Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

Probiotics and its Applications in Dentistry

Probiotikler ve Diş Hekimliğinde Kullanımı

Vagish Kumar L S

Yenepoya Dentah College and Hospital, Mangalore, India

ABSTRACT

Probiotics are living bacteria that can benefit our health. They may reduce the overgrowth of pathogens and are used in the form of food and food supplements. Probiotics which is being commonly used for the management of intestinal tract problems has recently been used to promote oral health. The concept of administering beneficial bacteria with a view to replace harmful microbes by useful ones is revived by probiotic concept. In oral cavity probiotics form a biofilm that is protective against oral diseases. Probiotics can compete for adhesion sites as well as for nutrients and growth factors with cariogenic, halithogenic, fungal and periodontal pathogens thereby inhibiting their growth. Thus they may be useful in preventing and treating various oral diseases. Probiotics with gene therapy are capable of yielding amazing success in intercepting and treating diseases. A literature search in Pub-Med, Google scholar, EBSCO HOST, SciELO, ScienceDirect database was done for English articles, using the following search terms: "probiotics" ,"oral health", "dentistry"; no restrictions were used for publication dates. The aim of this article is to provide an insight about probiotics and their applications in dentistry.

Key words: Probiotics, oral health, dental caries, periodontal disease, halitosis.

ÖZET

Probiyotikler, sağlığa yararlı olabilen yaşayan bakterilerdir. Patojenlerin aşırı büyümesini azaltabilir ve besin veya besin desteği şeklinde kullanılabilir. Yaygın olarak intestinal sistem problemlerinin düzeltilmesi için kullanılan probiyotikler oral sağlığın desteklenmesi için son zamanlarda kullanılmaktadır. Zararlı bakterilerin yerine yararlı bakterilerin tatbik edilmesi konsepti ile probiyotik konsepti canlandı. Ağız boşluğundaki probiyotik formlarının oluşturduğu biyofilm oral hastalıklara karşı koruyucu olabilir. Probiyotikler kariyojenik, halitojenik, fungal ve periodontal patojenler için adezyon bölgeleri oluşturması sebebiyle büyümelerini inhibe ederler. Çeşitli oral hastalıkların

önlenmesi ve tedavisinde kullanışlı olabilirler. Probiyotiklerle gen terapisi hastalıkların durdurulması ve tehlikesinin önlenmesi için inanılmaz bir başarı potansiyeline sahiptir. Pub-Med, Google Akademik, EBSCO HOST, SciELO, ScienceDirect veritabanlarında İngilizce makale taraması şu terimler kullanılarak yapıldı ve yayınlanma tarihine göre zaman kısıtlaması yapılmadı: "probiyotik", "Ağız sağlığı", "diş hekimliği". Bu makalenin amacı diş hekimliğinde probiyotikler ve uygulamaları hakkında bir yeni bir bakış açısı sağlamasıdır.
Anahtar kelimeler: Probiyotik, oral sağlık, diş çürükleri, periodontal hastalıkları, halitoz.

Introduction

The term Probiotic, meaning "for life," is derived from Greek language and was first used by Lilly and Stillwell in 1965 to describe substances secreted by one microorganism which stimulates the growth of another[1]. In first decade of 1900 Ukrainian bacteriologist Elie Metchnikoff regarded as the originator of concept of probiotics claimed that longevity of some populations in Bulgaria, Turkey and Armenia was due to regular consumption of fermented milk products rich in live lactic acid bacteria which may neutralize deleterious effects of gut pathogens, thus extending life span. He discovered Lactobacillus bulgaricus and showed that cholera could be prevented by the presence of antagonistic organisms in the intestine. Mann and Spooering in 1974 discovered that the fermented yogurt reduced blood serum cholesterol. In 1984 Hull identified the first probiotic species, the *Lactobacillus acidophilus*. Later in 1991, Holcombh identified *Bifidobacterium bifidum*. World Health Organization (WHO) in 1994 described probiotics as the next most important in immune defense system following antibiotic resistance. These incidences paved way for a new concept of probiotics in medicine and dentistry[2-7]. The aim of this article is to provide an insight about probiotics in general and their various applications in dentistry.

Probiotics and Their Importance

Probiotics have been used to improve gastrointestinal health and their popularity has prompted interest for their role in promotion of oral health. Intestinal infections caused by *Escherichia coli*, *Campylobacter fetus subsp. jejuni*, *Clostridium perfringens* and *C. botulinum* has been found to be reduced by Lactobacillus supplements. The Lactobacillus has shown promising results and *Bifidobacterium longum* has been successfully used to reduce the after-effects of antibiotic therapy[8, 9].

Oral infections are more common disease affecting mankind. A healthy mouth is habituated by huge number of microorganisms that live in harmony with the host so as to maintain good oral health. Kazor & team in 2003[10] reported that there are more than 600 species that colonize the oral cavity. When pathogenic microorganisms predominate, disease ensures. Replacing the pathogenic bacteria with healthy bacteria is a novel idea. With the emergence of multiresistant strains, antibiotic resistance has become a booming problem that has led scientists to develop novel means for fighting infectious diseases. There has been a major shift of treatment from specific bacterial elimination to altering bacterial ecology by probiotics[11]. Mouth is the mirror of systemic health. So improving the oral health through probiotics can have significant improvement in systemic health. Normalization of oral microbiota is supported by the ecological plaque hypothesis which suggests that selective pressure in environmental conditions can change the balance between oral health and disease. As there are bacterial species associated with oral diseases, there are also species that seem to be associated with oral health. Such friendly bacteria can be used as probiotics to normalize oral microbiota[3, 12-15].

