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Probiotics in dentistry: review of the current status

Probiótica em odontologia: revisão do estado atual da questão

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Abstract

Objective: The aim of this comprehensive review is to present an update about the current status of probiotics in terms of its application in the field of dentistry. **Background**: The concept of administration of beneficial bacteria with a view to replace harmful microbes with useful ones has been revived by the probiotic concept. The main field of research has been in the gastrointestinal tract. However, past few years has seen investigation of probiotics from the oral health perspective. Probiotic approach has shown promising results in oral cavity with respect to control of chronic disease such as dental caries, periodontitis, and recurring problems like halitosis and candidial infections. Control of biofilm formation on voice prosthesis has also been documented. **Conclusion**: Despite the immense potential of probiotics, data is still deficient on the probiotic action in the oral cavity. Further double-blind, randomized, placebo-controlled trials are needed before any concrete clinical recommendations can be made.

Keywords: Probiotics. Oral health. Oral diseases.

Resumo

***Objetivo**: O objetivo desta revisão compreensiva é apresentar uma atualização (estado da arte) dos conhecimentos a respeito da probiótica, em termos de sua aplicação no campo da odontologia. **Fundamento**: O conceito da administração de bactérias benéficas com a intenção de substituir micróbios patogênicos foi redescoberto pelo conceito de probiótica. Seu principal campo de pesquisa tem sido no trato gastrointestinal. Entretanto, nos últimos anos a*

probiótica tem sido investigada pela perspectiva da saúde bucal. A abordagem probiótica tem mostrado resultados promissores em doenças crônicas, tais como a cárie dentária, a periodontite e problemas recorrentes como halitose e infecções por Cândida. O controle da formação de biofilme em próteses auxiliares da fonação tem sido bem documentado. ***Conclusão****: Apesar do grande potencial da probiótica, os dados ainda são escassos a respeito da ação probiótica na boca. Estudos duplo cegos, randomizados e com controle por placebos ainda são necessários antes que recomendações clínicas possam ser feitas.*

Palavras-chave*: Probiótica. Saúde bucal. Doenças bucais.*

Introduction

The role of diet in health and well-being is universally acknowledged. With the evolution of the science of nutrition, research is now being directed towards improving the understanding of specific physiologic effects of the diet beyond its nutritional effect (1). In this aspect, probiotics are the subject of intense and widespread research in food and nutritional science. Probiotics are described as live micro-organisms which when administered in adequate numbers confer a health benefit on the host (FAO/WHO 2001) (2). The term probiotic, meaning "for life," is derived from the Greek language. It was first used by Lilly and Stillwell in 1965 to describe "substances secreted by one microorganism which stimulates the growth of another" and thus was contrasted with the term antibiotic (3).

The term prebiotic was introduced by Gibson and Roberfroid who exchanged "pro" for "pre" which means "before" or "for". They defined prebiotics 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 (4). More specifically, prebiotics are short-length carbohydrates, such as fructooligosaccharides, that resist digestion or are fermented in the colon to produce short-chain fatty acids, such as acetate, butyrate, and propionate, which have positive effects on colonic cell growth and stability, generate many of the same bacteria as provided in probiotics (1).

The term synbiotic is used when a product contains both probiotics and prebiotics (4). According to this approach, a food or food supplement will include both the live cells of the beneficial bacteria and the selective substrate. The idea being that the beneficial bacterial cells can grow quickly and competitively because of the presence of selective substrate and establish their predominance (5).

Historical perspective

There is a long history of health claims concerning living microorganisms in food, particularly lactic acid bacteria. In a Persian version of the Old Testament (Gn 18,8) it states that "Abraham owed his longevity to the consumption of sour milk". In 76 BC the Roman historian Plinius recommended the administration of fermented milk products for treating gastroenteritis (4). Elie Metchnikoff was perhaps the first researcher to propose that fermented dairy products have beneficial properties (6). In 1894, he showed that *cholera* could be prevented by the presence of antagonistic organisms in the intestine (7). In 1907 the Ukrainian-born biologist and Nobel laureate, working at the Pasteur Institute in Paris, discovered *Lactobacillus bulgaricus*. He developed a theory that lactic acid bacteria (present in Bulgarian yoghurt) in the gastrointestinal tract could, by preventing putrefaction, prolong life. This was based on his observation that Bulgarians lived longer than other people. He devoted the last decade of his life to the study of lactic acid-producing bacteria as a means of increasing human longevity. The concept of probiotics was thus born and a new field of microbiology was opened (8).

