Oral Microbiology

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Review

Oral probiotics for dentistry.

A Mendi[1*], S Köse[2], D Yılmaz[3], D Uçkan[2]

Abstract

Introduction

The potential application of probiotics for oral health has recently attracted the attention of several teams of researchers. Although clinical studies have been conducted, the results to date could not safely suggest that probiotics could be useful in preventing and treating oral infections, including dental caries, periodontal disease and halitosis. This study aimed to review the body of knowledge relating to oral probiotics and to consider their effectiveness and selecting strains.

Conclusion

Different probiotic strains, if manage to be active in the mouth, would be expected to have different mechanisms of action in the oral cavity as they have different modes of action, and some of the observed effects of the probiotic bacteria were indeed strain specific. On the other hand, all of positive effects of the probiotic bacteria observed in studies were not specific for the probiotic strains but properties common to several species are even genera. In addition, previously reported probiotic properties beneficial to gut function do not necessarily correlate with probiotic activity in the oral cavity. We suggest it is also important to select newly isolated oral probiotic bacteria since the health benefits are varied among the strains.

Introduction

The bacterial colonisation of the mouth begins, as soon as a baby is born; Information about the early development of oral microbiota is scarce. According to culture-based methods, acquisition of microbes from the birth canal is of limited significance, only Staphylococcus epidermidis acquired at birth seems to persist for a longer time. Tooth eruption around the age of six months changes the oral cavity significantly. New bacterial genera begin to colonise in the mouth, and by the age of 3 years children have a multiform oral microflora, including also Gram-negative anaerobic species [1].

Although, it has been estimated that over 500 different bacterial species can colonise in the oral cavity, the number of species present in the oral cavity of a single individual is significantly lower. The number of predominant species in the oral cavity of a healthy adult seems to vary between 30 and 80 species[2].

The stability of resident microbiota, similarly to the other parts of the body, also protects the oral cavity from invading exogenous, potentially harmful microbes[3]. The phenomenon is called colonisation resistance which involves several mechanisms, such as occupation of adhesion sites, alteration of the physiochemical environment, production of antagonistic substances and utilisation of available nutrients[4]. Each member within the microbial community has a functional role and, thus, the degree of colonisation resistance is likely to be a consequence of the interactions between all the microbes in the niche in question. The stability of a mature oral microbiota can be demonstrated by the observation that it is more difficult to introduce new species into the oral cavity of older human than to that of younger ones[5]. In addition, loss of colonisation resistance can lead to severe health problems in the oral cavity[6].

Discussion

What are Probiotic bacteria?

The term probiotic –"for life"- is used with different meanings, but today two main definitions are used. According to WHO/FAO Report (2002)[7], probiotics are "Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host". International life Science Institute (ILSI) Europe suggests a definition according to which a probiotic is "a live microbial food ingredient that, when ingested in sufficient quantities, exerts health benefits on the consumer[8]. The most commonly used probiotic bacterial strains belong to the group of lactic acid bacteria, especially lactobacilli, or to the genus Bifidobacterium[9]. In addition to bacteria, yeast[10] and even helminthes are used as probiotics[11]

The International Dairy Federation has published a bulletin summarizing the evidence for the effect of probiotic cultures on a range of diseases and disorders in humans. The bulletin No 380/2003 contains a section reviewing the evidence for clinical effects in an extensive range of conditions including lactose malindigestion, diarrhea, immune modulation, inflammatory bowel syndrome, constipation, necrotising enterocolitis, Helicobacter pylori infection, small bacteria overgrowth, colorectal cancer, breast cancer, allergy, serum cholesterol and blood pressure decreasing, coronary heart disease, urinary tract infection, upper respiratory tract and related infections. Thereby probiotics have multiple mechanisms of action (Figure 1)[13], including prevention of pathogenic bacterial growth, binding to or penetration of pathogens to mucosal surfaces, stimulation of mucosal barrier function, production of antimicrobil agents or altering

*Corresponding author
Email: aysegulmendi@gmail.com

[1] Gazi University Faculty of Dentistry, Department of Medical Microbiology, Ankara, Turkey
[2] Hacettepe University, PEDİ-STEM Center for Stem Cell Research and Development, Ankara, Turkey
[3] Gazi University, Faculty of Dentistry, Department of Oral and Maxilofacial Surgery, Ankara, Turkey

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immunoregulation, decreasing proinflammatory cytokines [9].

Importantly, it was shown that one of the primary metabolic products of probiotics; called exopolysaccharides (EPSs) have recently received an increasing amount of attention because of their technological application in dairy products and their potentially beneficial properties for human health. Most of EPS-producing LAB have been isolated from fermented foods. Recently gut microbiota from animals and humans is the microenvironment where EPSs producing LAB are isolated. It is obvious that LAB strains from different ecological niches are able to produce EPSs, but the physiological role of these polymers play in producing bacteria still remains unclear. EPSs have been suggested that they have a role in the recognition of different ecosystems and also that they have a protective function against detrimental environmental factors[14]. EPSs may be a good tool to explain the mechanism of action of probiotics.

