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## REVIEW ARTICLE

# PROBIOTICS: CURRENT APPLICATIONS IN ORAL HEALTH CARE

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**ABSTRACT**

The application of 'health-promoting' bacteria for therapeutic purposes is one of the strongest emerging fields. In medicine, probiotics are used mainly in support therapy for gastro-intestinal diseases. In recent years, probiotics have been used as a treatment to promote oral health. Better knowledge of the ecology and microbiology of the oral cavity has laid to a change in understanding of the oral disease process. Very encouraging studies have come up in the recent past exploring probiotics in the fields of caries, periodontal diseases and few other areas and the results tend to suggest beneficial effects of probiotics on oral health and on the whole body in general. Extensive research to create a probiotic product intended to maintain dental and periodontal health is needed. This article reviews the role of probiotics in oral health.



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## INTRODUCTION

The term 'probiotic' is a relatively new word meaning "for life" and it is currently used when referring to bacteria associated with beneficial effects on humans and animals.[1]According to World Health Organization (WHO,2001) probiotics are 'Live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host'.They help to repopulate the beneficial bacteria which in turn would inhibit the proliferation of pathogenic species.[2] Till date, various chemotherapeutics agents are extensively used for treatment of infections caused by indigenous and exogenous microbes. However, development of pathogen resistance to a range of antibiotics has encouraged researchers in various fields of healthcare to develop alternative approaches. The application of 'health promoting' bacteria for therapeutic purposes is one of the strongest emerging field in this regard. Probiotic preparations are increasingly used to confer good health and it is verified with successful randomized clinical trials.In last decade, more research has been carried out to prevent and treat the oral diseases using probioticswhere they are expected to play an important therapeutic and/or preventive role.[3]

**Historical prospective:** Introduction of the concept of probiotics is attributed to *Élie Metchnikoff*, aNobel Prize recipient who in 1907 suggested that "the dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes[4].

*Lilley and Stillwell* (1974) were the first who coined the term "probiotics." Hull et al in 1984, identified*Lactobacillus acidophilus as* the first probiotic species and in 1991, Holcombh et al identified *Bifidobacterium bifidum*.Probiotics have traditionally been used to treatthe gastrointestinal tract diseases. The most widely used species belong to the genera *Lactobacillus* and *Bifidobacteria*.[1]

**Composition of probiotics:** Probiotics can be bacteria, moulds, yeast, but most probiotics includebacteria.

Some of these probiotic species are:[5]

- Lactic acid producing bacteria (LAB): *Lactobacillus acidophilus, Bifidobacterium, Streptococcus.*
- Non LAB species: *Bacillus, Propionibacterium*
- Non pathogenic yeasts: *Saccharomyces boulardii*

Fuller in 1989 listed the following organisms as species used in probiotic preparation- *Lactobacillus bulgaricus, Lactobacillus plantarum, Streptococcus thermophillus, Enterococcus faecium, Enterococcus faecalis, Bifidobacterium species, and Escherichia coli*. A probiotic preparation may be made out of a single bacterial strain or it may be a consortium as well (may contain any number up to eight strains). The advantage of multiple strain preparations is that they are active against a wide range of conditions and in a wider range of animal species.[6]

**Ideal requirements of probiotic products[5]**

- Should have beneficial effect on host.
- Should be non-pathogenic, nontoxic.
- Should replace and resist the intestinal micro-flora.
- Should be resistant to low pH.
- Should remain viable when stored.

**Mechanism of action:** Probiotics have three local or systemic modes of action [7,8,9]

- Indirectly, probiotics compete with pathogens for essential nutrients; they can also restrict the pathogen adhesion capabilities by changing the environmental pH.
- Directly, probiotics are involved in the production of antimicrobial substances (lactic acid, hydrogen peroxide, bacteriocins) that can kill or inhibit the growth of pathogens.
- Probiotics can act on the host by modulating the host's innate and adaptive immune response (reducing the production of pro-inflammatory cytokines: IL-6, IL-1β, TNFα and increasing production of anti-inflammatory cytokines: IL-10) and by improving the intestinal barrier integrity.[10]

**Different vehicles for administration of probiotics:** The most commonly used dietary lactobacilli are being consumed in milk products.[11] Different vehicles for probiotics administration are – Milk Products such asmilk drink,yoghurt, cheese, fruit Juices, lozenges, powder,gelatine,tablets,capsules.