Definition

WHO defined probiotics as live microorganisms which when administered in adequate amounts in food or as dietary supplement confer a health benefit on the host[16]. Probiotics act by inhibiting or reducing the number of pathogenic microorganisms and can have favourable impact on host health.

Probiotics can be bacteria, molds or yeast. However, most probiotics are bacteria and lactic acid bacteria are more popular[17]. Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus lactis, Lactobacillus helviticus, Lactobacillus salivarius, Lactobacillus plantarum, Lactobacillus bulgaricus, Lactobacillus rhamnosus, Lactobacillus johnsonii, Lactobacillus reuteri, Lactobacillus fermentum, Lactobacillus del-brueckii, Streptococcus thermophilus, Enterococcus faecium, Enterococcus faecalis, Bifidobacterium breve, B. bifidum, B. longum, and Saccharomyces boulardii are commonly used probiotics. A probiotic may be made out of a single bacterial strain or it may be a consortium as well[18].

Prebiotic and Synbiotic

Probiotics should not be confused with prebiotic. The term prebiotic was introduced by Gibson and Roberfroid[19] who exchanged "pro" for "pre" which means "before" or "for". Prebiotics are "non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of beneficial bacteria in the colon. They are short-length carbohydrates, such as fructooligosaccharides, gluco oligosaccharides, galctosaccharides and inulin that resist digestion. They 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 stability[16].

The term synbiotic is used when a product contains both probiotics and prebiotics. It includes both the live cells of the beneficial bacteria and the selective substrate[16].

Probiotic Bacteria for Oral Health

To be able to exert its properties in the oral cavity, it is essential for probiotic organism to resist the oral environmental conditions and defense mechanisms, to be able to adhere to saliva coated surfaces, to colonize and grow in the mouth and to inhibit oral pathogens. Generally, there is scarce evidence that probiotics permanently resides in the human body and in the mouth, in particular[11].

Oral probiotics are those bacteria that are intended to work in the mouth to alter the oral biofilm to be more healthful. A basic prerequisite to be an oral probiotics is the ability to bond and inhabitant over the oral mucosal surfaces.

Some of the oral probiotic strains are[20].

1. Lactic acid producing bacteria (LAB)- Lactobacillus, Bifidobacterium, Streptococcus
2. Non Lactic acid producing bacterial species- Bacillus, propionibacterium
3. Non pathogenic yeasts- Saccharomyces
4. Non spore forming and non flagellated rod or coccobacilli

The most commonly used strains belong to the genera *Lactobacillus* and *Bifidobacterium*[21], genera that are commonly found in the oral cavity. Researchers have proved that lactobacilli

strains maintain oro microbiological balance[22]. The lactobacilli show good survival in saliva and *Weissella cibaria* adheres to epithelial cells. Evidence indicates that these probiotics consumed in food products can colonize the oral cavity[23].

Lactobacillus rhamnosus GG, ATCC 53103 originally isolated from the human intestinal flora produces a growth inhibitory substance against *Streptococcus sobrinus* and it has been proposed to reduce the risk for caries[16]. A lactic acid bacterium has been shown to increase folic acid content of yogurt, buttermilk and kefir and to increase niacin and riboflavin levels in yogurt, vitamin B12 and vitamin B6 in cheese[24]. *Streptococccus salivarius* strains are early colonizers of oral surfaces and are amongst the most numerically predominant members of the tongue microbiota of healthy individuals without halitosis[25]. Other strains may include *L. casei Shirota*, *L. paracasei*, *Escherichia coli*[26,27]. *Dello vibrio bacteriovorous* is a newer probiotic strain introduced few years back. These bacteria are generally regarded as safe (GRAS) because they can reside in the human body causing no harm and, on the other hand, are also important for promoting health[11]. They play a crucial role in halting, altering, or delaying oral diseases.

The Lactobacillus species help in production of enzymes to digest and metabolize proteins and carbohydrates[15]. Lactic acid bacteria can produce different antimicrobial components such as organic acids, hydrogen peroxide, carbon peroxide, diacetyl, low molecular weight antimicrobial substances, bacteriocins, and adhesion inhibitors, which also affect oral microflora[7]. They aid in synthesis of vitamin B and vitamin K and facilitates break down of bile salts. They enhance innate and acquired immunity as well as help in inhibition of proinflammatory mediators[17,20]. They are helpful in infections and cancers due to their immune stimulatory properties. They inhibit pathogenic microorganisms in biofilm, are cariostatic, prevent candidal colonization, act as antioxidants and protect oral tissues from diseases[20]. Long term consumption of milk can cause a significant decrease in caries risk[28]. Lactic acid bacteria are harmful to dental tissues because of acids they generate. But when these bacteria are consumed with milk which has good buffering capacity and calcium content, acidity is minimized together with protection of tooth surface[17]. Lactococcus lactis and Streptococcus thermophilus was shown to be able to modulate the growth of the oral bacteria, and in particular to diminish the colonization of Streptococcus oralis, Veillonella dispar, Actinomyces naeslundii and of the cariogenic Strep. Sobrinus[29,30]. L. rhamnosus does not ferment sucrose and is safer for teeth. It has the ability to lower the counts of S.mutans[30].

