

**Role of probiotics as bacteriotherapy in dentistry:
a literature review**

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Abstract.

According to WHO and FAO, probiotics are “live microorganisms which when administered in adequate amounts confer a health benefit on the host”. The aim of this paper is to describe the beneficial effects of probiotics on oral disease prevention. The search included the last five years in the Web of Science, PubMed and SciELO. Results showed that probiotics can produce antimicrobials, compete for cell adhesion sites, modulate the immune system and degrade toxins. This has led to dental studies that focus on reducing caries incidence, improving the prognosis of periodontitis and decreasing halitosis and candidiasis. Probiotics may be a valuable adjunct for the prevention of oral diseases. However, there are still doubts about which are the best bacterial strain, dose and timing of administration. Therefore, future longitudinal studies are required.

Keywords: Probiotics, dental caries and prevention.

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Introduction

The term “probiotics” literally means “for life” and was coined for the first time in the 1960s^(1,2). According to the report of the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) (2002), probiotics are “live microorganisms which when administered in adequate amounts confer a health benefit on the host”⁽³⁾. It is from this view that the concept of bacteriotherapy emerges, which is the term used when a harmless strain is implanted in the host’s microflora to maintain or restore the natural microbiome through the interference and/or inhibition of other microorganisms, especially pathogens, which is consistent with the definition of probiotics. Bacteriotherapy provides alternative ways to fight against infectious diseases, with fewer side effects than conventional drugs, and it also helps treat disorders that seem to have no connection with the bacteria, such as asthma, obesity and diabetes⁽⁴⁻⁶⁾. From this perspective, scientific evidence has shown that probiotics can improve the condition of patients with medical disorders, such as diarrhea,

gastroenteritis, short-bowel syndrome, inflammatory bowel disease, cancer, immunosuppressed conditions, pediatric allergies, growth retardation, hyperlipidemia, liver diseases, infections with *Helicobacter pylori*, and urinary tract infections⁽⁷⁻⁹⁾. In the last decade, the use of probiotics has generated interest within the dental community with the development of studies focused on reducing caries incidence, improving the prognosis of periodontitis, eliminating halitosis and infections such as oral candidiasis^(4,7,9).

Method

A search was conducted in the following databases: Web of Science, PubMed and SciELO. The selection criteria were:

1. Period: 2011 – 2016
2. Type of documents: Articles and Reviews
3. Language: English/Spanish
4. Area of research: *Dentistry oral surgery medicine*
5. Research domains: *Science technology*.

Keywords: *Probiotics AND Dental Caries and Prevention*: we found 75 papers, of which 28 were selected as available in Free-Full-Text format.

Resource availability

There are several products with different probiotic bacterial strains in the market: chewing gum, tablets or pills and dairy products such as milk, ice cream, cheese, and yogurt. The latter are the most natural ones, easiest to find and most widely accepted by the population, especially children^(2,10,11). Several studies have compared the use of probiotics in dairy products with placebos or probiotic products with similar functions (fluoride, chlorhexidine, coconut oil, etc.), but very few have compared them to each other. A study conducted by T. Madhwani et al. compared the use of probiotics in ice cream and drinks, and showed that ice cream would be a better option as it maintains a

significant reduction of *S. mutans* in saliva levels after 90 days of consumption⁽¹⁰⁾. Regarding its use in dentistry, we must consider that dairy products should be the vehicle for the administration of probiotics, since they contain casein phosphopeptides (CPP) that have an inhibitory effect on demineralization and promote the remineralization of tooth enamel⁽⁵⁾.

Mechanism of action

Several mechanisms have been proposed for the potential beneficial effect of probiotics. These can be classified into four broad lines:

1. The production of antimicrobials (bacteriocins) or acids that can inhibit the proliferation of pathogens.
2. Competition for cell adhesion sites (competitive inhibition or replacement therapy) with pathogens and/or co-aggregation to biofilm.
3. Modulation of local and systemic immune functions.
4. Degradation of toxins.

