Probiotics for Oral Health: Myth or Reality?

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ABSTRACT

For some decades now, bacteria known as probiotics have been added to various foods because of their beneficial effects for human health. The mechanism of action of probiotics is related to their ability to compete with pathogenic microorganisms for adhesion sites, to antagonize these pathogens or to modulate the host's immune response. The potential application of probiotics for oral health has recently attracted the attention of several teams of researchers. 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.

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Each day, every human being ingests a large number of living microorganisms, predominantly bacteria. Although these organisms are naturally present in food and water, they can also be deliberately added during the processing of foods such as sausages, cheese, yogourt and fermented milk products. For several decades now, bacteria called probiotics have been added to some foods because of their beneficial effects for human health.[1] The bacteria in yogourt and fermented milk products constitute the most important source of probiotics for humans. The vast majority of probiotic bacteria belong to the genera *Lactobacillus, Bifidobacterium, Propionibacterium* and *Streptococcus*. Several clinical studies have already demonstrated the effectiveness of certain probiotics in the treatment of systemic and infectious diseases such as acute diarrhea and Crohn disease.[1] Other studies have suggested potential applications in the treatment of cardiovascular disease, urogenital infections, oropharyngeal infections and cancers.[1-3] Probiotics may also prove useful in addressing problems arising from the excessive use of antibiotics, specifically the appearance of bacterial resistance. To date, however, the potential beneficial effects of probiotics for oral pathology have had only limited study.

Characteristics of Probiotics

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).[4] The establishment of standards and guidelines constituted an essential step in the acceptance of probiotics as legitimate health-related products. To be called a probiotic, a bacterial strain must be fully characterized.[5] The genus and species of the microorganism must be identified according to internationally accepted methods, and its nomenclature

corroborated by reference to the Approved Lists of Bacterial Names.[6] In addition, both in vitro and in vivo studies must be conducted to demonstrate the mechanism of action of the probiotic, to allow prediction of its scope of applicability and its potential side effects. The FAO and the WHO have recommended that probiotic bacterial strains be characterized by their spectrum of resistance to antibiotics, their metabolic and hemolytic activities, their capacity to produce toxins, their infectious power in immunosuppressed animal models and their side effects in humans.[6] Probiotics that have been so characterized are then submitted to randomized clinical studies. The results of such studies should demonstrate an improvement in participants' health and quality of life.

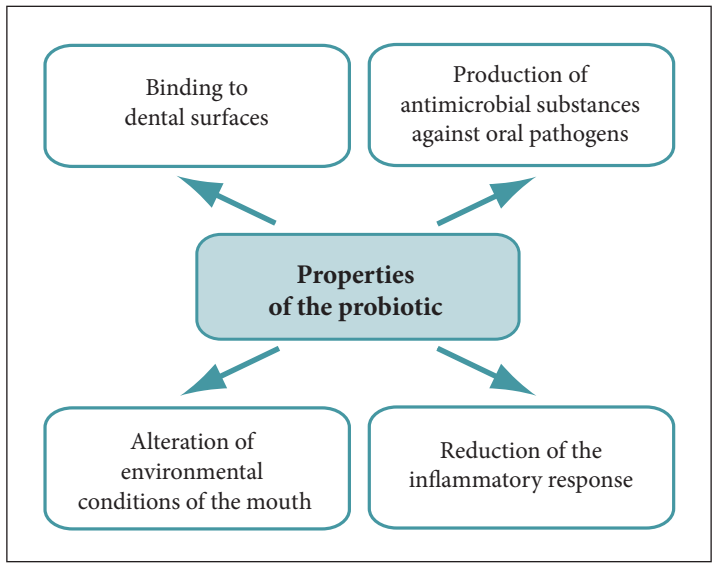

Figure 1: Ideal properties of a probiotic intended for use in disorders of the mouth.

How Probiotics Work

Several mechanisms have been proposed to explain how probiotics work (**Fig. 1**). For example, these bacteria secrete various antimicrobial substances such as organic acids, hydrogen peroxide and bacteriocins.[6] In addition, they compete with pathogenic agents for adhesion sites on the mucosa.[3,7] Probiotics can also modify the surrounding environment by modulating the pH and/or the oxidation–reduction potential, which may compromise the ability of pathogens to become established. Finally, probiotics may provide beneficial effects by stimulating nonspecific immunity and modulating the humoral and cellular immune response.[8] A combination of probiotic strains is often used to increase these beneficial effects.[5]

Application of Probiotics to Oral Health

Probiotics of Interest

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. An essential condition for a microorganism to represent a probiotic of interest for oral health is its capacity to adhere to and colonize various surfaces of the oral cavity.[9,10]

Lactobacilli constitute about 1% of the cultivable oral microflora in humans.[11] The species most often found in saliva are *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus fermentum*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus* and *Lactobacillus salivarius*.[11] *L. acidophilus*, *L. casei*, *L. fermentum* and *L. rhamnosus* are found in dairy products,[9,12] but there is no evidence that these species are present in the oral cavity as a result of frequent consumption of dairy products (leading to temporary colonization), nor is there evidence that the oral environment represents their natural and permanent habitat. Sookkhee and colleagues[13] isolated 3,790 strains of lactic acid bacteria from 130 individuals and found that the isolates identified as *Lactobacillus paracasei* ssp. *paracasei* and *L. rhamnosus* had a high capacity to antagonize important oral pathogens, including *Streptococcus mutans* and *Porphyromonas gingivalis*.

