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Probiotics and Their Efficacy in Improving Oral Health: A Review

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ABSTRACT

The changing food habits and lifestyle has resulted in deterioration of oral health in the people of all ages. The increasing global problems with the traditional disease management strategies have prompted the investigators to hunt for the new and better alternatives to deal with health issues. The global demand for chemical free, less harmful and easier solutions to health problems has increased in past few years. Probiotics or the foods with 'live cultures' have come up as one of the most promising alternate to traditional disease management. Probiotics are those viable microorganisms which are constituents of natural microflora of human body. Probiotic therapy decreases the risk of colonization by oral pathogens without depleting the friendly microflora. Probiotics resembles the human body microbiota and are readily incorporated in the natural microflora of human body. They are harmless and easy to consume in many edible forms (such as cheese, yoghurt, etc.). The inability of the antibiotics to discriminate good bacteria from the disease causing bacteria, the development of antimicrobial resistant mutants and the increasing rate of antibiotic associated side effects and complications suggests an urgent need to switch our therapeutic approach from traditional antibiotics to the probiotic therapy for oral care. The use of probiotics in routine life is likely to improve the oral health. This review demonstrates the action of Probiotics on oral health and disease.

INTRODUCTION

The term 'Probiotic' meaning "for life" was coined by Lilley and Stillwell (1965). Probiotics have amazingly come up with the potential for not only preventing the attack of oral pathogens but also the ability to treat various oral diseases. Thus, asssuring healthy living and increased longevity (Meurman, 2005). Probiotics reminds of the very old and forgotten concept of 'Bacteriotherapy' which stated that beneficial bacteria occurring naturally in the human body can be administered in the patient's body to restore patient's health and wellbeing (Meurman, 2005). Bacteriotherapy gave rise to the concept of modern day probiotics. Probiotics have been extensively studied for their intestinal benefits.

The human intestine has a reservoir of microorganisms naturally inhabiting the intestine as symbiont. They are referred to as 'gut or the intestinal flora'. In lieu of the shelter that the human body provides, the intestinal flora performs several important functions in the human body such as fermenting undigested energy substrate, strengthening the immune system, protection against the growth of the pathogenic bacteria, promoting gut development, production of vitamins (such as Vitamin K and Biotin) and production of hormones for fat storage. The process whereby probiotics are used to restore the normal intestinal microflora to provide resistance against antibiotics is termed 'Microbial interference therapy'**.** Probiotics being safe for human consumption and resistant to bile and acidic environment survives in the intestine, colonize the human gut and show bacteriocin production to block the invasion of intestine cells by enteroinvasive bacteria(Parvez *et al.*, 2006). On the other hand, Broad spectrum antibiotics, being unable to distinguish between beneficial and harmful bacteria, kill both and alter the number of natural microbiota. This results in a downfall in host's health. Earlier, Probiotics were associated with only gut health but recently several investigators have suggested their potential applicability in the improvement of oral health. The organism capable of adhering to and colonize the surface of the oral cavity constitute 'Oral Probiotics'. (Table-1) There is an urgent need to switch our therapeutic approach from traditional antibiotics to the probiotic therapy for oral care.

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Probiotic, Prebiotic and Synbiotic: Functional Foods

Probiotics are live, viable, non-digestible and non pathogenic microorganisms which when administered in adequate amounts confer health benefits on the host. Prebiotics were first identified and named by Gibson and Roberfroid in 1995. Prebiotics are nutrients that feed probiotic bacteria. They are non-digestable food ingredients that stimulates the growth and activity of beneficial resident bacteria in the body. Prebiotics provides nourishment for the probiotics or good bacteria in gut. They promote the growth of probiotic microorganisms and their activity which at the end will increase the digestivity and immunity, besides many other benefits of probiotics. Some examples of prebiotics are inulin-type fructans, maltodextrin, fructo-oligosaccharides, and galactosaccharides. The most common kind of prebiotic is fructo-oligosaccharide (FOS). This common carbohydrate is found in certain foods such as banana, wheat, honey, onions and tomatoes. Unlike probiotic bacteria, probiotic carbohydrates are not destroyed when cooked. (Roberfroid, 2001; Duggan *et al.*, 2002; Gibson and Roberfroid, 1995; Gibson *et al.*, 1995). Synbiotic is a combination of probiotics and prebiotics which beneficially affects the host by improving the survival and implementation of live microbial dietary supplements in the gastrointestinal tract by selectively stimulating the growth and/or by activating the metabolism of health promoting bacteria and thus improving host welfare (Gibson and Roberfroid, 1995). Functional foods are the foods with the additional benefits. Functional foods are those foods that have all the properties of the conventional foods like having satiety value, providing nutrients and energy for maintaining life and supporting growth with the additional ability of promoting one's health and preventing the occurrence of diseases. They may be natural or processed food. Probiotics and prebiotics have been investigated for their activity as functional foods. Since both the probiotics and the prebiotics have been shown to have prominent physiological and immune effects, they may be classified as the functional foods (Marcel, 2000). The evident physiological benefits and disease reduction activities of probiotics and prebiotics have been demonstrated in Figs. 1 and 2 respectively.