Probiotics were suggested to play a role in maintaining oral health recently. Hereunder, there is a need to define therapeutics that focus on the diminution of dental plaque, the reduction of number of pathogens and the modulation of host immune response by controlling the release of inflammatory cytokines for periodontal diseases. On the basis of their therapeutic role in inflammatory bowel diseases and allergic disorders, probiotics may participate in the management and/or prevention of periodontal diseases by the induction of an immunomodulatory effect. LABS, as probiotics, are novel unitary agents that are widely utilized for their therapeutic activity. Nevertheless, this attack is still an emerging idea and there is insufficient scientific evidence to back its clinical role in oral health[15]. Our team suggest that if probiotics could restore the composition of the gut microbiome and introduce beneficial functions to gut microbial communities, resulting in amelioration or prevention of gut inflammation and other intestinal or systemic disease phenotypes, they can exert the same functional properties in the oral microbiome also. Abrogation of oral pathogens especially, P. gingivalis by lactobacilli could be an advantage to prevent the development of periodontitis and/or other oral diseases. Lactic acid bacteria could compete with oral pathogens for adhesion to surface of cells for nutrition and as a consequence secretion of immunomodulatory cytokines from stromal cells and/or epithelial cells.

How probiotics should be used in dentistry?

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 in clinical trials[16]. However, only a few studies are available on the prevalence, role, and effects of probiotic bacteria in the mouth. A Russian study examined probiotic tablets in a complex treatment of gingivitis and different degrees of periodontitis[17]. The treatment of the patients of the control group was provided by the drug Tantum Verde (Aziende Chimiche Riunite Angelini Francesco A.C.R.A.F. S.p.A., Rome). The effect of probiotics on the normalization of microflora was found to be higher in comparison with Tantum Verde, particularly in the cases of gingivitis and periodontitis. Nasae et al. (2001) reported reduced tooth decay incidence in children taking probiotic L. rhamnosus GG–enriched milk versus a control group of children taking milk without probiotic enrichment[15]. Studies on periodontitis and gingivitis show differing results depending on the strains. For example, Lactobacillus reuteri can be used to reduce gingivitis and dental plaque in patients with moderate to severe gingivitis and also to reduce proinflammatory cytokine in gingival crevicular fluid[18]. On the other hand, Lactobacillus salivarius WB21 in tablets does not reduce the direct count of any specific periodontopathic bacteria-Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsyia, Trepenoma denticola and Aggregatibacter actinomycetemcomitans[19], (even though this probiotic improves periodontal clinical parameters (probing pocket depth, gingival index, bleeding on probing and plaque index) especially in smoker subjects[20]. Commercially available probiotics that contain Lactobacilli species interfere with the in vitro ability of Candida albicans to form biofilms on dentures[21], yet conventional approve intestinal probiotics surprisingly have no oral persistence and any oral cavity health benefits seem transitory. These conflicting results point out that not all the probiotics have beneficial effects on periodontal diseases. Therefore, it seems necessary that to perform specific screenings for selecting appropriate probiotic strains for preventing gingivitis or periodontitis and other oral health diseases. Sookkhee et al. (2001) verified this hypothesize by investigating 130 volunteers in Thailand and found 3790 lactic acid bacterial strains from healthy oral cavities. Of these, only five species expressed the inhibitory effect against other organisms, including oral

Benefit	Function	Proposed mechanism
Digestive comfort	Irritable bowel syndrome, symptoms affecting the gastrointestinal tract in general (constipation, non-pathogeni diarrhea, distension, flatulance, cramp)	Change in populations or activities of the intestinal microflora
	Lactose intolerance	Delivery of microbial lactase to small intestine
Defense	Allergy (atopical enzyme, allergy to the milk, rheumatoid arthritis)	Translocation, barrier effect
	Carcinogenicity, mutagenicity, tumor	Absorption of the mutagen, stimulation of the immune system, inhibition of carcinogen production by the intestinal microflora
	Diarrhea linked to antibotics, diarrhea caused by Rotavirus, colitis caused by *C. difficile*, nosocomial diarrhea	Competitive exclusion, translocation/barrier effect, immune response promoted
	Helicobacter pylori	Antipathogenic activity
	Immunomodulation (immune status, vaccinal response)	Interaction with the immune cells or cell receptors leading to an increase in the phagocytic activity of white cells, incresing IgA levels after exposure to the antigen, increasing the proliferation of the intra-epithelial leukocytes, regulating the Th1/Th2 ratio, induction of cytokine synthesis
	Excessive intestine bacterial growth	Antimicrobial activity, competitive exclusion
Oral disesases	SHOULD BE INVESTIGATED	EPS production, biofilm inhibition, antioxidative activity, competitive adhesion, immunomodulatory effect

Figure 1: The probiotic effects reported and their putative mechanisms.