Weissella cibaria (formerly classified in the genus *Lactobacillus*), a Gram-positive facultative anaerobic lactic acid bacterium[14] that has been isolated from humans, is present in fermented foods and is considered a potential probiotic agent. *W. cibaria* secretes a significant quantity of hydrogen peroxide,[15] as well as a bacteriocin that acts against Gram-positive bacteria.[16] This bacterial species has the capacity to coaggregate with *Fusobacterium nucleatum* and to adhere to epithelial cells.[15] These properties could enable *W. cibaria* to effectively colonize the oral cavity and limit the proliferation of pathogenic bacteria.

Recently, Haukioja and colleagues[17] assessed the survival in saliva and adherence to oral surfaces of various probiotics used by the dairy industry (specifically, species of both *Lactobacillus* and *Bifidobacterium*). All of the strains tested survived well in saliva, but they varied widely in their capacity to adhere to the surface of teeth and oral mucosa. More specifically, species in the genus *Lactobacillus* had an adherence capacity superior to that of the *Bifidobacterium* species. Moreover, it has been reported that people who have consumed yogourt containing *L. rhamnosus* on a daily basis host this microorganism in the saliva for up to 3 weeks after discontinuing yogourt consumption.[18] However, contradictory results were obtained by Yli-Knuuttila and colleagues,[19] who reported that a strain of *L. rhamnosus* colonized the oral cavity only temporarily and that consistent

consumption of the probiotic would be necessary for long-term beneficial effects. Together, these results suggest that the probiotics used in consumer products could colonize the oral cavity.

Probiotics and Dental Caries

Dental caries is a multifactorial disease of bacterial origin that is characterized by acid demineralization of the tooth enamel.[20] It appears following changes in the homeostasis of the oral ecosystem leading to proliferation of the bacterial biofilm, composed notably of streptococci from the mutans group. 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. Finally, metabolism of food-grade sugars by the probiotic should result in low acid production. The advantage of incorporating probiotics into dairy products lies in their capacity to neutralize acidic conditions. For example, it has already been reported that cheese prevents demineralization of the enamel and promotes its remineralization.[21,22]

Comelli and colleagues[10] reported that of 23 bacterial strains used in the dairy industry, *Streptococcus thermophilus* and *Lactobacillus lactis* ssp. *lactis* were the only ones with the capacity to integrate into a biofilm present on a hydroxyapatite surface and to interfere with development of the cariogenic species *Streptococcus sobrinus*. More recently, it was demonstrated that isolates of *W. cibaria* had the capacity to inhibit, both in vitro and in vivo, biofilm formation by *S. mutans* and to prevent proliferation of this bacterial strain.[23] In other studies, one strain of *L. rhamnosus* and the species *L. casei* inhibited in vitro growth of 2 important cariogenic streptococci, *S. mutans* and *S. sobrinus*.[12,24] More recently, Petti and colleagues[25] reported that yogourt containing *S. thermophilus* and *L. bulgaricus* had selective bactericidal effects on streptococci of the mutans group. Several clinical studies have demonstrated that regular consumption of yogourt, milk or cheese containing probiotics led to a decrease in the number of cariogenic streptococci in the saliva and a reduction in dental plaque.[12,26-28] More specifically, Nikawa and colleagues[28] reported that consumption of yogourt containing *Lactobacillus reuteri* over a period of 2 weeks reduced the concentration of *S. mutans* in the saliva by up to 80%. Comparable results were obtained by incorporating probiotics into chewing gum or lozenges.[27,29]

In 2001, Näse and colleagues[12] published the results of a long-term (7-month) study of 594 children 1 to 6 years of age that evaluated the effects on dental caries of consuming milk supplemented with a strain of *L. rhamnosus*. The authors concluded that children consuming milk containing this probiotic, particularly those 3–4 years of age, had significantly fewer dental caries and lower salivary counts of *S. mutans* than controls. These promising results suggest a potentially beneficial application of probiotics for the prevention of dental caries.

Probiotics and Periodontal Disease

Periodontal disease is classified into 2 types: gingivitis and periodontitis. Gingivitis is characterized by inflammation limited to the unattached gingiva, whereas periodontitis is a progressive, destructive disease that affects all supporting tissues of the teeth, including the alveolar bone.[30] The main pathogenic agents associated with periodontitis are *P. gingivalis, Treponema denticola, Tannerella forsythia* and *Aggregatibacter actinomycetemcomitans*.[30] These bacteria have a variety of virulent characteristics allowing them to colonize the subgingival sites, escape the host's defence system and cause tissue damage.[30] The persistence of the host's immune response also constitutes a determining factor in progression of the disease.[30]

> In one recent study, the prevalence of *Lactobacillus gasseri* and *L. fermentum* in the oral cavity was greater among healthy participants than among patients with chronic periodontitis.