Probiotic bacteria for oral health

The most commonly used strains belong to the genera *Lactobacillus* and *Bifidobacterium*, genera that are commonly found in the oral cavity, including caries lesions (9). These were the first probiotic species to be introduced into research (*Lactobacillus acidophilus* by Hull et al. 1984 and *Bifidibacterium bifidum* by Holcombh et al., 1991) (3). *Lactobacillus rhamnosus* GG, ATCC 53103 produces a growth inhibitory substance against *Streptococcus sobrinus* and it has been

proposed to reduce the risk for caries (9). *Lactobacilus rhamnosus* strain GG, ATCC 53103 was originally isolated from the human intestinal flora in 1985 and named after the discoverers, Sherwood Gorbach and Barry Goldin (8).

Also, *Streptococccus salivarius* strains appear to be excellent candidates for an oral probiotic, since they are early colonizers of oral surfaces and are amongst the most numerically predominant members of the tongue microbiota of healthy individuals (10).

Other strains considered as probiotics in the oral cavity include: *L. acidophilus*, *L. casei*, *L. casei Shirota*, *L. paracasei*, *L. reuteri*, *L .johnsonii*, *propionibacterium*, *W. cibaria* (11). A successful effector strain for replacement therapy of a bacterial disease must have the following basic properties. It must not cause disease itself or otherwise predispose the host to other disease states by disrupting the ecosystem in which it resides (12). To be able to have probiotic effects in the mouth, a bacterium must adhere to oral surfaces and become part of the biofilm (13). Finally, an effector strain should possess a high degree of genetic stability (12).

Current evidence indicates that probiotic effects are strain-specific; therefore, a beneficial effect attributed to one strain cannot be assumed to be provided by another strain, even when it belongs to the same species (14). A combination of strains can enhance adherence in a synergistic manner (8).

Probiotics products

Probiotics are provided in products in one of the four basic ways:

1) A culture concentrate added to a beverage or food (such as a fruit juice).
2) Inoculated into prebiotic fibres.
3) Inoculants into a milk-based food (dairy products such as milk, milk drink, yoghurt).
4) (Yogurt drink, cheese, kefir, biodrink);
5) As concentrated and dried cells packaged as dietary supplements (non-dairy products).
6) (Such as powder, capsule, gelatin tablets) (3).

Mechanism of probiotic action on oral health

The suggested mechanisms of probiotic action on oral health are drawn entirely from gastrointestinal studies. Several mechanisms have been suggested to contribute to the probiotic action in systemic health (8). They relate to immune modulation, modulation of gut immunological mechanisms, mucin production, down regulation of inflammatory responses, secretion of antimicrobial substances, competition with other flora, including potential pathogens by competitive blocking of adhesion sites at epithelial and mucosal surfaces, and inhibition of epithelial invasion by regulation of intestinal permeability, inhibition of pathogens mucosal adherence and stimulation of immunoglobin A production (15, 16).

There is also evidence of production of anti-microbial substances, such as organic acids, hydrogen peroxide and bacteriocins (17). Their applicability to oral health needs further studies. Nevertheless, since the mouth represents the first part of the gastrointestinal tract, there is every reason to believe that at least some probiotic mechanisms may also play a role in that part of the system. It may also be anticipated that resident probiotics could exist in the oral microflora, and that they may function in the complex ecosystem of dental plaque and in the formation and development of oral biofilms in general. Hypothetical mechanisms of probiotic action in the oral cavity (oral biofilms and microflora) are suggested in Table 1.

