**Review Article**

**PROBIOTICS: CONTRIBUTIONS TO ORAL AND DENTAL HEALTH**

**ABSTRACT**

Probiotics have been extensively researched for their beneficial health promoting effects. Previously, the mainstream of research was limited to the gastrointestinal flora, but in the past few years it has been more focused towards the oral and dental health perspectives. Few randomized controlled trials have been conducted in this area, though the investigations on probiotics versus oral and dental health are still in their cradle. The aim of this review is to assess the potential mechanisms of probiotic bacteria in the oral cavity and summarize observed effects of probiotics with respect to oral and dental health. The review focuses on probiotic lactobacilli and bifidobacteria, genera that are most widely used in various probiotic supplements. It also discusses the potential of probiotic strains in oral cavity colonization, interspecies interactions, and possible effects on host immunomodulation.

**Key Words:** Probiotics; Oral health; Lactobacillus; Bifidobacterium.

**INTRODUCTION**

According to the generally accepted definition, a probiotic’ is a live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance’.1 WHO2 (2002) describes probiotics as “live microorganisms which, when administered in adequate amounts in food or as dietary supplement confer a health benefit on the host”. This term has been derived from the Greek language which means “for life”. The term Probiotic, as an antonym to the term antibiotic, was first used by Lilly and Stillwell3 in 1965 to describe substances secreted by one microorganism which stimulates the growth of another. The concept of probiotics was brought forward in the first decade of 1900 by a Ukrainian bacteriologist and Nobel Laureate Elie Metchnikoff4 who observed that bacteria in the fermented milk competed with the microorganisms that are injurious to health. While studying the flora of the human intestine, he developed a concept that senility is caused by poisoning of the body by the products of some of the harmful bacterias of the gut. He proposed a diet containing fermented milk products rich in live lactic acid bacteria to neutralize deleterious effects of these gut organisms. He credited these fermented products for extending the longevity of some populations of Bulgaria, Turkey and Armenia. He discovered Lactobacillus bulgaricus and claimed that cholera could be controlled by the presence of antagonistic organisms in the intestine.

Fuller (1989) described probiotics as a live microbial food supplement, which beneficially affects the host animal by improving its microbial balance.5 Tanboga et al6 (2003) credited Hull et al (1984) and Holcombh et al (1991) for introducing Lactobacillus acidophilus and Bifidobacterium bifidum respectively, into research work as the first probiotic species.

**PROBIOTIC STRAINS IN THE ORAL CAVITY**

Probiotics can be bacteria, molds, or yeast. But the majority of probiotics are bacteria. The most common probiotic strains belong to the genera Lactobacillus and Bifidobacterium, the former one being more popular7. Lactobacillus species from which probiotic strains have been isolated include Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus lactis, Lactobacillus helviticus, Lactobacillus salivarius, Lactobacillus plantrum, Lactobacillus bulgaricus, Lactobacillus rhamnosus, Lactobacillus johnsonii, Lactobacillus reuteri, Lactobacillus fermentum, Lactobacillus del‑brueckii. Bifidobacterium strains include Bifidobacterium bifidum, Bifidobacterium longum, and Bifidobacterium infantis. Other strains include Streptococcus thermophilus, Enterococcus faecium, Enterococcus faecalis, and Saccharomyces boulardii. A probiotic may be made out of a single bacterial strain or it may be a consortium as well. Probiotics can be in powder form, liquid form, gel, paste, granules or available in the form of capsules, sachets, etc.8

