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The probiotics in dentistry: a narrative review

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Abstract. – The total number of microbes that colonize the human body is far greater than the number of cells that make it up. In recent years, it has been shown that bacteria play an essential role in the body; in fact, they are essential for the maturation of the intestine, the development and control of the immune system, the development of the brain, the metabolism of macronutrients, the synthesis of vitamins, and the energy balance. Bacteria play an essential role in defense of their territory against the entry of other bacteria that may be pathogenic to health. Metchnikoff, about a century ago, invented probiotics, assuming that the use of certain bacteria could be beneficial to maintaining health. Bacteria colonize our body from birth and breastfeeding, using the bacterial flora of the mother by accessing newborns through the mouth. Antibiotic therapies in pregnancy or cesarean section prevent this flow of probiotics to infants and open the way for very important diseases, such as diabetes and obesity. The alterations of oral bacterial flora are responsible for numerous diseases of the oral cavity and the idea of the use of probiotics is leading the way to new therapeutic perspectives.

Key Words
Probiotics, Microbiome, Microbiota, Dental caries, Periodontal disease, Gut.

Introduction

According to the World Health Organization (WHO), probiotics are "live microorganisms which, when administered in adequate amounts, confer a benefit to the health of the host". In several studies, it was demonstrated that the administration of probiotics can improve the health of the oral cavity.

At the beginning were (and still are) used to enhance the health of the gastrointestinal tract, but there is an increasing attention to their role in the maintenance of general and in particular the oral cavity homeostasis.

Probiotics can improve the condition of the patient in disorders such as diarrhea, gastroenteritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), cancer, inadequate lactase digestion, pediatric allergy, hyperlipidemia, liver disease, and infection with *Helicobacter pylori* infections, genitourinary.

Probiotics may be taken directly with the food (cheese, yogurt, fermented milk, fruit juice or chewing gum) or with pharmaceutical preparations (tablets, etc.) and in their passage in the gastro-intestinal tract play important functions at various levels in maintaining health. In particular at the level of the mouth, probiotics have the effect of reducing the occurence of dental caries, periodontal disease, reduced halitosis, and fighting oral infections by *Candida*. The localized activity of probiotics often has effects on the whole organism, by reducing the consequences of inflammation systemically. The control of periodontal disease may become strategic for the prevention of systemic diseases related to atherosclerosis processes[1,2], vascular disease[2-4], cardiac pathologies[2,5-12], preterm births and low newborn weight[13].

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History

The first studies on the beneficial effects of probiotics on our health date back to the beginning of the twentieth century. The Nobel Prize Eli Metchnikoff, who worked at the Institute Pasteur in the early years of the twentieth century, hypothesized that these effects resulted from an improvement in the intestinal microbial balance through inhibition of pathogenic bacteria.

Metchnikoff was convinced that the longevity of the Bulgarian population was linked to the habit of eating yogurt, and the bacteria contained in it were able to reduce the intestinal fermentation produced by other bacterial strains. He self-administered milk acid, containing what he called the "*Bacillus Bulgaricus"* and published its beneficial effects (1907). It was a revolutionary hypothesis that offered a not invasive solution to mental illness that the German doctor Hermann Senator (1860) attributed to a "self-infective" process, triggered by bacteria. Concept resumed in 1887 by French physician Charles Bouchar that coined the term "autointoxication", and attributed the onset of psychological problems to the products of putrefactive bacteria. The theory of autointoxication, in the absence of medical solutions, was addressed with surgical methods. In the early years of the last century Sir William Arbuthnot Lane (Willie), in England, and began to treat depression with the surgical ablation of the colon with results that defined positive but with a mortality of 30%[14]. Immediately after entering the viewfinder were bacteria in the mouth. In the USA, the dentist Henry Cotton decided to treat his wife and daughter suffering from psychiatric problems removing all of their teeth and diffused the method to hundreds of patients[15].

The work of Metchnikoff is development in a period very fertile for microbiology. In 1905 the French pediatrician Henry Tissler was isolating *Bifidobacterium* from breast-fed infants. In the following year, the same author showed that, compared to healthy children, patients with diarrhea had feces that presented a reduced number of *Bifidobacteria* and they were able to be treated with the administration of the lacking bacterium, inventing the first probiotic method.

The work of Metchnikoff gives life to a conceptual revolution in which bacteria do not always produce diseases but may be tools to promote health[16].

Life would be impossible without the presence of the bacteria. Our body coexists and collaborates with billions of bacteria. The amount of bacteria present in our body exceeds to number the total amount of our cells (Table I).