Bifidobacterium species is anaerobic and is present mostly in large intestine. They are among the first anaerobes in the oral cavity[31]. Benefits of these species include metabolization of lactose, generate lactic ions from lactic acid, synthesize vitamins, ferment indigestible carbohydrates, produce short chain fatty acids, reduce antibiotic associated diarrhea, traveller's diarrhea, relieve constipation, alleviate inflammatory bowel disease and prevent DNA damage. They may also prevent the onset of cancers. Bifidobacterium species reduce gingival and periodontal inflammation[16,17].

Streptococcus thermophillus and L. bulgaricus are primary cultures used in yoghurt production. Benefits of these species are to metabolize lactose, improve lactose intolerance and antimicrobial activity[17, 20].

Saccharomyces boulardii: it is a non colonizing lactic acid producing yeast. It prevents antibiotic associated diarrhea, Clostridium difficle associated disorders, acute diarrhea, traveller's diarrhea, AIDS related diarrhea, and to prevent relapse of Crohn's disease. Most of the beneficial species enhance vitamin production and reduce serum cholesterol level and have anticarcinogenic activity. It helps in immune function enhancement, secretes proteases and other substances that breakdown bacterial enterotoxins and inhibits their binding to intestinal receptors[20].

Mechanism of Action

In oral health, possible mechanisms may be[30]

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[22]. The increase in the number of Immunoglobulin A producing cells is the most remarkable property induced by probiotic organisms and also by fermented milk yogurt[27]. Other mechanism may include mucin production, down regulation of inflammatory responses[32], 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[11, 16, 27]. Probiotics 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 occur easily[33].

Probiotic Sources

Probiotics are available to consumers mainly in the form of dietary supplements and foods. Yogurt and other fermented foods, soybeans, asparagus are the main sources of naturally occurring probiotic bacteria in the diet and are considered as ideal vehicles. The fresher the yogurt, the more viable bacteria it contains. These dairy sources of probiotics are rich in calcium and thus may prevent demineralization of teeth. Other carriers for probiotics may include kombucha, miso, kefir, biodrink etc.

Probiotics are provided in products in one of the five basic ways[26,30].

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, yoghurt, cheese).
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.

In India, Sporlac, *Saccharomyces boulardii* and yoghurt are commonly used. Lactobacilli solution is an example of probiotic given to pediatric patients. The recent one is genetically modified *Bacillus mesentricus* which acts as an alternative to B-Complex capsules. Only sporulating lactobacilli are used with some of the antibiotic preparations. "BION" commercially available in Indian market (combination of pro- and pre-biotic) has 0.48 billion spores of *Lactobacillus bifidum*, *Streptococcus thermophilus*, and 0.10 billion spores of *Saccharomyces boulardi* along with 300 mg of fructo-oligosaccharides, is prescribed as single dose daily before meals in the morning[11,17,20].

Swallowing a tablet won't do as much for the oral ecology as letting it dissolve in the mouth. Probiotics are administered in different quantities that allow for colonization. Permanent and daily consumption of probiotics has been recommended for optimal results. The probable benefits increase with an early childhood use. Maternal use of some probiotic strains seems to influence the composition of breast milk[31,34]. However, caution should be exercised in the administration of probiotics in children because their oral microflora is not been established yet. Current evidence indicates that probiotic effects are strain-specific; therefore, a beneficial effect attributed to one strain cannot be assumed to be provided by another strain, even when it belongs to the same species. A combination of strains can enhance effects in a synergistic manner[16].

Criteria for Selection of Probiotics

Fuller in 1989 listed the features of good probiotic. An ideal probiotic must have following properties[9,24]:-

1. Nontoxic and non pathogenic preparation.
2. Produce beneficial effects to host.
3. Should withstand gastrointestinal juices and be capable of surviving and metabolizing in gut environment.
4. Should have good shelf life.
5. Should replace and reinstate the intestinal microflora.
6. Should be present as viable cells, preferably in large numbers.
7. an effector strain should possess a high degree of genetic stability[16].
8. They should be of human origin[27].

Therapeutic Actions of Probiotics

Probiotics have multiple areas of action (Table 1). The areas of their medical therapeutics include heart diseases, allergic reaction, irritable bowel syndrome, reduction of liver toxicities, hypertension, urogenital health, respiratory tract infections, infections with *Helicobacter pylori,* optimize effects of vaccines, etc[24,27,29,32, 35].

Probiotics Applications in Dentistry

Dental Caries

To limit or prevent dental caries a probiotic must adhere to dental surfaces and integrate into the 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[23]. Inclusion of *Lactobacillus rhamnosus GG* and *L. rhamnosus LC 705* in milk or processed cheese lowers salivary counts of *S. mutans* and reduces the incidence of dental caries in children[37]. *Lactobacillus reuteri* as probiotic in fluid or tablet form, chewing gum[38] or lozenge[39,40], or as administered in yoghurt[41] has been found to decrease *S mutans* level in saliva. *L. reuteri* secretes two bacteriocins, reuterin and reutericyclin, that inhibits the growth of a wide variety of pathogens. It also has strong capacity to adhere to host tissues and has anti inflammatory effects[23]. Ice creams containing *Bifidobacterium Lactis* Bb-12 showed a significant growth inhibitory effect against *S. mutans*[21,42]. *Bifidobacterium* DN-173 010,

ingested once daily with yogurt demonstrated a significant reduction of salivary *S. mutans*[43]. Effects of lactic strains used as probiotics in oral cavity were evaluated by Comelli et al[44]. *Lactobacillus paracasei* and *Lactobacillus plantarum* also interfere with mutans streptococci[30]. Plidenta Pro-t-action toothpaste is the first toothpaste in the world to contain probiotic (*Lactobacillus paracasei*) which co-aggregates mutans Streptococci and thus reduces caries-causing bacteria in the mouth[26].