 An essential property of a microorganism to be ‘an oral probiotic’ is its ability to adhere and to and colonize surfaces in the mouth. Probiotic microorganisms may not have oral cavity as their inherent habitat, hence their role to confer benefit on oral health remains questionable. Paster et al9 (2001) used culture-independent molecular methods to determine bacterial diversity in human subgingival plaque and estimated around 500-600 total species diversity in the oral cavity. Kazor et10 al (2003) detected 200 additional unknown species on the tongue dorsa of patients with halitosis and healthy patients. This made the number of species in the mouth to reach 700. Marsh and Martin11 (1999) reported that Lactobacilli genera constitute approximately 1% of the cultivable oral microflora. Teanpaisan and Dahlen12 (2006) implemented polymerase chain reaction techniques to differentiate oral Lactobacillus species from saliva and recovered the most common species like L. fermentum, L. rhamnosus, L. salivarius, L. casei, L. acidophilus, and L. plantarum. Similar observation was reported by Colloca et al13 (2000) regarding diversity in the oral lactobacilli flora in healthy human mouth. Ko˜ ll-Klais et al14 (2005) detected no differences in salivary counts between chronic periodontitis and healthy mouths. They also found L. gasseri and L. fermentum being the predominant lactobacilli species among other isolates. After one year, the same workers15 observed a higher prevalence of homofermentative lactobacilli in healthy mouths compared to mouths affected with chronic periodontitis. These research work suggests that lactobacilli as members of resident oral microflora could play a vital role in the microecological balance in the mouth. The probiotic lactobacilli strains found were due to frequent consumption of dairy products or if mouth is their permanent habitat is questionable. Long-term follow-up studies to support this evidence are not available.

**PREBIOTIC AND SYNBIOTIC**

Human gastrointestinal tract (GIT) constitutes an enormously complex ecosystem of bacterial flora. Some of these microorganisms are beneficial like Lactobacillus and Bifidobacterium, but some are harmful like Salmonella species, Helicobacter pylori, and Clostridium perfringens. Prebiotics are some dietary substances, which favor the growth of these beneficial bacterias over that of harmful ones. Prebiotics are non-digestible food constituents which include short-length carbohydrates like inulin, fructo-oligosaccharides (FOS), galacto-oligosaccharide and lactulose.16, 17 FOS are natural carbohydrates that cannot be digested or absorbed by humans but support the growth of beneficial bacteria like Bifidobacteria. Prebiotics are fermented in the colon to produce short-chain fatty acids, such as acetate, butyrate, and propionate and also have positive effects on colonic cell growth and stability2. Williams et al18 (1994) recommended that patients taking bifidobacteria also supplement with FOS. Bertelsen19 (2001) showed that prebiotic ingestion is characterized by changes in microbial population density. Salvini et al20 (2004) observed reduction of harmful or potentially harmful bacteria in the intestine after the ingestion of prebiotics, which reduces the risk of infectious diarrhea and general intestinal malaise. It also causes an increase in large bowl motility and decrease in transit time improves stool quality and bowl regularity as well as increases stool mass. This maintains healthy intestinal functions and reduces the chances of constipation. The product containing both probiotics and prebiotics, is termed as “symbiotic”. This term should be reserved for a product in which the prebiotic compound selectively favors the probiotic compound.21 Symbiotic includes both the live cells of the beneficial bacteria and the selective substrate2.

**PROBIOTICS: FEATURES, PRODUCTS AND THERAPEUTIC ACTIONS**

An ideal probiotic agent must have following properties22, 23:

1. Non-pathogenic and non-toxic in preparation.
2. Belong to human origin.
3. Present as viable cells, preferably in large numbers.
4. Replace and reinstate the intestinal microflora.
5. Possess good shelf life.
6. Possess a high degree of genetic stability.
7. Withstand or resist gastrointestinal juices or gastric acid or bile acid.
8. Capable of surviving and metabolizing in gut environment.
9. Produce beneficial effects to host.
10. Adhere to gut epithelial tissue and produce antibacterial substances.
11. Avoid the effects of peristalsis.