**Probiotics and general health:** Probiotics have traditionally been used to treat diseases related to the gastrointestinal tract[2]. Studies suggest that probiotics may be useful in treatment of patients with coronary heart disease and hypertension[14], urogenital infections[15], lactose intolerance, elevated levels of cholesterol[16]. Other areas of application include probiotic effects against *Helicobacter pylori* infections in the stomach[2], alcoholic liver diseases, hepatic encephalopathy[20], small bowel bacterial overgrowth, ulcerative colitis and crohn's disease[17], allergy to milk protein, juvenile chronic arthritis, asthma and they are also used as vaccine delivery vehicles.[2]Recently probiotics have been tried out in colon cancer, oral cancer, for neutralization of diatary carcinogens[18], in retroviral gastroenteritis, fungal infections, atopic eczema[19], vaginal infections, immune enhancement, rheumatoid arthritis and liver cirrhosis.[20]Study carried out by Lin Tao et al. in 2008 suggested slow progression of AIDS due to the lactobacilli strains that bind to mannose found on HIV envelope. This binding causes the colonization of HIV and prevents its further spread.[21]

**Probiotics and periodontitis:** Periodontitis is a chronic inflammatory condition affecting both the hard and soft tissues surrounding the teeth, caused by a combination of specific bacteria and inflammatory host responses and resulting in the destruction of the connective tissue of the gingiva, periodontal ligament and alveolar bone.[22]Periodontitis is also considered a risk factor for cardiovascular disease, pulmonary disease, type II diabetes, rheumatoid arthritis and adverse pregnancy outcomes.[23]The current concepts regarding the etiopathogenesis of periodontitis involve three factors which determine the risk for a patient to develop periodontitis. These include (i) host susceptibility (ii) presence of periodontopathogens and (iii) the absence of 'beneficial bacteria.[11]Scaling and root planning are the gold standard treatmentsfor reduction of bacterial load. However, recolonization towards pretreatment level by periodontal pathogens occurs within weeks to months. The adjunctive use of local or systemic antibiotics only temporarily improves the outcome of periodontal therapy and excessive use may lead to development of antibiotic resistance. The use of probiotics to reduce the number of periopathogenic bacteria and increase the number of commensal organisms will favour the long-term treatment outcomes.

Guided Periodontal Pocket Recolonization is the concept of replacing the pathogenic bacteria in the gingival sulcus with beneficial bacteria.This is pioneered by Teughels et al in 2007. He observed that when a bacterial mixture that contained *Streptococcus sangius, Streptococcus mitis and Streptococcus salivarius* was cultured and supplemented with 1 mg/mL Yeast Extract (Difco), when injected into the periodontal pockets, the recolonization of *Porphyromonas gingivalis* and *Prevotella intermedia* were suppressed. These strains resulted significant reduction in pocket depth and attachment level gain.[24] *Streptococcus sanguis* has shownto produce prominent inhibitory properties against *Aggregatibacter actinomycetemcomitans* (Aa) colonization. Hydrogen peroxide produced by streptococcus sanguis either directly or by host enzyme amplification can kill Aa.[25]These findings highlight the importance of the indigenous microbiota in oral ecology and suggest the replacement therapy, may offer a new therapeutic approach for the prevention of plaque related periodontal diseases. Significant improvement in jaw bone density and alveolar bone gain was found in periodontal pockets that received beneficial bacteria adjunctive to scaling and root planing.[26] Oral administration of *Lactobacillus salivarius (WB21),* in the form of tablets have shown to decrease the plaque index and probing pocket depth of subjects, suggesting clinical improvement of the periodontal condition by probiotic intervention.[27]L. casei 37 showed reduced number of most common periodontal pathogens and L. salivarius TI 2711 inhibit *P. gingivalis* when given for 4 or 8 weeks.[28]