All available data show that the effects of probiotics are species- and strain-specific^(4,8,12-15). The optimal dose for dental diseases has not yet been explored, as the dose regimens adopted so far are based on standards for the gastrointestinal tract and for pediatric health care. However, we know there are between 75 and 100 bacterial species in the mouth of each person, and that different people have different combinations of species. In other words there is no “one size fits all” solution, so we may need a mixture of beneficial strains rather than a single strain as oral bacteriotherapy, comparable to the use of broad-spectrum antibiotics⁽⁵⁾.

Strains of probiotics used in mouth

The probiotic bacterial species most widely studied belong to the *Lactobacillus* and *Bifidobacterium* genera^(2,10,11,14,16). *Lactobacillus* are considered a normal component of oral biofilm and account for approximately 1%. *Bifidobacterium* are produced only in

small amounts in oral biofilm^(17,18). The focus is on these species because they are produced in the dairy industry and are rarely involved in human infections. In fact, these bacteria have a symbiotic relationship with human beings. They are present in the mucous membrane of intestinal epithelial cells, inhibiting the growth and attachment of pathogenic bacteria through the production of bactericides, acting like a coating that protects tissues^(2,4,10).

From a dental perspective, *Lactobacillus* and *Bifidobacterium* are acidogenic and aciduric. They are generally considered cariogenic and could be considered a risk for dental health^(6,8,14,16,17,19,20). However, the buffering capacity of dairy products containing these bacteria counteracts their acidity^(15,21). In addition, several studies have shown that *Lactobacillus* are late mediators in the progression of carious lesions due to their poor adhesion properties. Therefore, they do not increase the incidence of new lesions, although little is known about the effect they could have on pre-existing lesions^(15,17,18). Additionally, several species of *Lactobacillus* have been isolated from healthy mouths^(18,19). However, not all strains of *Lactobacillus* or *Bifidobacterium* are probiotics⁽¹⁷⁾.

Table 1. Strains tested in controlled and randomized clinical trials:

Anti-pathogenic action	Bacterial strain
Significantly increases salivary pH	<i>Lactobacillus acidophilus</i> ⁽²⁾
It significantly reduces the levels of <i>Streptococcus mutans</i> in saliva	<i>Lactobacillus acidophilus</i> ⁽²⁾ <i>Lactobacillus reuteri</i> ^(6,10,12,13,19) <i>Lactobacillus rhamnosus</i> ^(13,19) <i>Lactobacillus rhamnosus</i> LRH08: In addition, these clinical results showed a statistically significant reduction in the incidence of new caries lesions and a reduction in individuals with new caries lesions ⁽¹⁷⁾ . <i>Lactobacillus paracasei</i> strains SD1 and DSMZ

	16671 ^(19,22-24) <i>Lactobacillus paracasei</i> subspecies <i>casei</i> , <i>Lactobacillus acidophilus</i> , <i>Lactobacillus rhamnosus</i> and <i>Bifidobacterium</i> : combination of probiotic strains in Laive yogurt ⁽²⁵⁾
Adhesion to hydroxyapatite crystals (competition with the <i>Streptococcus sobrinus</i> for a place on the enamel)	<i>Streptococcus thermophilus</i> and <i>Lactococcus lactis</i> ⁽²⁾

These studies claim that probiotics strains can be detected in the saliva during their consumption, but when consumption ceases, they disappear from the oral cavity within a few weeks⁽⁶⁾. Some of the studies were short-term clinical trials (days or weeks), and others long-term studies (six months to one year). They used different vehicles (tablets, milk, ice cream, cheese, and sweets) and worked with different age groups (preschoolers, school children and young adults) as research subjects.

The literature also mentions in vitro studies, where the following strains are used:

- ***Lactobacillus rhamnosus* LCR35 and *Lactobacillus Johnsonii* LA1:** they reduce the colonization of *Streptococcus mutans* in vitro. Both probiotics are used in Chilean dairy products: *Lactil* and *Chamyto* respectively. Their effect was evaluated in four different concentrations (1, 1/10, 1/100 and 1/1000), but no significant differences were found. However, the probiotic strain *Lactobacillus casei*, *rhamnosus* LCR35 variety (lactil) showed significant inhibition halos in comparison to the *Lactobacillus johnsonii* LA1 strain (Chamyto)⁽¹⁵⁾.
- ***Lactobacillus reuteri* strains ATCC PTA 5289:** it adheres and forms a biofilm on the hydroxyapatite coated with saliva, competing with *Streptococcus mutans* for a place on the enamel⁽²⁶⁾. These results were obtained in an in vitro study. However a clinical trial showed that short-term (three weeks) administration of *L. reuteri*

ATCC 55730 combined with PTA 5289 did not affect the production of lactic acid or *Streptococcus mutans* counts⁽⁶⁾.