Probiotics and dental caries

A number of researchers are developing "probiotic" methods to treat the caries causing infection. "Probiotic", as used here, means that mechanisms are employed to selectively remove only the (odonto) pathogen while leaving the remainder of the oral ecosystem intact (18). One of the replacement therapy options entails the application of a genetically engineered "effector strain" of *S. mutans* that will replace the cariogenic or "wild strain" to prevent or arrest caries and to promote optimal remineralization of tooth surfaces that have been demineralized but that have not become cavitated. *S. mutans* strain BCS3-L1 is a genetically modified effector strain designed for use in replacement therapy to prevent

dental caries. Recombinant DNA technology was used to delete the gene encoding lactate dehydrogenase in BCS3-L1 making it unable to produce lactic acid. This effector strain was also designed to produce elevated amounts of a novel peptide antibiotic called mutacin 1140 that gives it a strong selective advantage over most other strains of *S. mutans* (19).

A clinical trial began early in 2005 to test the effectiveness of replacement therapy. Thus, it is too early to determine the potential of this treatment method to prevent new caries lesions and to arrest existing lesions without any significant side effects. Another approach is based on a genetic modification of two plaque streptococci to create organisms that produce ammonia from urea and arginine. These organisms will reside in dental plaque, and the ammonia produced from salivary and dietary substrates will prevent the colonization of cariogenic bacteria and ensure internal pH homeostasis. If the effector strain is better adapted than the pathogen, colonization or outgrowth of the pathogen will be prevented by blocking the attachment sites, by competing for essential nutrients, or via other mechanisms. As long as the effector strain persists as a resident of the indigenous flora, the host is protected potentially for an unlimited period of time (19).

A different way of accomplishing the removal of the pathogens is to develop "targeted antimicrobials". The basic idea is to develop an inexpensive targeting molecule that will reliably attach to only the organism of interest, in this case *S. mutans*, *S. sobrinus*, or other chosen pathogen. Once the targeting molecule is perfected, then a "killer" molecule is optimized and chained to the targeting molecule. The combined unit then selectively eliminates the infection of interest. In the case of the oral cavity and dental caries, this system is attractive from the perspective of eliminating all the pathogens thereby precluding the regrowth of the original infection. There is also compelling evidence from clinical trials and laboratory efforts demonstrating that once the bacterial ecosystem is free of *S. mutans*, it is difficult to reintroduce the organisms (another competitive inhibition situation) (18).

Probiotics and *malodour*

A diverse *consortium* of gram-negative and gram-positive bacteria have been found to contribute to the problem and by contrast, certain bacterial species that predominate in the mouths of healthy subjects become noticeably absent in subjects with halitosis. Current treatments focus on the use of chemical or physical antibacterial regimes to reduce the numbers of these bacteria. Antimicrobial treatment

Table 1 - Suggested mechanisms of probiotic in the oral cavity (8)

Direct interactions in dental plaque	- Involvement in binding of oral micro-organisms to proteins (biofilm formation).
	- Action on plaque formation and on its complex ecosystem by competing and intervening with bacteria-to-bacteria attachments.
	- Involvement in metabolism of substrates (competing with oral micro-organisms of substrates available).
	- Production of chemicals that inhibit oral bacteria (antimicrobial substances).
Indirect probiotic actions in the oral cavity	- Modulating systemic immune function.
	- Effect on local immunity.
	- Effect on non-immunologic defence mechanisms.
	- Regulation of mucosal permeability.
	- Selection pressure on developing oral microflora towards colonization by less pathogenic species.

indiscriminately depletes populations of both the problematic bacteria and those bacteria that are not thought to be implicated in halitosis, but which are likely to be important in the maintenance of a normal oral microenvironment. The outcome of antimicrobial treatment is inevitably only a temporary reduction in *malodour*, until the halitosis-causing bacteria become re-established.

Preventing the re-growth of odour-causing organisms by pre-emptive colonization of the oral cavity with nonvirulent, commensal microorganisms seems like a reasonable alternative (10).

A definite inhibitory effect on the production of volatile sulfur compounds (VSC) by *F. nucleatum* was observed after ingestion of *Weissella cibaria* both in vitro and *in vivo*. In children, a marked reduction in the levels of H_2S and CH_3SH was registered after gargling with *W. cibaria* containing rinse. The possible mechanism in the VSC reduction is the hydrogen peroxide generated by *W. cibaria* that inhibits the proliferation of *F. nucleatum*. *Streptococcus salivarius*, also a possible candidate for an oral probiotic, has demonstrated inhibitory effect on VSC by competing for colonization sites with species causing an increase in levels of VSC. *S. salivarius* strain K12 produced two lantibiotic bacteriocins, compounds that are inhibitory to strains of several species of gram-positive bacteria implicated in halitosis (11).