Probiotics are mainly furnished to consumers in the form of dietary supplements and foods. Culture manufacturers recommend formulation of probiotic products at 106 probiotic per gram or milliliter of dairy products, but viable counts may fall below these levels, especially at the end of shelf life. While defined in terms as ‘medical probiotics’ (microbial preparation) and ‘other probiotics’ (functional food), probiotics are usually provided in products in one of the five basic ways21, 24, 25:

1. A culture concentrate added to a beverage or food (such as a fruit juice).
2. Inoculated into prebiotic fibers.
3. Inoculants into a milk‑based food (dairy products such as milk, milk drink, yogurt, yogurt drink, cheese, kefir, and bio‑drink).
4. As concentrated and dried cells packaged as dietary supplements (non‑dairy products) such as powder, capsule, gelatin tablets.
5. They can also be supplied as mouth washes, lozenges, chewing gums, tooth pastes and straws.

Probiotics have a wide range of areas of action like medical, dentistry, nutrition and food sciences, immunology, oncology, agriculture (soil fertility), animal and poultry industry, and veterinary practice, etc. The major areas of their medical therapeutic clinical actions include23, 26-29:

1. Reduction of liver toxicities.
2. Reduction of blood cholesterol levels.
3. Prevention of colon cancer.
4. Enhancement of calcium absorption.
5. Regulation of immunity.
6. Prevention of diarrhea caused by clostridium difficile toxin.
7. Reduction in AIDS progress.
8. Optimization of effects of vaccines.

**PROBIOTICS: MECHANISM OF ACTION**

The possible mechanism of action of probiotics contributing in oral and dental health may be15

1. Production of antimicrobial substances such as Organic acids, Hydrogen peroxide and Bacteriocins. Some produce lactase.

2. Binding in Oral Cavity

a) Compete with pathogens for adhesion sites

b) Involvement in metabolism of substrates (competing with oral micro organisms for substrates available) as well as for available nutrients and growth factors.

3. Immuno-modulatory

c) Stimulate non specific immunity

d) Modulate humoral and cellular immune response

e) Effect on local immunity

4. Modify oral conditions

f) Modulating pH

g) Modification of oxidation reduction potential

h) Regulation of mucosal permeability

i) Selection pressure on developing oral microflora towards colonization by less pathogenic species.

Probiotics act on dental plaque formation, its complex ecosystem and are involved in binding of oral microorganisms to proteins. They stimulate macrophages, produce cytokines, escalate natural killer cell and raise the levels of immunoglobulins.30The increase in the number of Immunoglobulin A producing cells is the most remarkable property induced by probiotic organisms and also by fermented milk yogurt.26Other mechanism may include mucin production, down regulation of inflammatory responses28, defensin production, inhibit pathogen induced production of pro-inflammatory cytokines, inhibiting collagenases, decreasing Matrix Metalloproteinase (MMP) production, induction of expression of cytoprotective proteins on host cell surfaces, etc. Since mouth represents the first part of the gastrointestinal tract, at least some probiotic mechanisms may also play a role in this part of the system and also they can be introduced here at much higher concentration with minimum loss in number. 2, 26, 31Probiotics inhibit pathogens but do not inhibit friendly bacteria. Studies have shown that once the pathogenic organisms are replaced the reintroduction of the pathogen does not occurs easily.32

**PROBIOTICS FOR ORAL AND DENTAL HEALTH**

**PROBIOTICS AND DENTAL CARIES**

The role of oral administration of probiotics on dental caries has been studied in several research experiments using different test strains of probiotic bacteria. Several researchers32, 34-36 have proved the potential of these probiotic strains (Lactobacillus rhamnosus GG and Lactobacillus casei) to hamper growth of oral streptococci. Ahola et al35 (2002) studied effect of a short-term consumption of probiotic-containing cheese on dental caries and found reduction in the incidence of dental caries in children. Inclusion of Lactobacillus rhamnosus GG and Lactobacillus rhamnosus LC 705 in milk or processed cheese lowered the salivary counts of S. mutans.Caglar et al37 (2006) observed a definite S. mutans count reduction after a 2-week consumption of yogurt containing the probiotic bacterium Lactobacillus reuteri. This indicated the necessity of continual administration of the probiotic in order to achieve its effect. Similarly, the relationship between probiotic bifidobacterium and counts of S. mutans was tested by Caglar et al3, 38 (2005). They observed a statistically significant reduction in salivary mutans streptococci. However, further investigations are needed for concluding the relation between S. mutans and bifidobacterium strains.