The bacteria operate in symbiosis with our body and they are delegated functions critical to the survival:

- Intestinal development[17];
- Development and operation of nervous system;
- Dental care[18,19];
- Host nutrition;
- Resistance to pathogens[20,21];
- Regulating the intestinal epithelium proliferation;
- Energy production[22,23];
- Immune System development[24-26].

The bacterial colonization of our organism starts from the mouth and it spreads all over the gastro-intestinal tract. For a long time it was considered that the first act of the colonization occurs with the passage in the birth canal and with the contact with the bacteria present in the vagina. After birth the contact source widens to the mother's teat and breast, and gradually to those who provide parental care, as well as to the bacteria present in the environment. A few hours after birth, the mouth is richly colonized. *Streptococcus salivarius* is detectable in the oral cavity eight hours after birth[27], a Gram-positive bacterium considered the pioneer of bacterial colonization. In the first 8 days, the oral flora is enriched with both aerobic and anaerobic bacteria and for the 98% will constitute the oral microbiome until dentition[28].

For the first two weeks, the oral bacterial flora will be the major source of colonization of the intestine[29].

Babies born by vaginal delivery have profound differences in microbiome compared to born by cesarean section. In the first group, at three months of age, it is observable a greater variability of the oral and intestinal flora, and a late colonization by *Streptococcus albicans*[30,31].

Table I. The amount of bacteria present in our body.

Cells of our body (excluding blood and neurons)	1012
Resident bacteria on the skin	1012
Resident bacteria in the mouth	1010
Resident bacteria in the gut	1014
Weight of intestinal bacteria	> 1 kg
The number of bacteria in 1 g feces	1012

Microbiome > 100 times the number of genes of the human genome

The different bacterial colonization, due to the role of bacteria in the immune system[32], has been related to the subsequent onset of various diseases. Babies born by cesarean have a higher incidence of diseases such as allergic rhinitis[33], type 1 diabetes[34], celiac disease[35], and obesity[36].

Breast-feeding and the resulting bacterial exchange with the mother, or the use of artificial milk (infant formula) not containing maternal bacteria, have a profound effect on bacterial colonization and inflammatory homeostasis. The breast-fed infants, in contrast to those babies fed with infant formula, at three months show a rich presence of lactobacilli in the oral cavity (real maternal probiotic) and enjoy resistance against pathogens[30,37] and an important immune-mediated protection toward diseases such as asthma and inflammatory Bowel disease[38].

It starts to emerge the hypothesis of using probiotics bacterial strains from mothers of children born by cesarean section and/or not breastfed[39].

In recent times there are accumulating evidence that the first contact with the bacteria occurs before the birth. Bacteria have been isolated in the placenta, umbilical cord, the amniotic fluid, in meconium, and in fetal membranes[40-45].

As further support of prenatal bacterial contact, there is evidence that the bacterial flora isolated from the placenta is genetically closer to the phyla present in the mouth (tongue and tonsils), and not to the phyla of bacteria present in the vagina and the intestine[40].

Currently, on how the oral bacterial flora arrives at the placenta, there are not many data, and different hypotheses were formulated, among which the passage of bacteria into the bloodstream on the occasion of gingivitis, very frequent during pregnancy[46].

The arrival of bacteria in the placental environment induces an immune tolerance in the fetal immune system, inducing the infant toward the maternal microbiome, that inevitably moves to the newborn with childbirth and breastfeeding, playing an essential role in the newborn's health. This immune tolerance is meant to last until adulthood[47].

More than 700 bacterial strains were identified in the oral cavity, and the microbial flora is different from subject to subject. Each individual can count on a bacterial population composed by an average of 30-100 species that constitute a custom ecosystem, making the flora of the oral cavity an essential part of the biological uniqueness of individuals. This uniqueness is formed during a time process in which genetics, bacterial exchange with the mother, age, dietary habits, use of drugs, diseases, play an important role.

The efficacy of probiotic cannot set aside the biological individuality of the patient[29,48,49].

Dynamics of colonization by the probiotics

There are many variables that can affect the permanence in the oral cavity of new bacterial strains.

First of all, it should be considered that in the mouth the composition of the bacterial flora tends to remain stable over time. In the saliva, for example, the microbiome composition in individuals was constant during the periodic analysis carried out in an arc of 7 years[50]. However, it must take into consideration that the mouth is not a uniform environment for the bacteria, this has led to the creation of the Human Microbiome Project (HMP) at the NIH, a data base that comprehend at least nine biological niches with specific characteristics for the bacterial composition: mucosa of the mouth, hard palate, *Keratinized Gingiva*, palatine tonsils, plaque above and below the gingiva, saliva, throat, tongue dorsum[49].

The arrival of new bacteria enters in a very complex system of interactions with the resident flora. At least five types of interaction have been described: competition for nutrients, synergy, antagonism, neutralization of virulence factors, and interference with the bacterial signaling systems (quorum sensing)[51].