Table 1- Areas of probiotic actions

1	Medical
2	Dentistry
3	Nutrition and Food sciences
4	Immunology
5	Oncology
6	Agriculture- to restore soil fertility
7	Animal and poultry industry- to prevent diseased food
8	Veterinary practice-infections, food allergies, Gastrointestinal diseases, Horses in competition,etc

Urease enzymes of oral bacteria hydrolyze urea to ammonia which neutralizes plaque acids. Urease activity appears to influence plaque biochemistry and metabolism in a manner that reduces cariogenicity, suggesting that recombinant, ureolytic bacteria may be useful to promote dental health[30]. These recombinant microorganisms will reside in dental plaque, and the ammonia produced from salivary and dietary substrates (urea and arginine) will prevent the colonization of cariogenic bacteria and ensure internal pH homeostasis. As long as this effector strain persists as a resident of the indigenous flora, the host is protected[16]. Lactobacillus, streptococci and bifidobacterium species, are genetically designed to have greater adhesion and hence competitively inhibit *S. mutans*[33].

Probiotic milk powder containing *L. paracasei* SD1 was found to reduce mutans streptococci counts and apparently able to colonize the oral cavity of the orthodontically treated cleft lip and palate patients and it could be detected up to 4 weeks following cessation of dosing[45]. *L. casei* ATCC 11578 has been shown to 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[21].

S. mutans strain BCS3-L1 is a genetically modified effector strain designed for use in replacement therapy to prevent dental caries. Recombinant DNA technology was used to delete the gene encoding lactate dehydrogenase in BCS3-L1 making it unable to produce lactic acid. This effector strain was also designed to produce elevated amounts of a novel peptide antibiotic called mutacin 1140 that gives it a strong selective advantage over most other strains of *S. mutans*[9,16].

Genetically modified probiotics with enhanced properties can be developed ("designer probiotics"). For example, a recombinant strain of *Lactobacillus* that expressed antibodies targeting one of the major adhesions of *S. mutans* (antigen I/II) was able to reduce both the viable counts of *S. mutans* and the caries score in a rat model[30].

ProBiora3 mouth wash is a probiotic containing three GRAS probiotics; *Streptococcus rattus* JH145, *Streptococcus oralis* KJ3, and *Streptococcus uberis* KJ2. These low-acid–producing oral inhabitants quickly colonize the oral cavity to inhibit the growth of pathogenic streptococci strains. *Streptococcus oralis* KJ3 produces hydrogen peroxide to inhibit adjacent pathogenic bacteria by oxygenating the plaque[26].

Lactobacillus casei variety rhamnosus (LCR32) contained in Lactyl and Lactobacillus johnsonii (LA1) contained in Chamyto was found to decrease the colonization of main dental caries producing bacteria *S. mutans*. Thus these probiotics could be used as support in the prevention and prophylaxis in high risk cariogenic patients[46].

Halitosis

Bad breath in oral cavity is mainly ascribed to the production of volatile sulfur compounds (VSC) predominantly by gram negative anaerobes residing in periodontal pockets and on the dorsal surface of tongue[21]. Probiotics are able to breakdown putrescence odors by fixating on the toxic gases (volatile sulfur compounds) and changing them to gases needed for metabolism.

A definite inhibitory effect on the production of VSC by *Fusobacterium nucleatum* was observed after ingestion of *Weissella cibaria* both in vitro and in vivo. In children, a marked reduction in the levels of hydrogen sulphide and methanethiol was registered after gargling *with W. cibaria* containing rinse. Hydrogen peroxide and bacteriocins generated by *W. cibaria* inhibits proliferation of *F.nucleatum*.

Streptococcus salivarius produces bacteriocin salivaricin reducing the number of bacteria producing VSC including hydrogen sulphide, methyl mercaptan and dimethyl sulphide. Gum or lozenges containing *S. salivarius* K12 reduces levels of VSC by inhibiting gram positive microorganisms in patients with halitosis. *S. salivarius* K12 secrete powerful antimicrobial molecules called BLIS: Bacteriocin Like Inhibitory Substances and boosts immune system. It also decreased Streptococcus mutans count in saliva of orthodontic adolescents and long term intake prevented sore throat in childrens. *Weissella confusa* isolates and microorganisms forming lactic acid also appear to decrease halitosis[22,23,26,29,31,34,47].

Periodontal Disease

A decrease in gum bleeding and reduced gingivitis has been observed with the application of L. reuteri. Acilact, a probiotic complex of five live lyophilized lactic acid bacteria, has been claimed to improve both clinical and microbiologic parameters in gingivitis and mild periodontitis patients[11]. Chewing gum containing *L. reuteri* ATCC55730 and ATCCPTA5289 decreased the levels of pro-inflammatory cytokines TNF-α and IL-8 in GCF[48]. Probiotic strains included in periodontal dressings at optimal concentration of 108 CFU/ml diminished the number of most frequently isolated periodontal pathogens: *Bacteroides sp., Actinomyces sp.* and *S. intermedius*, and also *Candida albicans*. Inhabitant lactobacilli inhibit *P. gingivalis and Prevotella intermedia*[16].