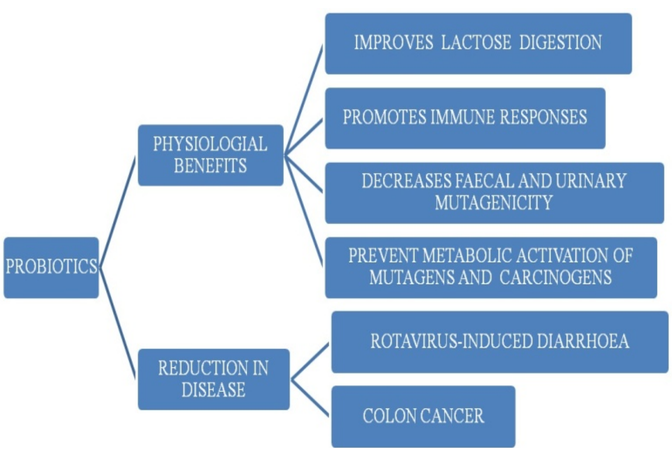
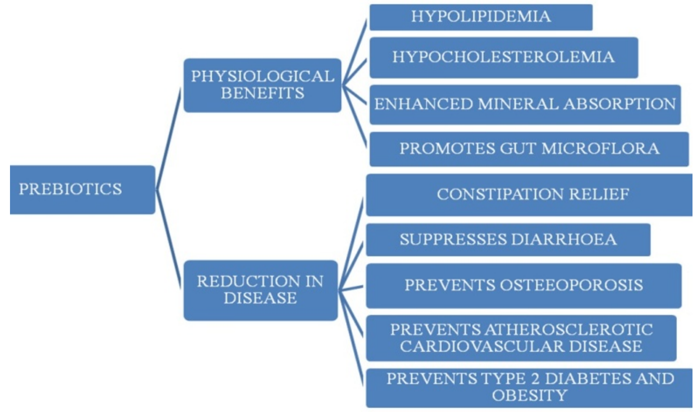


Fig. 1:



Figs 1 & 2: Probiotic and probiotic as functional foods (Marcel, 2000).

The Beginning of Probiotics

In 20th century, Russian scientist and noble laureate Elie Metchnikoff was the first one to suggest the possibility to modify the gut microflora by replacing the harmful microbes with the useful microbes. Metchnikoff observed that certain rural populations in Europe, for example, in Bulgaria and the Russian steppes who mainly depended on milk fermented by lactic acid bacteria for their sustenance had comparatively longer lives. By that time, it was known that milk fermented with lactic acid bacteria inhibits the growth of proteolytic bacteria because of its low pH which is caused by the fermentation of lactose. Based on these facts, Metchnikoff proposed that consumption of fermented milk would 'seed' the intestine with harmless lactic acid bacteria, decreases the intestinal pH thereby suppressing the growth of proteolytic bacteria. Metchnikoff introduced into himself the sour milk fermented with the bacteria he called "Bulgarian bacillus" and found his health benefitted. (Metchnikoff, 1907) *Bifidobacteria* was the first isolated probiotic bacteria. Henry Tissier (1905) isolated it from a breast-fed infant. Tissier (1906), a french pediatrician, observed a low number *Bifidobacteria* in the stool of the infants with diarrhea as compared to the healthy infants.