The competition for nutrients and essential element to consider for the survival of the probiotic, as colonization, is closely dependent on the availability of nutrients that can be used by different strains. In 1998, Roberfroid[52] coined the term "prebiotic" to define "a non-digestible food ingredient that beneficially affects the host by entitled stimulating the growth and/or the activity of one or a limited number of bacteria in the colon". Between prebiotics are enumerated fructans, maltodextrins, fructo-oligosaccharides, and galacto-oligosaccharides, practically all the components of our diet that becomes one of the critical elements for the distribution and composition of the oral microbiome.

For our microbiome many foods in our diet are to be regarded as prebiotics: soya beans, artichokes, oats, honey, berries, asparagus, many fruits, and goat milk[53,54].

The possibility of promoting colonization of some bacterial strains using nourishment competition has led the joint administration of probiotics with their preferred prebiotics-giving rise to the so-called symbionts[52].

The bacterial colonization must take to account the oral medium constituted by the saliva, which contains numerous bactericidal or bacteriostatic substances, and proteins that can cause damage to the bacteria in their planktonic state, like lysozymes, lactoferrin, histatins, salivary peroxidases, cystatin, and secretory IgA.

The saliva greatly influences the dynamics of bacterial colonization by favoring or by mobilizing the microfilm[53].

The dental caries

In spite of the various prevention programs implemented in recent decades, dental caries remains one of the world's diseases more prevalent in both infants and adults.

Dental caries (from the latin careo, "to be free of") is a degenerative disease of the teeth hard tissue (dental enamel, dentin) on infectious base, which originates from the surface and goes in depth, up to the dental pulp. This is a multifactorial disease with essentially four basic factors: bacteria, sugars, predisposing factors, time. They are the result of a demineralization of the dental structure, as determined by an interaction between different cariogenic bacterial species, a diet rich in fermentable carbohydrates, and by components in the "host", as the intrinsic properties of teeth and saliva.

Among the many bacterial species present in the saliva, *Streptococcus mutans* (SM) is universally considered as the most important pathogen for the initial development of tooth decay, while *Lactobacillus* has an important role in the progression of tooth decay.

The main characteristics of virulence of the *Streptococcus mutans* are their acidogenicity, ability to survival in acidic environments, the ability of biofilm formation and adherence to the tooth.

Various hypotheses have been proposed regarding the mechanism of action of probiotics, including the production of antimicrobial substances, in antagonism with the pathogenic agents, preventing cell adhesion, invasion, and the modulation of both local and systemic immune actions.

Clinical Evidences

In a recent systematic review, several clinical studies have demonstrated the ability of probiotics to reduce the concentration of the *Streptococcus mutans*, but it was also noted a shorter duration of the effect.

Several studies were carried out on the prevention and increase of the oral cavity immune capacity.

Nase et al[55] and Wu et al[56] (2014-follow-up to six months) have studied the effect of the probiotic *Lactobacillus rhamnosus* GG on the risk of tooth decay and have demonstrated a reduction in caries and reduced levels of *Streptococcus mutans* in patients taking the probiotics of *Lactobacillus* group.

Caglar et al[57] have estimated the effectiveness of the Xylitol based chewing gums and probiotics on the *Streptococcus mutans* and *Lactobacilli* counts, stating that probiotic microorganisms could reduce the salivary concentration of *Streptococcus mutans* in a meaningful way.

Steckson-Blicks et al[58] have reported that daily use of probiotics and fluorine determines a reduction of caries in preschool children.

Also, Caglar et al[59] have studied the effect of the probiotic bacterium *Lactobacillus reuteri* ATCC 5573 on *Streptococcus mutans* and *Lactobacillus salivarius*, demonstrating that in the short term their consumption reduces the concentration of the *Streptococcus mutans* in children significantly.

Not all probiotics have these properties. In fact, in a study of Nozari et al[60] it has been shown that the introduction in the diet of the probiotic *Bifidobacterium lactis* has not changed the concentration of the *Streptococcus mutans* and *Lactobacilli*.

Several studies have demonstrated the positive effect of probiotics on the concentration of the *Streptococcus mutans* and *Lactobacillus salivarius* in the oral cavity, microorganisms involved in the formation of dental caries in children.

A recent work revealed that only a certain species of bacteria, *Lactobacillus salivarius and Streptococcus mutans*, are linked to the development of tooth decay for their ability to produce high levels of acidity and for their ability to create an adhesive biofilm.

