
Caglar *et al*.[25]	RCT, DB	*L. reuteri* lozenges once daily for 10 gays.	Reduced the levels of salivary mutans on consumption of probiotic lozenges
Stecksén *et al*.[28]	Cluster-randomized study, DB	Milk supplemented with *Lactobacillus rhamnosus* LB2 and 1 2.5 mg fluoride per liter. 150 ml/day for 21 months	Reduced caries
Montalto *et al*.[29]	RCT	*Lactobacillus* spp. In liquid and capsule	Increased salivary counts of LB, MS unchanged for both the groups
Lexner *et al*. [30]	RCT, DB, pilot study	*L. rhamnosus* 2.5 dl milk/day for 2 weeks	Unchanged MS and LB in the saliva
Caglar *et al*.[22]	RCT, cross-over	*Bifidobacteria* Yoghurt, placebo 200 gm once daily	Decreased counts of MS in saliva
Taipale *et al*[24]	Pilot study	Tablet contained 300 mg xylitol and 0.5 x 10(10) colony-forming units of *Bifidobacterium lactis*	Result in salivary xylitol concentrations high enough to inhibit mutans streptococci *in vivo*.
Cildir *et al*.[27]	Double-blind, randomized crossover study	Fruit yogurt containing probiotic *bifidobacteria* in fixed orthodontic patients 200 gm/day	Decreased counts of MS in saliva

RCT: Randomized control trial, DB: Double-blind, MS: Mutans streptococcus, LS: Lactobacilli

Riccia and colleagues studied the anti-inflammatory effect of *lactobacillus brevis* in a group of patients with chronic periodontitis. Sucking lozenges with *L. brevis* for 4 days improved plaque index, gingival index, and bleeding on probing with also a significant reduction in salivary levels of prostaglandin E_2 and matrix metalloproteinases.[35] Although promising results has been obtained by all these studies, most studies are of very short duration, small sample size, and the difference in results being very small though statistically significant.

Halitosis

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 sulfur compounds, including hydrogen sulfide and methanethiol. In a pilot study, *Streptococcus salivarius* K12, a pioneering colonizer of oral surface and excellent numerically predominant non-disease-associated member of the oral microbiota of healthy humans, have been effectively used as a probiotic to replace bacteria implicated in halitosis. Decrease in volatile sulfurcompounds was seen after administration, but it was used after the use of an antimicrbial mouthwash. *Weissella cibaria* has also shown to reduce the levels of volatile sulfur compounds produced by *Fusobacterium nucleate.*[36]

Conclusion

Probiotic represents a new area of research in dentistry to combat oral diseases in a model approach. The preliminary data obtained from numerous studies have shown promising results; however, the effects of individual strains have to be studied in detail. The long-term effects as well as colonization of the probiotic species in the oral cavity also has to be explored. The mode of use or the vehicle of delivery of these probiotic, to be effective for oral use, also needs further research. Hence, continued expansion of such information in the future may enable an exogenous modulation of the interactions between oral biofilm constituents, and thereby result in novel approaches for controlling biofilm activities and oral diseases.

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