Anderson and Shi39 (2006) suggested that the operative approach in caries management might be challenged by probiotic implementation with subsequent less invasive intervention in clinical dentistry. Future studies are required before this goal could be achieved. Majority of studies describing the correlation between probiotic strains and streptococci pathogens do not fulfil the criteria of investigations for evidence-based medicine.

Bonifait et al40 (2009) discussed the role of probiotics in prevention of dental caries. They believed that a probiotic must adhere to dental surfaces and integrate into bacteria that make up the dental biofilm, compete with and antagonize cariogenic bacteria to prevent their proliferation, and produce little acid in the metabolism of food-grade sugars. Two bacteriocins (reuterin and reutericyclin) secreted by L. reuteri found inhibiting the growth of a wide variety of pathogenic bacterias. This lactobacilli strain has strong capacity to adhere to host tissues and has inflammatory effects.

Probiotic L. reuteri in various forms like chewing gum41, tablets37, lozenge42, or as administered in yogurt43 has been observed to decrease S. mutans level in saliva. Some workers38, 44 have shown a significant growth inhibition of S. mutans when yogurt with Bifidobacterium DN-173 010 was administered in young adults. Stamatova and Meurman44 (2009) have shown that L. casei ATCC 11578 affect the adherence of the streptococci to saliva coated hydroxyapatite (HA), by slightly inhibiting the adherence of S. mutans and it could even release the already bound streptococci from the HA. Caglar et al45 (2008) demonstrated a significant reduction of S. mutans when ice-cream containing Bifidobacterium lactis Bb-12 was administered. Comelli et al46 (2002) evaluated the effects of various lactic strains used as probiotics in oral cavity. Bhushan and Chachra21 showed that Lactobacillus strains like L. paracasei and L. plantarum also interfere with S. mutans. These strains hydrolyze urea to ammonia with the help of their urease enzymes. This activity influences plaque biochemistry and metabolism which reduces cariogenicity, thus indicating the usefulness of ureolytic bacteria in promoting dental health.21These species reside in dental plaque and the ammonia released from salivary and dietary substrates prevent the colonization of cariogenic pathogens. This action also ensures internal pH homeostasis. Reddy et al2 (2010) believed that the presence of this effector strain in indigenous flora would keep the host protected. The first toothpaste (Plidenta Pro-t-action) in the world which contained L. paracasei probiotic was found to co-aggregates S. mutans and reduces caries activity in the oral cavity.25 Jose et al32 (2010) studied the effect of systemic consumption of probiotic curd and use of probiotic toothpaste on the count of S. mutans in plaque around orthodontic brackets. They agreed that lactobacillus, streptococci and bifidobacterium species are genetically designed to have greater adhesion and hence competitively inhibit S. mutans.

Ritthagol et al47 (2014) carried a double-blinded, randomized, placebo-controlled study to evaluate the effect of probiotic milk powder containing L. paracasei SD1 on the count of S. mutans in the mouth of the orthodontically treated cleft lip and palate patients. They found that this probiotic strain reduces S. mutans count and also able to colonize the oral cavity in those patients. They reported that it could be detected up to 4 weeks following cessation of dosing. Some authors2, 22 discussed the role of genetically modoified probiotics which possessed enhanced properties. S. mutans strain BCS3-L1 was such modified strain which was designed to prevent dental caries. Recombinant DNA technology deleted the gene encoding lactate dehydrogenase in BCS3-L1 which made it unable to produce lactic acid. This strain was designed to produce elevated amounts of a novel peptide antibiotic (mutacin 1140) that offers it a strong selective benefit over other S. mutans strains. A designer probiotic Lactobacillus strain expressed antibodies targeting one of the major adhesions of S. mutans and was able to decrease both the viable counts of S. mutans and the caries score in a rat model.21 A probiotic mouthwash (ProBiora3) containing low acid-producing Streptococcus rattus JH145, Streptococcus oralis KJ3, and Streptococcus uberis KJ2 was found to inhibit the growth of pathogenic streptococci strains. Rebolledo et al48 (2013) evaluated the effect of L. rhamnosus and L. johnsonii containing probiotics on the growth of S. mutans and found that it decreased the colonization of dental caries producing S. mutans. They suggested that these probiotics could be used in the prevention and prophylaxis in high risk cariogenic patients.