In contrast to these cariogenic bacteria, *Lactobacillus paracasei*, isolated from patients free of caries, possesses the ability to suppress the growth of *Streptococcus mutans*. In one paper, the probi-

otic *Lactobacillus paracasei* SD1 was introduced and utilized in the oral cavity for its known properties to inhibit the growth of *Streptococcus mutans*, to reduce its production of acid, and to have a good adhesion to oral epithelial cells.

In a randomized double-blind study, it was demonstrated that the administration of the probiotic *Lactobacillus paracasei* SD1 in milk increased the levels of the peptide HNP1-3, which seems to be interested in the reduction of the presence of caries in children.

These human neutrophils peptides as HNP1-3 are antimicrobial peptides cationic that provide the first line of host defense against a broad spectrum of microorganisms. These are released by the submandibular salivary glands and secreted into the saliva. They are also present and release in the gingival crevicular fluid.

The preventive role of HNP1-3 against dental caries was suggested by the finding of a significant increase in levels of HNP1-3 salivary in children with the absence of caries. Since one of the mechanisms of probiotics has been involved in the regulation of the immune system of the host, it was therefore assumed that the administration of probiotics may help to prevent dental caries through their ability to increase and modulate the production of salivary HNP1-3.

The significant increase in the saliva of the levels of the peptide HNP1-3 after the recruitment of the probiotic *Lactobacillus paracasei* SD1 is of great interest.

It is likely that the *Lactobacillus paracasei* SD1 can exert an effect of reducing the production of caries in children through various mechanisms, such as the reduction of salivary acidity, the reduction in the formation of biofilm adhesive of various bacteria, and the increase of the peptide HNP1-3.

A long-term study has shown that the recruitment of probiotics through *Lactobacillus reuteri* based on chewing gums resulted in a drastic decrease in the concentration of *Streptococcus mutans* in the saliva, and an increase in the concentration of the *Lactobacillus paracasei*.

Recently Sidhu et al[61] with follow-up to a year, demonstrated a variation in the concentration of *Streptococcus mutans* and *Lactobacillus salivarius* for children aged 10 to 15 years after regular intake of probiotics.

In another study to Terai et al[62], yet were taken into account some pathogenic bacteria, assessing their risk of primary carcinogenicity, and the ability to produce infectious endocarditis.

From this work, were isolated and selected probiotics such as *Lactobacillus crispatus* YIT 12319, the *Lactobacillus fermentum* YIT 12320, *Lactobacillus gasseri* YIT 12321, and *Streptococcus mitis* YIT 12322, that have shown a high non-cariogenic potential in an artificial mouth system, and a lower risk of infectious endocarditis in a rat model.

These are new probiotics with potential benefits for the oral health and without harmful effects for the general health.

In addition to being able to prevent dental caries, it seems, according to some studies, that through their local application in a concentration of 108 CFU, probiotics may reduce the concentration of various bacteria involved in periodontitis, as Bacteroides sp, Actinomyces sp., *Staphylococcus intermedius*, and *Candida albicans*.

Conclusions

From this analysis of the literature, we can say that the effects of probiotics suggested in the oral cavity may be divided into three groups:

- Modulation of the inflammatory response of the oral cavity;
- Direct effects against pathogenic bacteria;
- Indirect effects against pathogenic bacteria.

The available studies on probiotics and oral health are heterogeneous regarding set-up, the use of the various strains of probiotics, the methods of recruitment and the concentrations used.

Most of the strains used in the studies belong to the genera *Lactobacillus* and *Bifidobacterium*.

The possible mode of administration of probiotics is also very different, such as chewing gum, milk, cheese, yogurt, ice cream, drops, dust, and mouthwashes. Also, the evaluation of these studies is compromised by their often-short follow-up period.

Probiotics for the oral health are still a promising new field of research. Obviously, further research is necessary to demonstrate the effects of probiotics in the prevention and treatment of dental caries, periodontal disease and bad breath.

The results so far are encouraging, but further research is needed to demonstrate the apparent effects of some probiotic strains on oral health, their necessary concentration, and the delivery method. However, probiotics are increasingly available on the market.

It is, therefore, important that a dentist should be informed about their beneficial effects to be able to advise, in a correct way, the probiotics to

assume, in what concentration, and for how long, always remembering that the effects are limited in time and dose-dependent manner.

The selection of probiotics should be based on products that have been tested clinically for any disorders that could eventually cause. However, even if the use of probiotic products in healthy patients is safe, they are not recommended in patients with specific risks, such as immunocompromised patients or patients suffering from diseases of the cardiac valves.

Before using probiotic for oral health, it is necessary to perform a proper protocol of prophylaxis, as it is amply demonstrated that it is difficult to destroy a biofilm already acquired. It is also important to clarify that probiotics are an additional tool, not a substitute for the classic oral hygiene methods.

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Conflict of interest

The Authors declare that they have no conflict of interests.

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