- ***Lactobacillus salivarius***: significantly increases oral pH⁽¹⁰⁾.
- ***Lactobacillus salivarius* WB21**: reduces plaque buildup, depth of periodontal pocket, bleeding on probing and oral malodor⁽¹⁹⁾.
- ***Lactobacillus salivarius* TI 2711**: it showed antibacterial activity against *Porphyromonas gingivalis* in mixed culture experiments, but recovered when administration ceased⁽¹⁹⁾.
- ***Streptococcus salivarius* K12**: it presents antimicrobial activity against several bacteria including *S. moorei*, which is a major contributor to oral malodor. It could be an interesting and valuable candidate for developing antimicrobial therapy to treat oral malodor⁽²⁷⁾.

There are currently patented dental probiotics available that include *Lactobacillus reuteri* and *Streptococcus salivarius*⁽¹²⁾.

Despite the large amount of scientific evidence, more randomized clinical trials are needed to identify the best combinations of probiotic strains, as well as their vehicles and dose for specific uses.

Terai et al. accepted the challenge and proposed new potential candidates. They selected 14 *Lactobacillus* strains and 36 *Streptococcus* strains from 896 oral isolates taken from 56 healthy volunteers aged between 25 and 66, based on the following parameters: the bacteria should not produce VSC (volatile sulfur compounds), should have antibacterial activity against pathogens that cause periodontal disease and dental caries, should have adherence to salivary-coated hydroxyapatite and to oral epithelial cells in vitro, should not have cariogenicity potential in an artificial mouth system, and should not induce endocarditis in a rat model. Based on these parameters, the best

candidates to be tested in a randomized clinical trial with humans would be: ***L. crispatus* YIT 12319, *L. fermentum* YIT 12320, *L. gasseri* YIT 12321, 12322** and ***S. mitis* YIT⁽²⁰⁾**.

Action in relation to oral diseases

The oral cavity is a habitat for a large diversity of microorganisms including bacteria, yeasts and viruses; all associated with oral infections. Bacteria are dominant in this microflora, and the diversity of species found in the oral cavity reflects the various types of habitat for colonization and the opportunity to survive as biofilm. However, the balance between this microflora and the host can be interrupted, resulting in diseases of the oral structures such as dental caries, gingivitis, periodontitis, halitosis, candidiasis and peri-implantitis⁽⁸⁾.

Dental caries

To understand the role of probiotics in the prevention of dental caries, we must first understand dental caries as a disease. According to the “Ecological Plaque Hypothesis”, caries pathogens may occur (or be transmitted) in a low number in the oral biofilm, which is compatible with oral health. However, if there is an imbalance in this oral biofilm due to changes in local environmental conditions, there would be a higher number of pathogens, which would cause dental caries. Some of these changes or “ecological pressures” are: a diet rich in carbohydrates, decreased salivary flow and low oral pH. Under these circumstances, the pathogens that compete with the indigenous microflora reach the numerical dominance levels necessary for the disease to occur^(17,21). Complementing this theory, the current definition of dental caries presents it as a complex disease. Although it starts through microbial action, the main pathogenic species linked to its development are endogenous and not exogenous, which significantly increase their number when there is a favorable change of the intraoral environment. In other words, it is no longer defined as a communicable and infectious disease⁽²¹⁾.

Therefore, dental caries can be prevented by implementing two approaches: 1) directly attacking potentially pathogenic microorganisms (e.g., use of antimicrobials or antiadhesive agents) and 2) indirectly by interfering in “the ecological pressure” responsible for pathogen selection⁽¹⁷⁾. In view of this, the studies conducted in the last few years focus on controlling pathogenic microorganisms through bacteriotherapy with the use of probiotics (first approach) and making favorable ecological changes to the disrupted oral environment, such as increasing local pH and salivary flow (second approach)^(2,13).