**PROBIOTICS AND PERIODONTAL DISEASE**

Lactobacillus reuteri caused a decrease in gingival bleeding and gingival inflammation. Twetman et al49 (2009) performed a short-term study where they tested an effect of chewing gums containing probiotic Lactobacillus reuteri ATCC55730 and ATCCPTA5289 on the levels of inflammatory mediators in gingival crevicular fluid (GCF). They noted a drastic decrease in the levels of pro-inflammatory cytokines TNF-α and IL-8 in GCF. Reddy et al2 (2010) reported that inclusion of probiotic strains in periodontal dressings at optimal concentration of 108CFU/ml reduced the number of most frequently isolated periodontal pathogens which included Bacteroides sp., Actinomyces sp., and S. intermedius, and also C. albicans. It was also observed that inhabitant lactobacilli inhibit P. gingivalis and Prevotella intermedia. Haukioja50 (2010) showed that tablets containing L. salivarius WB21 reduced pathogens in subgingival plaque and decreased pocket probing depth and plaque index in individuals with high risk of periodontal disease such as smokers. Some authors51, 52 observed a significant suppression of the recolonization of P. gulae and P. intermedia after a subgingival application of S. sanguinis, S. salivarius, and S. mitis in a beagle dog model, following scaling and root planning. Dave et al31 (2013) claimed that Acilact (a probiotic complex of five live lyophilized lactic acid bacteria) improve both clinical and microbiologic parameters in gingivitis and mild periodontitis patients. L. brewis probiotics reflected their anti-inflammatory effects in chronic periodontitis conditions. This species when delivered through lozenges found to improve plaque index, gingival index, and bleeding on probing. The anti-inflammatory effects of these strains are due to their capacity to prevent production of nitric oxide and consequently the release of Prostaglandin E2 and activation of MMPs induced by nitric oxide. Other lactobacillus strains like L. helveticus produces short peptides that act on osteoblastic cell and increase their activity in bone formation. This effect reduces bone resorption associated with periodontitis. Bonifait et al40 (2009) reported lower probing depths and less loss of clinical attachment in individuals who consume regular yogurt or beverages containing lactic acid compared to those who consume few of these products. Mallikarjuna et al25 (2013) observed a greater prevalence of L. gasseri and L. fermentum among healthy patients than those patients with chronic periodontitis. Messora et al53 (2013) experimented the effects of probiotic Bacillus subtilis in rats with ligature induced periodontitis (LIP) and found reduction in attachment loss and alveolar bone loss. It was also identified that it protected the small intestine from reactive changes induced by LIP, thus improving the intestinal morphology. Teughels et al54 (2013) conducted a randomized placebo-controlled study in patients with chronic periodontitis and observed that L. reuteri containing probiotic lozenges caused significant pocket depth reduction, attachment gain in moderate and deep pockets and reduction in P. gingivalis. Probiotics decrease pH and don’t allow plaque bacteria to form dental plaque and calculus which are the causative factors for periodontal disease. It also forms antioxidants which neutralizes the free electrons needed for the mineral formation, thus prevents plaque formation.