In a beagle dog model, subgingival application of *Streptococcus sanguinis, Streptococcus salivarius*, and *Streptococcus mitis* after scaling and root planning, significantly suppressed the re-colonization of *Porphyromona gulae and P. intermedia*[47,49]. 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[31]. *Lactobacillus brevis* demonstrated anti-inflammatory effects in patients with chronic periodontitis. This when delivered through lozenges and sucked improved plaque index, gingival index, and bleeding on probing. Anti-inflammmatory effects of *L.brevis* are attributed to its capacity to prevent production of nitric oxide and consequently the release of Prostaglandin E2 and activation of MMPs induced by nitric oxide. *Lactobacillus helveticus* produces short peptides that act on osteoblasts and increase their activity in bone formation, thereby reducing bone resorption associated with periodontitis. Individuals with a regular

intake of yogurt or beverages containing lactic acid have lower probing depths and less loss of clinical attachment compared to those who consume few of these products[23].

In one study the prevalence of lactobacilli, particularly *Lactobacillus gasseri* and *Lactobacillus fermentum*, in the oral cavity was greater among healthy participants than among patients with chronic periodontitis[26]. Probiotics decrease pH and ensures that plaque bacteria cannot form dental plaque and calculus which causes the periodontal disease. Also antioxidants produced by them prevent plaque formation by neutralizing the free electrons that are needed for the mineral formation. *S. oralis* and *S. uberis* have been reported to inhibit growth of periopathogens of the Socransky‟s red and green complex both in laboratory and animal models. In the absence of these bacteria, tissues become more prone to periodontal disease. Chewing gum "PERIO BALANCE" a combination of two strains of *L. reuteri* specially selected for their synergetic properties in fighting cariogenic bacteria and periodontopathogens. Each dose of lozenge contains at least 2×10^8 living cells of *L. reuteri prodentis*. Lozenge has to be used daily after meal or in the evening after brushing teeth, to allow probiotics to spread and adhere to various oral surfaces.

Staab B, Eick S, et al found reduction of MMP-3, Elastase activity in 50 students with plaque induced gingivitis after having probiotic milk drink for 8 weeks containing *L. casei* species. In another study by Kang et al. mouth rinse with probiotic *W. cibaria* CMS1 reduced plaque scores. Hence, *W. cibaria* isolates possess the ability to inhibit biofilm formation[11]. Probiotic *Bacillus Subtilis*, reduced attachment loss and alveolar bone loss in rats with ligature induced periodontitis and also it protected the small intestine from reactive changes induced by LIP[50]. *Lactobacillus reuteri*-containing probiotic lozenges used in chronic periodontitis patients caused significant pocket depth reduction, attachment gain in moderate and deep pockets and reduction in *Porphyromonas gingivalis*[51].

Candidiasis

A reduction in the prevalence of *Candida Albicans* in elderly after consumption of probiotic cheese containing *L. rhamnosus strains GG* and LC705 and *Propionibacterium freudenreichii* ssp. *shermanii JS* has been demonstrated. Lactobacilli probiotics inhibits the growth of *C. albicans* possibly due to the low pH milieu produced by the lactobacilli. *Candida*-infected mice fed with *L. acidophilus* exhibited accelerated clearance of *C. albicans* from the mouth. Also *Lactobacillus fermentum* appears to be promising. Hasslof P et al (2010) found that two *L. plantarum* strains

and *L. reuteri* ATCC 55730 displayed the strongest inhibition on Candida albicans[16,21,26,47,52,53]. *B. animalis* reduces the incidence and severity of mucosal candidiasis[27].

Orthodontics

The presence of fixed orthodontic appliances in the mouth can allow microorganisms to accumulate, causing enamel demineralization that produces white spot lesions. Studies have shown that short-term consumption of fruit yogurt containing bifidobacteria alters the levels of salivary mutans streptotocci and lactobacilli in patients with fixed appliances. In one study 200 g once daily fruit yogurt containing Bifidobacterium animalis subsp lactis N 173010 significantly reduced salivary mutans streptococci counts in two weeks. No effect was produced on lactobacilli counts[54]. A study showed that the consumption of probiotic curd (Active plus) and the topical application of probiotic toothpaste (GD) caused significant decreases in the S mutans levels in the plaque around the brackets of orthodontic patients[33].

Voice Prosthesis

Turkish yogurt containing Streptococcus thermophilus and Lactobacillus bulgaricus effectively abolished the biofilm formation on indwelling voice prostheses. Patients in Netherlands consuming buttermilk containing Lactococcus cremoris, Lactococcus lactis spp. which produces antimycotics and other substances prolonged the lifetime of indwelling voice prostheses. Lactobacilli have long been known for their capacity to interfere with the adhesion of uropathogens to epithelial cells and catheter materials, while S. thermophilus can effectively compete with yeasts in their adhesion to substratum surfaces, like silicone rubber[16,18].

Xerostomia

Evidence suggests that probiotics can also efficiently lessen the risk xerostomia[53].

HIV

Probiotic bacteria may slow down AIDS progression. Studies of Lin Tao and his colleagues showed that *Lactobacillus strains* produce proteins capable of binding Mannose found on HIV envelope. The binding of sugar enables the bacteria to stick to the mucosal lining of the mouth and digestive tract forming colonization. One strain secreted abundant mannose binding protein particles into its surroundings, neutralizing HIV by binding to its sugar

coating. They also observed that immune cells trapped by lactobacilli formed a clump. This would immobilize any human cells harboring HIV and prevent them from infecting other cells[15]. Lactobacilli given at high concentrations is viricidal for HIV-1 and there is inverse association between vaginal *Lactobacilli* and HIV seroconversion[27].