**Probiotics and dental caries:** Dental caries is a multifactorial disease of bacterial origin and is characterized by acid demineralization of the tooth structure. It occurs following changes in the homeostasis of the oral ecosystem leading to proliferation of the streptococcusmutans biofilm. A probiotic must be able to adhere to tooth surfaces and integrate into the bacterial communities making up the dental biofilmto have a beneficial effect in limiting or preventing dental caries. It should also antagonize the cariogenic bacteria andprevent their proliferation. Finally, the probiotic should cause metabolism of food sugars which result in low acid production. The probiotics in dairy products have capacity to neutralize acidic conditions. For example, it has already been reported that cheese prevents demineralization of the enamel and promotes its remineralisation.[29,30,31]Studies have proven that one strain of *L. rhamnosus* and the species *L. casei* inhibited in vitro growth of two important cariogenic *streptococci, S. mutans* and *S. sobrinus.*It is proved that children consuming milk containing probiotic,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.[29]

**Table 1. Marketed probiotic formulations claiming improved oral health[12,13]**

| Name of Formulation | Description |
|---|---|
| 1) Gum PerioBalance (marketed by Sunstar, Etoy, Switzerland) | The first probiotic specifically formulated to fight periodontal disease. It contains a patented combination of two strains of L. reuteri which have synergistic properties in fighting cariogenic bacteria and periodonto pathogens. Each dose of lozenge contains $2 \times 10^8$ living cells of L. reuteri Prodentis. Users are advised to use a lozenge every day. |
| 2) Nature Wise, Time Release Probiotics, Oral Health, Fresh Mint Flavour, Chewable Tablets | Claims to help in inhibiting certain harmful bacteria responsible for bad breath, tooth decay, sore throat, and other upper respiratory infections. BLIS K12 and BLIS M18 strains help in preventing the formation of dental plaque and significantly boost ear, nose, and throat immune defenses. |
| 3) Hyperbiotics - Pro-Dental Probiotic Natural Mint | Claims to target bad breath and it contains top oral probiotic Strains i.e. S. salivarius K12, S. salivarius M18, L. reuteri and L. paracasei) combating the indiscriminate effects of antibacterial. These strains reside on the tongue, tonsils, and ear, nose and throat area so chewing them is the perfect delivery method combating bad breath and promote healthy teeth, gums, ears, throat, and sinuses. |
| 4) Sunstar Gum PerioBalance | A food supplement, containing the patented lactic acid bacterium, L. reuteri DSM 17938 and L. reuteri ATCC PTA 5289 that promote good microbes and restore a natural balance in the oral cavity. |
| 5) Jarrow Formulas - Jarro-Dophilus Oral Probiotic Peppermint - Lozenges | Consists of two probiotic strains L. brevis CECT 7480 and L. plantarum CECT 7481, claims to promote the health of the gums, teeth, and better breath. |

Recently the Regina T. C. et al studied the effect of oral probiotic lozenges provided by Hyperbiotics Pro□Dental, USA on the Caries Risk Factors among High□Risk Caries Population showed significant reduction in plaque and calculus formation among participants with high risk of developing new caries lesion.[32]

**Probiotics and gingivitis:** Krasse P etal(2006) assessed the influence of the probiotic on plaque and the lactobacilli population in the saliva. They found that Lactobacillus reuteri was efficacious in reducing both gingivitis and plaque in patients with moderate to severe gingivitis.[33]It was suggested that[11]

- *Lactobacillus reuteri* produce an anti-microbial substance Reuterin, that effectively inhibits a wide range of pathogenic bacteria.
- Strains of *Lactobacillus reuteri* have an ability to block binding of pathogenic bacteria to host tissue.
- Anti-inflammatory effects of *L.reuteri* on the intestinal mucosa through the inhibition of pro-inflammatory cytokines invitro and invivo might be the basis of a direct or indirect effect of this bacterium on the gingiva in subject with gingivitis.