**PROBIOTICS AND HALITOSIS**

Halitosis or bad breath or the oral malodor, is mainly due to the production of volatile sulfur compounds (VSC) predominantly by gram negative anaerobes residing in periodontal pockets and on the dorsal surface of tongue.44 Probiotics breaks these putrescence odors by fixating on the toxic gases/ VSCs and converts them into gases required for metabolism. In vitro and in vivo studies revealed that the production of VSC by Fusobacterium nucleatum was inhibited after the ingestion of Weissella cibaria. A marked reduction in the levels of hydrogen sulfide and methanethiol was detected after gargling with W. ciberia containing mouth rinse. It was seen that hydrogen peroxide and bacteriocins produced by W. ciberia was responsible for causing inhibition of F. nucleatum growth. S. salivarius produces a bacteriocin known as salivaricin, has been found to reduce the number of microflora producing VSC including hydrogen sulfide, methyl mercaptan and dimethyl sulfide. Chewing gum or lozenges containing S. salivarius K12 reduces levels of VSC by inhibiting gram positive bacterias in patients with halitosis. S. salivarius K12 secrete bacteriocin like inhibitory substances (BLIS) which acts as powerful antimicrobial molecules which boosts immune system of the host. It also decreased S. mutans count in saliva of orthodontic adolescents and long term ingestion prevented sore throat in childrens. Researchers55-59 found that Weissella confusa isolates and bacterias forming lactic acid also appear to decrease halitosis.

**PROBIOTICS AND ORAL CANDIDIASIS**

Candida albicans is among the most common infectious organisms in the oral cavity. The elderly individuals are vulnerable to Candida infection, which is frequently provoked by chronic diseases, medication, poor oral hygiene, reduced salivary flow, or the impairment of the immune system.57 Candida colonization may be asymptomatic, but heavy growth usually causes local candidiasis which may display various types of mucosal lesions and symptoms.57This makes to control the proliferation of yeast. Probiotic L. rhamnosus GG has been observed to modify human gut microbial balance by reducing the proliferation of Candida albicans.58, 59 Wagner et al60 (1997) tested the biotherapeutic effects of probiotic Lactobacillus GG on candidiasis in immunodeficient mice and observed a drastic reduction in Candida counts in the alimentary tract. Manzoni et al61 (2006) conducted a randomized study in preterm neonates and found that oral supplementation of lactobacillus rhamnosus GG reduced the enteric colonization of candida, as measured by colonies isolated from oro-pharyngeal, gastric aspirate, stool, and fecal specimens. Some species of lactobacilli possess the ability to adhere the mucosal epithelium competing for adhesion sites with candida.61These species produce hydrogen peroxide and antifungal cyclic dipeptides, which inhibit the in vitro growth of candida.61, 62

Elahi et al63 (2005) detected an enhanced clearance of candida albicans from the oral cavities of mice following oral administration of Lactobacillus acidophilus. The authors believed this effect possibly lactobacilli caused the production of IL-4 and IFN- in lymph nodes and nitric oxide (NO) in the saliva which shortened the candida growth in the mouth. Two species of lactobacilli, L. plantarum and L. reuteri ATCC 55730 exhibited the strongest inhibition on candida albicans.25, 44, 51, 64, 65The results obtained in animals, however, require further experimentation of the effect of the strains on cases with clinically manifested C. albicans infection in humans.

**PROBIOTICS AND ORTHODONTICS**

Fixed orthodontic appliances in the mouth can permit microorganisms to accumulate, grow and proliferate, leading enamel demineralization. Short-term intake of fruit yogurt containing bifidobacteria has shown to alter the levels of S. mutans and lactobacilli in patients with orthodontic fixed appliances. Cildir et al66 (2009) showed in experimental studies that 200 g once daily fruit yogurt containing Bifidobacterium animalis N 173010 significantly reduced S. mutans counts in two weeks. Lactobacilli count was not altered. Jose et al32 (2013) showed that the consumption of probiotic curd (Active plus) and the topical application of probiotic toothpaste (GD) caused significant decrease in the S. mutans levels in the plaque around orthodontic brackets.