Preliminary trials of the use of a chlorhexidine rinse followed by strain K12 lozenges, the majority (8/13) of subjects with confirmed halitosis maintained reduced breath levels of volatile sulphur compounds for at least 2 weeks (20). The replacement of bacteria implicated in halitosis with the bacteriocin-producing commensal bacterium *S. salivarius* K12 appears to provide an alternative therapy for the long-term reduction of halitosis (21).

Probiotics and periodontal diseases

Mucosal immune responses may be invoked by probiotic immunization. Studies of adhesion molecules have shown that superficial cell layers of the gingiva can be affected and can be stimulated to enhance the presence of immune potent cells. Regulation of microflora composition (e.g. by probiotics and prebiotics) may offer the possibility to influence the development of mucosal and systemic immunity, but it can also play a role in the prevention and treatment of diseases such as periodontitis (22). In a Russian study using probiotic tablets in complex treatment of gingivitis and different degrees of periodontitis, the effect of probiotics to the normalization of microflora was found to be higher in comparison to the controls, particularly in the cases of gingivitis and periodontitis. Probiotic *bifidobacterium* species reduced gingival and periodontal inflammation (23).

A decrease in gum bleeding and reduced gingivitis has been observed with the application of *L. reuteri* (11, 24). Probiotic strains included in periodontal dressings at optimal concentration of 10^8 CFU mL^{-1} were shown to diminish the number of most frequently isolated periodontal pathogens: *Bacteroides sp.*, *Actinomyces sp.* and *S. intermedius*, and also *C. albicans*. Nevertheless, similar to the case with dental caries, however, there is not yet any true evidence on the effect of probiotic therapy on periodontal disease (11, 25).

Probiotics and yeasts

A reduction in the prevalence of *C. albicans* in the elderly after consumption of probiotic cheese containing *L. rhamnosus GG* and *Propionibacterium freudenreichii ssp.* has been demonstrated (26). A concomitant feature of the probiotic activity observed in this study was the diminished risk of hyposalivation and the feeling of dry mouth of the subjects. The authors had no explanation to this and the finding certainly needs to be confirmed in further investigations. It could be hypothesized that extending research on oral pathology, such as yeast infections, with respect to probiotics, and analyzing the molecular mechanisms of probiotic activity, might further broaden the field of their potential applications (11).

Probiotics and voice prosthesis

It should be noted that there is no research regarding relationship between dental restorative materials and probiotics. However in larynx, the second barrier after oropharynx, probiotics strongly reduce the occurrence of pathogenic bacteria in voice prosthetic biofilms (3). There is anecdotal evidence among patients in The Netherlands that the consumption of buttermilk, which contains *Lactococcus cremoris*, *Lactococcus lactis spp.* that can produce antimycotics and

other substances, prolongs the lifetime of indwelling voice prostheses. Recent research has suggested that consumption of 2 kg/day of Turkish yogurt effectively eliminates biofilm formation on indwelling voice prostheses, possibly related to the presence of *Streptococcus thermophilus* and *Lactobacillus bulgaricus* in Turkish yogurt. *Lactobacilli* have long been known for their capacity to interfere with the adhesion of uropathogens to epithelial cells and catheter materials, while *S. thermophilus* can effectively compete with yeasts in their adhesion to substratum surfaces, like silicone rubber. Further research should be carried out to determine if it will possible to treat other infections of the upper digestive tract, like esophagitis, with probiotic containing dairy products rather than with antibiotics (27).

Conclusion

The research regarding the benefits of probiotics in oral health and disease has been undertaken in the recent years. Further double-blind, randomized, placebo-controlled trails with specifically selected and defined strains are the need of the hour before clinical recommendations for possible use can be made.

Conflict of interest statement

The authors declared no conflict of interest in the present manuscript.

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