There are a number of randomized clinical trials that indicate that probiotics from *Lactobacillus* and *Bifidobacterium* may have an antagonistic effect on *Streptococcus mutans* (the main bacterial species that causes dental caries)^(8,10-13,17,19,22-25). However, a short-term reduction in the count of *Streptococcus mutans* is not necessarily associated with fewer cavities or reduced risk of tooth decay. Attempts have been made to combine professional dental cleaning and the use of antibacterial agents with the use of probiotics, in order to amplify the inhibitory effect and slow the growth of the pathogen^(5,9).

Hedayati-Hajikand et al. found that the combined use of chewable tablets with ProBiora3® (combination of *S. uberis* KJ2, *S. oralis* KJ3 and *S. rattus* JH145) and the daily use of fluoride toothpaste decreased early demineralization of the enamel, but had no effect on carious lesions. However, preschoolers who consumed these chewable tablets presented no new caries lesions in the period under study. This suggests that the appearance of tooth decay could be reduced through daily administration of these probiotics as adjuncts to the daily use of fluoride toothpaste in preschoolers⁽¹²⁾.

Periodontal disease

Efforts to prevent and treat periodontal disease focus mainly on reducing endogenous pathogens, eliminating superinfection with exogenous pathogens and strengthening the epithelial barrier, thus helping reduce susceptibility to infection. Probiotic bacteria can promote periodontal health if they can establish themselves in the oral biofilm and inhibit the growth of periodontal pathogens and their metabolism. Less is known about probiotics and their effect on periodontal disease than about probiotics and caries. Efforts are being made to study the effect of probiotics on clinical parameters (plaque index, gingival index, etc.) and on the interference in periodontal microbiology^(4,9,14).

Toiviainen et al. found that the short-term consumption of *Lactobacillus rhamnosus* GG (LGG) and *Bifidobacterium animalis sub species lactis* Bb-12 (BB-12) reduces the amount of plaque and it is clinically relevant for the reduction of gingival inflammation. The combination of LSG and BB-12 seems to be even more effective in comparison to each one alone. On the whole, it would improve the periodontal condition of healthy subjects, without affecting the composition of the adhesion properties or the oral microbiota of the plaque⁽¹⁴⁾.

It has been recently shown that *Lactobacillus reuteri* (Periobalance®) decreases the count of periodontal pathogens such as *Aggregatibacter actinomycetem comitans*, *Campylobacter rectus* and species of *Capnocytophaga* and *Tannerella forsythia*, reducing plaque levels and gingival inflammation in subjects with moderate to severe gingivitis. The host's immune modulation could explain their action in improving periodontal status, since there was no change in the oral microbiota or the adhesion properties of the plaque. Additionally, consuming *L. reuteri* reduces pro-inflammatory cytokines in the crevicular fluid of adults with gingival inflammation. This finding may reflect a local effect on oral immune responses^(8,9,14).

According to Terai et al., lactic acid bacteria (LAB) showed antibacterial activity against *Porphyromonas gingivalis*, *Prevotella intermedia* and *Aggregatibacter actinomycetem comitans*. As periodontal pathogens are sensitive to the attack of acids, it is believed

that the antibacterial activity of LAB is linked to the production of lactic acid and other organic acids that could act as bacteriocins⁽²⁰⁾.

Iniesta et al. conducted a literature review in the years before the period covered in this study and obtained the following results⁽⁹⁾:

- 2006: chewing gum with *L. reuteri* led to a statistically significant reduction in the plaque index and in the gingival index in patients with gingivitis
- 2007: chewable tablets containing *Lactobacillus brevis* improved the clinical parameters of plaque index, gingival index, tartar, and bleeding on probing in patients with chronic periodontitis
- 2008: Tablets containing *L. salivarius* improved plaque index and probing depth in patients with chronic periodontitis and smokers. In addition, subgingival plaque showed a statistically significant reduction in the total number of pathogens studied: *Aggregatibacter actinomycetem comitans*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia*.

Halitosis

Halitosis is a condition that affects a large section of the population; it is mainly attributed to the production of volatile sulfur compounds (VSC) predominantly anaerobic Gram-negative organisms that reside in the oropharynx (tongue, gums, tonsils), basically the same microorganisms linked to the progression of periodontal disease. It has been shown that bacteriotherapy can also improve this condition^(4,9,20).