**ADMINISTRATION OF PROBIOTICS**

Several literatures have discussed the appropriate forms of administration of probiotic strains. Dairy products supplemented with probiotics are a natural means of oral administration and easily adopted in dietary regime. However, for the purposes of prevention or treatment of oral diseases, specifically targeted applications, formulas, devices, or carriers with slow release of probiotics might be needed. Montalto et al67 (2004) performed a double-blind, randomized, controlled study, in which they administered probiotic mix both in capsules and in liquid form and found that this means of administration increases salivary counts of lactobacilli. Caglar et al37 (2006) designed a special straw with a reservoir containing probiotics for comparing the effect of two non-dairy delivery methods. They used a Life top straw (BioGaia AB, Stockholm, Sweden) and a lozenge for delivering probiotics and checked the effectiveness of L. reuteri to reduce the number of S. mutans. Both means of administration showed significant reduction in salivary S. mutans levels in half of the patients when compared with subjects who received placebo. A recent invention for dental caries prophylaxis is a chewing gum containing L. reuteri Prodentis. This gum was recommended to consume twice daily and was marketed to regulate S. mutans counts in the mouth. However, the most suitable means of delivery and dosages of probiotics for various oral health purposes have not been defined.68

**PROBIOTICS: SAFETY MEASURES**

In the past few years, the tremendous probiotic supplementation of different food products led to discuss an important aspect of safety regarding its consumption. The putative probiotic strains should not be pathogenic, should not possess any growth-stimulating effects on bacteria causing diarrhea. They should not have an ability to transfer antibiotic resistance genes. The probiotics should be able to maintain genetic stability in oral microflora environment.69The increased consumption of probiotic containing supplements leads to increased concentrations of these strains in the host. Excessive consumption of probiotics containing lactobacilli strains may cause lactobacillus bacteremia, which is a rare entity. The data on the clinical significance of this entity are mainly found through case reports published in scientific journals. Boriello et al70 (2003) found the documentation of approximately 180 reported clinical cases in the last 30 years. Clinical features of Lactobacillus bacteremia shows great variations ranging from asymptomatic to septic shock-like symptoms. Any viable bacteria are capable enough to cause bacteremia in immuno-compromised patients or those who have severe underlying diseases. Husni et al71 (1997) and Cannon et al72 (2005) reviewed the pathogenic relevance of Lactobacillus and found that the affected patients were already registered with other systemic diseases such as diabetes, cardiovascular diseases, gastrointestinal disorders, malignancies, or organ transplant patients. This realized the need of careful monitoring in this issue in the future. Various authors carried research studies in immuno-compromised patients to check the relevance of lactobacilli strains. Wolf et al73 (1998) conducted a controlled study, in which 35 HIV-positive patients were exposed to Lactobacillus reuteri strains and found no clinically significant side effects. Salminen et al74 (2002) observed no increase in Lactobacilli (Lactobacillus rhamnosus GG) in blood culture samples when screening the Finnish population for the period of 1990-2000. Salminen et al75 (2006) again reported no adverse effects from Lactobacillus rhamnosus GG ingestion in general or HIV-positive patients. In the participated HIV-positive patients, CD4 cell counts were analyzed and were given suitable and highly active antiretroviral therapy. LGG-containing probiotics are not likely to exert any major health associated risks among HIV-positive patients. Animal experiments have also proved an induction of mucosal and systemic immune responses rendering protection against pathogenic bacterias after inoculating lactobacilli species as antigens at mucosal sites. 76, 77 Grangette et al76 (2001) have shown that recombinant Lactobacillus plantarum are capable of inducing mucosal immune response against tetanus toxin, delivered by an intranasal route. Similarly, Oliveira et al77 (2006) have demonstrated the induction of systemic and mucosal immune response and decrease in Streptococcus pneumonie colonization by nasal inoculation of mice with recombinant lactic acid bacteria expressing pneumococcal surface antigen.