Cancer

Probiotics represent an emerging option for cancer prevention. Probiotics can interfere at various stages of cancer process such as interfering with chromosomal and DNA damage[17]. They may also detoxify carcinogens such as β-glucuronidase, for example *Lactobacillus Bulgaricus* and *Streptococcus thermophilus* in colon preventing colon cancers[20,27]. In a recent study probiotic *Lactobacillus salivarius REN* isolated from centralians showed highly potent anti-genotoxicity in rat oral cancer models in an initial assay. High dose of *L. salivarius REN* effectively suppressed 4NQO-induced oral carcinogenesis in initial and post-initial stage and the inhibition was in a dose-dependent manner. It also decreased neoplasm incidence (65% to 0%). Probiotic acts by protecting DNA against oxidative damage and down regulating Cyclooxygenase (COX)-2 expressions. It also significantly decreased the expression of proliferating cell nuclear antigen (PCNA), and induced apoptosis in a dose-dependent manner. The findings of this study suggest that probiotics may act as potential agents for oral cancer prevention[55].

Miscellaneous

Few strains of lactic acid bacteria, such as *S. thermophilus*, *L. bulgaricus* and other lactobacilli in fermented milk products, can alleviate symptoms of lactose intolerance by providing bacterial lactase to the intestine and stomach and favouring calcium absorption, thus minimizing osteoporosis[17,20,24]. Studies have indicated a decrease in the numbers of lactobacilli, preceding the development of an allergy. Probiotics have been shown to reduce the incidence of childhood eczema by half. They may exert a beneficial effect on allergic reaction by improving mucosal barrier function. In addition, probiotics consumption by young children may beneficially affect immune system development. Probiotics such as *Lactobacillus* GG may be helpful in alleviating some of the symptoms of food allergies such as those associated with milk protein[9,24].

Probiotic Augmentation with Gene Therapy

Gene therapy can be used to manipulate the gene components of potential probiotics strains which currently can't be used because of possible undesired effects. Its main thrush is not only on reducing the harmful properties of pathogenic strains naturally colonizing the oral cavity, but also to enhance the properties of a potentially beneficial strain[31]. In field of oral immunology, probiotics are being used as passive local immunization vehicles against dental caries. Bacteriophages have been detected in oral pathogens, such as Actinobacillus actinomycetemcomitans, and they may play a role in the pathogenicity. Phage therapy must be studied for oral and dental diseases in the same way as has been attempted for systemic infections[32].

Several mutated strains of *S. mutans* that lack the machinery to efficiently meatbolize fermentable carbohydrates to organic acids have been developed. One example is *S. mutans* with a glucosyltransferase C (gtfC) gene mutation. The introduction of mutated gtfC gene affects the ability of *S. mutans* to produce extracellular glucans resulting in decrease of extracellular matrix component of mixed oral biofilms[15].

Probiotics and Future

Any probiotic bacterial strain must be fully characterized and undergo in vitro and in vivo studies demonstrating its mechanism of action and potential side effects. Spectrum of resistance to antibiotics, metabolic and hemolytic activities, ability to produce toxins, infectious power in immunosuppressed animal models, and side effects in human subjects should be investigated.

Efficient methods of probiotic administration in oral cavity, their dosages for different optimum therapeutic uses, their actions on various pathogens in the oral cavity and also on the safety of use of these in various pathological conditions should be determined.

Advances in biomedical engineering will help in developing systems that deliver probiotics to the host. This includes encapsulating probiotics, such that they rehydrate at specific sites, and encasing prebiotics in nano-aggregates that protect against adverse body environments. Capsules with biosensor coat in future may detect optimal conditions for the release of probiotic contents. Molecular, nano, biochemical, microbiological and engineering sciences hold the key to future advances in the clinical applications of probiotic products[15].

Precautions and Contraindications

Side effects of probiotics tend to be mild and digestive (such as gas or bloating). They possibly can cause unhealthy metabolic activities, too much stimulation of the immune system, or gene transfer.[18] Uncertainty about specificity of probiotics effects is a cause of concern[26]. There always remains the possibility that probiotic consumption can cause infection and that individuals will respond in different ways to a specific strain[9].

Probiotics might cause infections in critically ill or severely immunocompromised patients. *Lactobacillus* strains have been reported to cause bacteremia in patients with short-bowel syndrome. Fungemia has been reported when Saccharomyces capsules were opened and administered in patients with central venous catheters. Lactobacillus preparations are contraindicated in persons with a hypersensitivity to lactose or milk. S. boulardii is contraindicated in patients with a yeast allergy[18]. Lactobacillus endocarditis was reported after dental treatment in a patient taking L. rhamnosus[49]. Liver abscess was reported in an individual on L. rhamnosus GG. Stimulation of immune system by probiotics showed degradation in autoimmune diseases, and transferred antibiotic resistance to pathogens. The mode and time of the administration as well as the age of the subject taking probiotics is crucial[11].

Conclusion

The application of probiotic strategies may, in near future provide an end to many infections occurring in oral cavity. The selection of the best probiotic for oral health is an issue that calls for further study. Probiotics provide an effective, natural, non invasive and economic means to combat oral diseases. Thus, a mere change in diet by including probiotic foods may halt, retard, or even significantly delay the pathogenesis of oral diseases, promoting a healthy lifestyle to fight oral infections. A complete understanding of the broad ecologic changes they induce in the mouth is essential to assess their long term consequences for oral health and disease.