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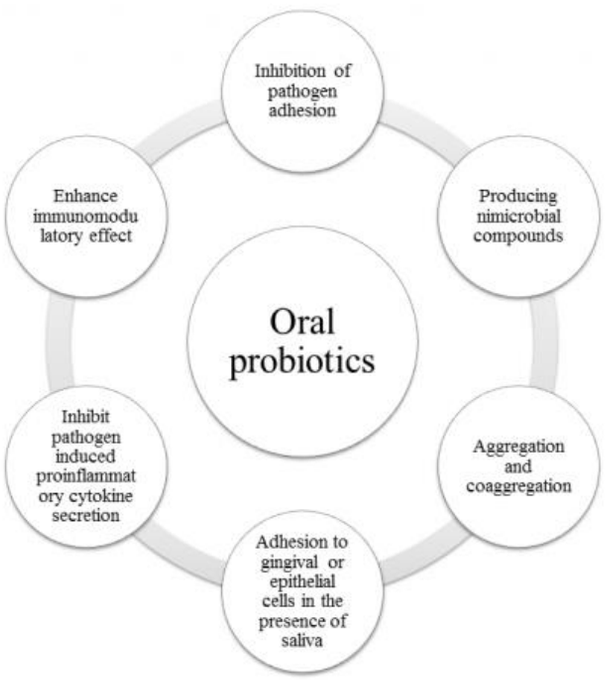

Figure 2: Functional properties of oral probiotics.

Candida. The authors reported that the antimicrobial potentials of the bacteria were affected by several factors, such as pH, catalase, proteolytic enzymes, and temperature[22]. Also it cannot be assumed that research published on one strain of probiotic applies to another strain, even of the same species. The key point is to realize that all probiotics do not have the same efficacy[23, 24]. It is important that probiotic strains should be well characterized before and comprehensive in vitro research studies should be conducted.

Selecting Oral probiotics

Several requirements have been proposed for novel probiotic strains[7]. Isolates from healthy humans are advised and their functional properties and safety should be assessed by in vitro tests[25] (Figure 2). It has been shown that good antimicobial properties of probiotic strains are necessary to eradicate or inhibit pathogenic bacteria. At the same time, significant fermentation type-, species-, and strain specific variability in functional probiotic properties of lactobacilli, such as antimicrobial activity as well as acid and bile tolerance of lactobacilli, has been observed[26]. Therefore several strains from various fermentation types and species should be tested to choose the best, those with high antimicrobial activity and high tolerance of environmental stress. Furthermore, one of the important issues is the safety of probiotics trains. There is growing concern about the development of antibiotic resistance in pathogenic microorganisms. The spread of antibiotic-resistance genes between bacterial species through lateral gene transfer may occur [27] and therefore, knowledge of the resistance pattern of the probiotic strains would be useful to avoid inducing strains that carry transferable genes.

As shown in Figure 1 there are topics which should be explained by researchers. Since most of the functions ascribed to EPSs are of a protective nature. The ability of a microorganism to surround itself with a highly hydrated exopolysaccharide layer may provide it with protection against desiccation and predation. It is suggested that in terms of oral environment in clinical studies considering the stressful conditions created by saliva and teeth surface, high EPSs productive strains, may survive better (in vivo environment would be different from controlled in vitro conditions).

Questions that remain unanswered

Studies in dental clinics with probiotics are characterized by a high level of heterogenicity due to the different behavior of oral hygiene of human. Furthermore there are no sufficient *in vitro* models regarding probiotic effect. On the other hand Ibnou-Zekri et al (2003)[28] highlighted that the activity of probiotic strains in vitro may not parallel similar in vivo behavior.

To determine further the role of probiotics in the dentistry, large, well designed, multicenter controlled clinical trials are needed. The fact that not all lactobacills and bifidobacterim species are equally beneficial should not be discarded. Individual mechanism of each strain should be characterised and the researchers should be aware of that the action of mechanism is dependent on the host characteristics such as oral hygiene, and nutrition habit.

Since different bacteria may have dominant effects in different genetic backgrounds and in diseases that vary in their pathogenesis, researchers should prefer oral microbiome origin probiotics to use in clinical trials.

It is however important to realize that probiotic microorganisms do not act exclusively by affecting the microbiota. They can also exert effects either by modulating immunological parameters, epithelial permeability and bacterial translocation, or by providing bioactive or regulatory metabolite. Thus, probiotic bacteria-host interactions could be investigated by designing in vitro models which encompass mucosal stem cells.

Conclusion

Functional properties of probiotic strains are different among the strains and they do not show the same health benefit efficacy. Therefore strains isolated from gut micro flora could not give the same results in oral micro biome. Researchers should set their goal in identifying strains from oral micro biome. Selecting the new oral probiotic strains should be focused on the diminution of dental plaque, the reduction of the number of periodontal pathogens and the modulation of the host immune respose by controlling the release of inflammatory cytokines, which may slow down the destruction of supporting tissues. Probiotic strain- oral mucosal cell interactions should also be investigated.

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