The safety criterion which must be given a significant value is related to the absence of acquired antibiotic resistances in potential probiotic individuals. Probiotics may cause transferral of antimicrobial resistance genes in between microorganisms. Lester et al78 (2006) showed an in vivo transfer of the vanA resistance gene from an Enterococcus faecium isolate of animal origin to an E. faecium isolate of human origin in the intestines of human volunteers. Antibiotic susceptibility tests claimed that the genes in some probiotic strains are responsible for certain antibiotic resistances. Huys et al79 (2006) have searched the genetic basis of tetracycline and minocycline resistance in potentially probiotic Lactobacillus plantarum strain CCUG 43738. Similar study was carried by Masco et al80 (2006), who agreed antimicrobial susceptibility of Bifidobacterium strains from humans, animals, and probiotic products. These experiments suggest the requirement of a minimal safety evaluation while selecting strains for probiotic preparation. Further studies are needed in this area as the resistance developed to most commonly recommended antibiotic drugs is of great global concern. Hence, before recommending any probiotic therapy, transferral of resistance genes needs to be carefully investigated.

**PROBIOTICS: FUTURE ASPECTS**

The issue of safety is of utmost importance during the past few years due to the increased probiotic supplementation of different food products. Oral lactic acid bacteria and bifidobacteria have been isolated and experimented for various oral and dental health purposes, including dental caries, periodontitis, and halitosis.81-87 Several authors46, 88 studied the various dairy strains with the aim of characterizing potential new oral probiotics. However, the new probiotic products targeted for oral health purposes do not necessarily comprise the same strains as products now available in market. Burton et al89 (2006) claimed that the species might not necessarily belong only to genera Lactobacillus or Bifidobacterium for which they carried a preliminary study of the effect of probiotic S. salivarius K12 on oral malodor parameters. Zahradnik et al90 (2009) assessed the safety and effectiveness of a probiotic mouthwash containing three different oral streptococci (ProBiora3) for reducing the number of pathogenic bacteria associated with dental caries and periodontal disease.

Genetically designed bacterias might open a new door to the concept of probiotics. The designed strain could be used to replace the original pathogenic strains that naturally colonize the oral cavity. Hillman et al91 (2007) attempted the modification of an effector strain for replacement therapy of dental caries. This resulted the generation of an S. mutans strain with a complete deletion of the open reading frame of lactate hydrogenase and thus significantly reduced cariogenicity. Marcotte et al92 (2006) suggested an another option that could enhance the properties of a potentially beneficial strain and constructed the Lactobacillus paracasei strain with a functional scVF (single-chain variable fragment) antibody against RgpA protease of Porphyromonas gingivalis. Though various strains of probiotic microflora were tested for their viability through culture tests, a significant proportion of bacteria are not yet cultivable. Sliepen et al93 (2009) discussed microbial interactions influence inflammatory host cell responses. They claimed that heat-killed beneficial oral streptococcus strains exert effects similar to those of a living bacterium. Lahtinen et al94 (2008) Degradation of 16S rRNA and attributes of viability of viable but nonculturable probiotic bacteria. Viable but nonculturable probiotic bacteria maintain properties of viable bacteria.94

**CONCLUSION**

During last decades, a keen interest has been developed in the field of oral probiotic therapy. Several experiments have been carried on probiotic strains residing in the gastrointestinal microflora, however, it is important to evaluate each of the suggested health benefits should be researched for each individual bacterial strain. A probiotic bacterium in the oral cavity is not necessarily an oral probiotic. Same species of bacteria might not have beneficial effects for oral and dental health issues. Different desirable properties are expected in those strains in respect to oral and dental health purposes. Some of the probiotic strains used in various probiotic supplements may colonize the oral cavity during their consumption period; thereby it necessitates understanding the effects of probiotic strains in the oral cavity. Probiotics seem to affect both microbial flora and immune responses of the host. Additionally, it is difficult to predict the extent to which probiotic supplements can influence relatively stable microbial environment. Moreover, the risk of transferring antibiotic resistance from probiotics to virulent microorganisms cannot be ignored. Thus, experimental research work unraveling the mechanism of possible probiotic effects adjoined with long-term clinical trials is a need of time, so that benefits of probiotic therapy can be rendered to humans. Health-promoting effects of probiotics are well documented in the literature; however, their recommendation for oral and dental health benefits is not yet justified.

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