References

1. Caglar E, Kargul B, Tanboga I. Bacteriotherapy and probiotics role on oral health. Oral Dis. 2005;11:131-7.
2. Metchnikoff E. The prolongation of life. Optimistic studies New York, Putman's Sons; 1908.

3. Patil MB, Reddy N. Bacteriotherapy and probiotics in dentistry. KSDJ. 2006;2:98-102.
4. Boden EK, Snapper SB. Regulatory T cells in inflammatory bowel disease. Curr Opin Gastroenterol. 2008;24:733-41.
5. Manisha N, Ashar, Prajapathi JB. Role of probiotic cultures and fermented milk in combating blood cholestrol. Indian J Microbiol. 2001;41:75-86.
6. Reid G, Bruce AW, Mcgroarty JA, Cheng KJ, Costerton JM. Is there a role for Lactobacilli in prevention of urogenital and intestinal infections? Clin Microbiol Rev. 1990;3:335-44.
7. Meurman JH. Probiotics: do they have a role in oral medicine and dentistry? Eur J Oral Sci. 2005;113:188-96.
8. Food and Agriculture Organization of the United Nations (FAO). Guidelines for the Evaluation of Probiotics in Food. Ontario, Canada,WHO, 2002.
9. Bhargava R., Bhargava R., Ranjan V. Probiotics in dentistry. Journal of Orofacial Health Sciences. 2011;3: 52-60.
10. Kazor CE, Mitchell PM, Lee AM, Stokes LN, Loesche WJ, Dewhirst FE et al. Diversity of bacterial populations on the tongue dorsa of patients with halitosis and healthy patients. J Clin Microbiol. 2003;41:558-63.
11. Dave H D, Shah C S, Shah M, Deshpande N. Probiotics in periodontics. good for bad: a review. Research and Reviews: Journal of Dental Sciences. 2013;1:7-12.
12. Suvarna VC, Boby VG. Probiotics in human health. A current assessment. Current Science. 2005;88:1744-8.
13. Izumita D. A new approach in dentistry. Clinical and Basic Medical Research on EM-X-A Collection of Research Papers. 2001;2:77-81.
14. Minna K S, Sorle T, Hilpi R, Maija S, Marltivaree PR. Lactobacillus bacterium during a rapid increase in probiotic use of L. Rhamnosus GG in Finland. Clin Infect Dis. 2002;35:1155-60.
15. Narwal A. Probiotics in dentistry– a review. J Nutr Food Sci. 2011;1:114.
16. Reddy JJ, Sampathkumar N, Aradhya S. Probiotics in dentistry: review of the current status. Rev Clín Pesq Odontol. 2010;6:261-7.
17. Nagraj T, Ravi B, Sankara SN, Madhu K. Probiotics and oral health. J Indian Aca Oral Med Radiol. 2012;24:146-8.
18. Chopra R, Mathur S. Probiotics in dentistry: A boon or sham. Dent Res J (Isfahan). 2013;10:302–6.
19. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr. 1995;125:1401-12.
20. Saraf K, Shashikanth MC, Priy T, Sultana N, Chaitanya NC. Probiotics--do they have a role in medicine and dentistry? J Assoc Physicians India. 2010;58:488-90.
21. Stamatova I, Meurman HJ. Probiotics: health benefits in the mouth. Am J Dent. 2009;22:329-38.

22. Ramachandran S, Vijaybala S, Dhinesh Raj KS. Probiotics the promising future-A review. The Southeast Asian Journal of Case Report and Review. 2013;2:98-105.
23. Bonifait L, Chandad F, Grenier D: Probiotics for oral health: Myth or reality? J Can Dent Assoc. 2009;75:585-90.
24. Singh K, Kallali B, Kumar A, Thaker V. Probiotics: A review. Asian Pacific Journal of Tropical Biomedicine. 2011:S287-90.
25. Burton JP, Chilcott CN, Tagg JR. The rationale and potential for the reduction of oral malodour using Streptococcus salivarius probiotics. Oral Dis. 2005;11(Suppl. 1):29-31.
26. Mallikarjuna K, Gupta S, Singh S, Dadarya B, Dausage P, Gupta P. Probiotics in dentistry: Review of the current status. International Journal of Contemporary Dentistry. 2013;4:66-75.
27. Gupta V, Garg R. Probiotics. Indian J Med Microbiol. 2009;27:202-9.
28. N Chitra, Kanakam E T, K Viswaja. Probiotics in dentistry. Adv Bio Tech. 2011;10:13-5.
29. Flichy-Fernández AJ, Alegre-Domingo T, Peñarrocha-Oltra D, Peñarrocha- Diago M. Probiotic treatment in the oral cavity: An update. Med Oral Patol Oral Cir Bucal. 2010;15:e677-80.
30. Bhushan J, Chachra S. Probiotics-their role in prevention of dental caries. J Oral Health Comm Dent. 2010;4:78-82.
31. Haukioja A. Probiotics and oral health. Eur J Dent. 2010;4:348-55.
32. Sareen M, Roy S, Singh SK, Gupta A. A review on probiotics and their implications in dentistry. Journal of Dentofacial Sciences. 2012;1:7-10.
33. Jose E J, Padmanabhan S, Chitaranjan B A. Systemic consumption of probiotic curd and use of probiotic toothpaste to reduce Streptococcus mutans in plaque around orthodontic brackets. Am J Orthod Dentofacial Orthop. 2013;144:67-72
34. Puri S M, Grover S H, Puri N, Dewan A, Gupta A. Use of probiotics for oral health. Oral Health Comm Dent. 2011;5:149-52.
35. Goldin R B, Gorbach S L. Clinical indications for probiotics: an overview. Clin Infect Dis. 2008;46:S96–100.
36. Vijayavel T, Ponni V. Probiotics-boon for dentistry. Universal Journal of Pharmacy. 2013;2:36-7.
37. Ahola AJ, Yli-Knuuttila H, Suomalainen T, Poussa T, Ahlström A, Meurman JH et al. Short-term consumption of probiotic-containing cheese and its effect on dental caries risk factors. Arch Oral Biol. 2002;47:799-804.
38. Caglar E, Kavaloglu SC, Kuscu OO, Sandalli N, Holgerson PL, Twetman S. Effect of chewing gums containing xylitol or probiotic bacteria on salivary mutans streptococci and lactobacilli. Clin Oral Investig. 2007;11:425-9.
39. Caglar E, Cildir SK, Ergeneli S, Sandalli N, Twetman S. Salivary mutans streptococci and lactobacilli levels after ingestion of the probiotic bacterium Lactobacillus reuteri ATCC 55730 by straws or tablets. Acta Odontol Scand. 2006;64:314-18.