Replacing the bacteria involved in halitosis with colonization with probiotic bacterial strains from the oral microbiota of healthy human beings may have a potential application in the prevention and treatment of halitosis. Besides, it can be a reasonable alternative to chemical or physical antibacterial regimes^(4,9,27). As the back of the tongue is the origin of most malodor problems, a candidate to counter this condition must be able to survive in this particular ecosystem. It would be ideal to have a probiotic strain

able to efficiently colonize the surface of the tongue without producing odorous metabolic byproducts⁽²⁷⁾.

Little research has been conducted on how probiotics may reduce the levels of volatile sulfur compounds. The strains that have been studied are: *Streptococcus salivarius* and *Lactobacillus salivarius* in chewable tablets and *Weissella cibaria* in the form of colutory. They have all obtained statistically significant reductions in the levels of volatile sulfur compounds in patients⁽⁹⁾. Terai et al. found, in an in vitro study, that *Lactobacillus crispatus* YIT 12319 and LBS11-17 have a greater adherence to the HSC cells from the human tongue. Their results suggest that there may be receptor-ligand systems between the epithelial cells of the tongue and these bacteria, which would be very helpful as a property to develop anti-halitosis probiotics⁽²⁰⁾. Masdea et al. determined that *Streptococcus salivarius* K12 has an excellent potential use as probiotics for halitosis-producing bacteria, as it is a pioneer colonizer of oral surfaces and is found predominantly in “healthy” human beings who are not affected by halitosis. This strain produces two natural antibacterial peptides: salivaricin A212,13 and salivaricin B,14. These peptides are bacteriocins that inhibit the colonization of bacteria involved in halitosis such as *Streptococcus T29*, *Saburreum Eubacterium*, *Micromonas micros* and types of pigmented black colonies present in saliva⁽²⁷⁾.

***Candida albicans* infection (Candidiasis)**

Candida albicans is the most common cause of fungal infections in the oral cavity. Especially in elderly and immunocompromised patients. Probiotic bacteria have been used to modify the microfloral ecosystem and have shown some success as a therapeutic agent for oral diseases⁽²⁸⁾. Daily consumption of cheese supplemented with *L. rhamnosus* GG, *L. rhamnosus* LC705 and *Propionibacterium freudenreichii* ssp *shermanii* JS has led to a reduction in the prevalence of *C. albicans* and also an increase in salivation. This last point is interesting as we know that decreased salivary flow is a risk factor for candida infection in older people⁽⁹⁾. Another important factor

regarding this infection is that the colonization site for *Candida albicans* is provided by the carious lesion, since acid production favors an ecological niche for this microorganism. In addition, in vitro studies have shown that the presence of *Candida albicans* improves the adherence of *S. mutans* to oral biofilm and carious tooth substance⁽²⁸⁾. Therefore, it would be logical to deduce that a greater control of dental caries pathogens through probiotics would result in a decreased incidence of *Candida albicans*.

Conclusions

Many recent studies indicate that treatment with probiotics can be a valuable preventive complement to measures already tested, such as the use of fluorides. Most articles selected for this review state that, in the short term, daily consumption of probiotics can effect changes directly in the oral microbiota, such as reducing the number of pathogens, and indirect changes that enhance the growth of indigenous microorganisms, and in the long term, decrease the development and growth of oral pathogens. Therefore, probiotics can be adopted as a novel approach to prevent the demineralization of enamel, improve periodontal health, eliminate halitosis and reduce the prevalence of *Candida albicans* in adults.

In terms of patient compliance and costs, the fact that probiotics need to be consumed daily is a challenge (or at least 4-5 days a week). This could be solved by adding probiotics to the milk consumed by preschoolers attending kindergartens, as a public health measure.

To have a greater impact it would be necessary to combine the use of multiple probiotic species that can significantly affect the levels of cariogenic bacteria in saliva and periodontal pathogens in subgingival plaque. Finally, more clinical trials are needed to determine the best combinations of probiotic strains, and to identify the ideal vehicles and doses for this specific use.

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