Probiotic mouthwash containing lactobacillus $2\times10^8$ colony-forming units/g(sporlac sachets dissolved in distilled water) found to be as e□ective as chlorhexidine as an adjunctive chemical plaque control agent.[34]

**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. An anaerobic bacteria degrade salivary and food proteins to generate amino acids, which are in turn transformed into volatile sulphur compounds, like hydrogen sulphide and methane thiol. *Streptococcus salivarius*is abundantly detected among people without halitosis and is therefore considered a commensal probiotic of the oral cavity.[29,31]Bacteriocins *produced by S. salivarius*, known to contribute in reducing the number of bacteria that produce volatile sulphur compounds. The use of gum or lozenges containing *S. salivarius* K12 reduced levels of volatile sulphur compounds among patients diagnosed with halitosis.[29]

**Probiotics and candidiasis:** Candida species are able to cause a clinically apparent lesion if the immune defense are breached either on the local or systemic level.

Studies have shown that the subjects who consumed cheese containing the probiotic L.rhammnosus GG exhibited reduction in the prevalence of oral Candida which subsequently may confer protective effect against oral candidiasis. Various commercially available strains of lactobacilli probiotics can inhibit the growth of C. albicans possibly due to the low pH environment produced by the lactobacilli. In a laboratory study **c**andida-infected mice which were fed with L.acidophilus exhibited accelerated clearance of C**.** albicans from the mouth.[35]The probiotic bacteria that have been investigated against Candida species to date include Streptococcus salivarius K12, Lactobacillus rhamnosus GR-1, Lactobacillus reuteri RC14, and also clinical isolates of Lactobacillus.[36]Administration of probiotics in along with antifungal drugs have proven to synergize clearance of Candida.[37] Ishikawa et al have reported that, when palatal surfaceof maxillary dentures regularly cleaned with the probiotic containing*Lactobacillus rhamnosus* HS111, *Lactobacillus acidophillus* HS101, and *Bifidobacterium bifidum* daily reduced oral candidal burden in healthy denture wearers.**[38]**Evidence suggests that probiotics can also reduce the risk of hypo-salivation and feeling of dry mouth.[39]

**Probiotics and oral cancer:** *Lactobacillus plantarum* induces apoptosis in oral cancer KB cells through upregulation of phosphatase and tensin homolog (PTEN) and downregulation of mitogen-activated protein kinases(MAPK) signaling pathways, *L. plantarum* is proposed as a potential candidate for probiotics cancer therapy,[40]nevertheless such proposition needs to be thoroughly examined in the relevant animal models prior to its translation into clinical uses.

**Safety and Dosage:** According to the U.S. Food and Drug Administration, probiotics are Generally Recognized as Safe (GRAS). Regarding dosage, there is no standard dosage recommended for the administration of probiotics. Studies carried out showed a wide range of dosages that are safe for various probiotics. For lactobacilli, dosages ranged from 100 million to 1.8 trillion colony-forming units per day. *Saccharomyces* dosages ranged between 250 mg and 500 mg/day. Variations are seen in dosages depending on the age, where dosages for children are typically half the adult dose and for infants, it is one-fourth the adult dose.[41]

**Side effects:** According to a 2002 report jointly released by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations "probiotics may theoretically be responsible for four types of side effects:

- Systemic infections like bacteremia, endocarditis.
- Deleterious metabolic activities such as deconjugation of bile salts,D-lactic acidosis
- Excessive immune stimulation in susceptible individuals.
- Minor gastrointestinal symptomssuch as abdominal cramping, nausea, soft stools, and taste disturbance have been reported.[42]

**Future research:** The WHO/FAO working group recommended that new probiotic strains be evaluated for safety by testing for antibiotic resistance, toxin production and hemolytic potential, assessing metabolic activities such as D-lactate production and bile salt deconjugation, conducting human studies to evaluate side effects and post-market surveillance of commercial consumers, and ideally, studying their use in immunocompromised animals to determine infectivity of the probiotic organism in this type of host. Also,more independent studies are need to carry out to look into specific probiotic strains, doses, delivery methods, treatment schedule, mechanisms of action, safety and how to maintain the results of the probiotic interventions.Finally, possibilities to genetically modify or engineer potential probiotics strains may offer totally new visions need to be studied.

**Conclusion**

In the recent times when organisms are fast developing resistance to antibiotics, the emergence of probiotics appears to be a boon for the treatment of diseases. Researches have confirmed that the oral diseases are not only confined to the oral cavity but have strong systemic effects. Hence a good oral health confers a good systemic state and probiotics offer a natural and promising option to establish this.

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