40. Caglar E, Kuscu OO, Cildir SK, Kuvvetli SS, Sandalli N. A probiotic lozenge administered medical device and its effect on salivary mutans streptococci and lactobacilli. Int J Paediatr Dent. 2008;18:35-9.
41. Petti S, Tarsitani G, Simonetti D'Arca A. Antibacterial activity of yoghurt against viridans streptococci in vitro. Arch Oral Biol. 2008;53:985-90.
42. Caglar E, Sandallii N, Twetman S, Kavaloglu S, Ergeneli S, Selvi S. Effect of yogurt with Bifidobacterium DN-173 010 on salivary mutans streptococci and lactobacilli in young adults. Acta Odontol Scand. 2005;63:317-20.
43. Caglar E, Kuscu OO, Kuvvetli SS, Cildir SK, Sandalli N, Twetman S. Short-term effect of ice-cream containing Bifidobacterium lactis Bb-12 on the number of salivary mutans streptococci and lactobacilli. Acta Odontol Scand. 2008;66:154-8.
44. Comelli EM, Guggenheim B, Stingele F, Neeser JR. Selection of dairy bacterial strains as probiotics for oral health. Eur J Oral Sci. 2002;110:218-24.
45. Ritthagol W, Saetang C, Teanpaisan R. Effect of probiotics containing Lactobacillus paracasei SD1 on Salivary Mutans Streptococci and Lactobacilli in orthodontic cleft patients: a double-blinded, randomized, placebo-controlled study. Cleft Palate Craniofac J. 2014;51:257-63.
46. Rebolledo M, Rojas E, Salgado F. Effect of two probiotics containing Lactobacillus rhamnosus and Lactobacillus johnsonii variety on the in vitro growth of Streptococcus mutans. Int J Odontostomat. 2013;7:415-9.
47. Agarwal E, Bajaj P, Guruprasad N C, Naik S, Pradeep RA. Probiotics: a novel step towards oral health. AOSR. 2011;1:108-15.
48. Twetman S, Derawi B, Keller M, et al: Short-term effect of chewing gums containing probiotic Lactobacillus reuteri on the levels of inflammatory mediators in gingival crevicular fluid. Acta Odontologica Scand. 2009;67:19-24.
49. Gupta G. Probiotics and periodontal health. Journal of Medicine and Life. 2011;4:387-94.
50. Messora R M, Oliveira FFL, Foureaux C R, Taba M Jr., Zangeronimo G M, Furlaneto CAF et al. Probiotic therapy reduces periodontal tissue destruction and improves the intestinal morphology in rats with ligature-induced periodontitis. J Periodontol. 2013;84:1818-26.
51. Teughels W, Durukan A, Ozcelik O, Pauwels M, Quirynen M, Haytac MC. Clinical and microbiological effects of Lactobacillus reuteri probiotics in the treatment of chronic periodontitis: a randomized placebo-controlled study. J Clin Periodontol. 2013;40:1025-35.
52. Rastogi P, Saini H, Dixit J, Singhal R. Probiotics and oral health. Natl J Maxillofac Surg. 2011;2:6-9.
53. Hatakka K, Ahola AJ. Probiotics reduce the prevalence of oral candida in the elderly-a randomized control trial. J Dent Res. 2007;86:125-30.

54. Cildir SK, Germec D, Sandalli N, Ozdemir FI, Arun T, Twetman S et al: Reduction of salivary mutans streptococci in orthodontic patients during daily consumption of yoghurt containing probiotic bacteria. Eur J Orthod. 2009;31:407-11.
55. Zhang M, Wang F, Jiang Lu, Liu Hai Rui, Zhang L, Lei X et al. Lactobacillus salivarius REN inhibit rat oral cancer induced by 4-nitroquioline 1-oxide. Cancer Prev Res (Phila). 2013;6:686-94.

Correspondence Address / Yazışma Adresi
Vagish Kumar L.S
Oral Medicine & Radiology Department,
Yenepoya Dental College and Hospital, Yenepoya University,
Mangalore-575018, Karnataka, India
e-mail: vagishkumar_12@rediffmail.com