In one recent study, the prevalence of lactobacilli, particularly *Lactobacillus gasseri* and *L. fermentum*, in the oral cavity was greater among healthy participants than among patients with chronic periodontitis.[31] Various studies have reported the capacity of lactobacilli to inhibit the growth of periodontopathogens, including *P. gingivalis*, *Prevotella intermedia* and *A. actinomycetemcomitans*.[13,31] Together, these observations suggest that lactobacilli residing in the oral cavity could play a role in the oral ecological balance.

Krasse and colleagues[32] assessed the beneficial effect of *L. reuteri* against gingivitis. After 14 days of ingesting the probiotic incorporated into chewing gum, the oral cavity of patients with a moderate to severe form of gingivitis had been colonized by *L. reuteri* and the plaque index had been reduced. Although the exact mechanisms of action of *L. reuteri* remain to be elucidated, previous studies have suggested at least 3 plausible possibilities: first, *L. reuteri* is known for its secretion of 2 bacteriocins, reuterin and reutericyclin, that inhibit the growth of a wide variety of pathogens[33,34]; second, *L. reuteri* has a strong capacity to adhere to host tissues, thereby competing with pathogenic bacteria[35]; and third, 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 people with periodontal disease.[36,37] However, additional studies with larger patient cohorts are needed to confirm the long-term potential of *L. reuteri* in preventing and/or treating gingivitis.

Riccia and colleagues[38] recently studied the anti-inflammatory effects of *Lactobacillus brevis* in a group of patients with chronic periodontitis. The treatment, which involved sucking on lozenges containing *L. brevis* over a period of 4 days, led to improvements in the targeted clinical parameters (plaque index, gingival index, bleeding on probing) for all patients. In that study, a significant reduction in salivary levels of prostaglandin E_2 (PGE_2) and matrix metalloproteinases (MMPs) was also observed. The authors suggested that the beneficial anti-inflammatory effects of *L. brevis* could be attributed to its capacity to prevent the production of nitric oxide and, consequently, the release of PGE_2 and the activation of MMPs induced by the nitric oxide.[38] However, *L. brevis* may also be antagonistic, leading to a reduction in the quantity of plaque and therefore an improvement in the gingival index.

During the fermentation process in milk, *Lactobacillus helveticus* produces short peptides that act on osteoblasts and increase their activity in bone formation.[39] These bioactive peptides could thereby contribute to reducing the bone resorption associated with periodontitis.

Recently Shimazaki and colleagues[40] used epidemiological data to assess the relationship between periodontal health and the consumption of dairy products such as cheese, milk and yogourt. The authors found that individuals, particularly nonsmokers, who regularly consumed yogourt 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 not observed with milk or cheese. By controlling the growth of the pathogens responsible for periodontitis, the lactic acid bacteria present in yogourt would be in part responsible for the beneficial effects observed. Longitudinal studies are required, however, to clarify the observed relationship between regular consumption of products containing probiotics and periodontal health.

Sunstar (Etoy, Switzerland) recently began marketing the first probiotic specifically formulated to fight periodontal disease. Gum PerioBalance contains a patented combination of 2 strains of *L. reuteri* specially selected for their synergetic 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. Additional studies are required to evaluate the long-term effects of using these products.

Summary Box

- Probiotics are living microorganisms, principally bacteria, that are safe for human consumption and have beneficial effects on human health.
- Probiotic therapy is being considered for application in oral health due to the emergence of antibiotic-resistant bacteria.
- Probiotics incorporated into dairy products neutralize acidic conditions in the mouth and interfere with cariogenic bacteria.
- Patients with periodontal disease who used chewing gum or lozenges containing probiotics saw their periodontal status improve.
- Probiotics in gargling solutions or gum inhibit the production of volatile sulphur compounds that contribute to bad breath.

Probiotics and 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.[41] 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 methanethiol.[41] Kang and colleagues[15] reported the capacity of various strains of *W. cibaria* to inhibit the production of volatile sulphur compounds by *F. nucleatum*. They concluded that this beneficial effect resulted from the production of hydrogen peroxide by *W. cibaria*, which inhibited the proliferation of *F. nucleatum*.[15] These authors also found that gargling with a solution containing *W. cibaria* was associated with a net reduction in the production of hydrogen sulphide and methanethiol and consequently a reduction in bad breath.[15]

One recent study[42] 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.[42] *S. salivarius* is known to produce bacteriocins, which could contribute to reducing the number of bacteria that produce volatile sulphur compounds.[43] 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.[44,45]

Conclusions

Probiotics represent a new area of research in oral medicine, the examination of the close relationships between food and oral health. Preliminary data obtained by various research laboratories have been encouraging, but numerous randomized clinical studies will be required to clearly establish the potential of probiotics in preventing and treating oral infections. Such studies will allow identification of the probiotics that are best suited to oral use, as well as the most appropriate vehicles: food products (cheese, milk, yogourt) or supplements (chewing gum, lozenges). The existence of probiotics in the indigenous oral microflora of humans warrants exploration because these bacteria offer the advantage of being perfectly adapted to the human oral ecosystem.

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