The *Escherichia coli* strains isolated from the faeces of an unaffected soldier was used for the treatment of acute gastrointestinal infections by German professor Alfred Nissle (1917) when the antibiotics were not yet available.

1930s witnessed the first clinical trials on probiotics for their effect on constipation. Ever since then, various probiotics have been investigated for their role in the treatment of different diseases. (Parvez *et al.*, 2006)

Oral microbiota in health and disease

More than 700 species of oral microbiota have been detected in the human mouth. Tongue is a microorganism laden organ. It is densely populated with salivary microbes, supragingival and subgingival plaque microorganisms (Socransky and Haffajee, 2005; Kolenbrander *et al.*, 2006). The resident microbiota of one individual may consist of 30-100 species (Aas *et al.*, 2005; Paster *et al.*, 2006; Aas *et al.*, 2008). Resident microbiota plays many important functions such as reducing the susceptibility to pathogen attack, prevention of pathogen colonization and developing immune response against pathogens. Figure 3 demonstrates the various functions of the resident microbiota.

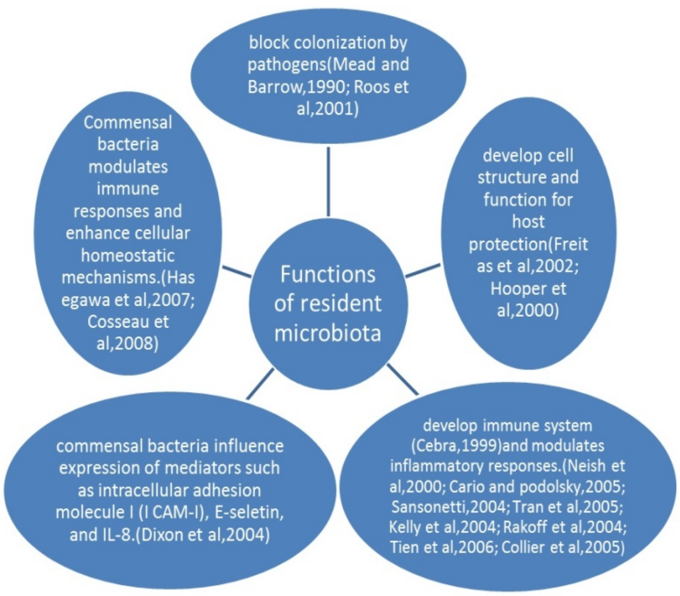


Fig. 3: Functions of the Resident Microbiota.

In the oral cavity, bacteria resides either integrated into the oral biofilm or in planktonic state. The integration of planktonic bacteria into biofilm results into the activation of certain distinct genes which differentiates them from the planktonic counterparts. Now they tend to be much more resistant to the environmental factors and the antimicrobial agents. Oral biofilm is dynamic and hence its composition keeps changing. The complexity of oral biofilm increases as they mature. (Burme *et al.*, 1999; Rudney, 2000).

Saliva is a complex medium in mouth which contains different bactericidal, bacteriostatic and inhibitory proteins that collectively may damage a variety of species in planktonic state. Ingested Probiotics are first exposed to the salivary proteins such as lysozyme, lactoferrin, histatin, salivary peroxidase, cystatins, and secretory IgA which affects the adhesion, morphology, metabolic activity and viability of the probiotic microorganism. On the other hand, Saliva tends to propagate oral biofilm and contributes to the microbial diversity in mouth. The continuous salivary flow in the oral cavity can lead to detachment of some microbes from the biofilm surfaces, modulating microbial colonization. Different strains show specific response to proteolytic enzymes and this strain-specific response need to be considered when selecting probiotics for the oral cavity (Germaine and Tellefson, 1986; Rudney *et al*.,1991; Bosch *et al.*, 2003; Hahnel *et al.*, 2008; Groschl *et al.*, 2009;). Many bacterial species have been found to survive within buccal epithelial cells (Rudney *et al.*, 2005). *Lactobacilli* from saliva samples include *Lactobacillus paracasei*, *L. plantarum*, *L. rhamnosus*, and *L. salivarius* (Ahrne *et al*.,1998; Colloca *et al.*, 2000; Simark-Mattsson *et al.*, 2007; Maukonen *et al.*, 2008). Bifidobacterial species isolated from oral samples include *B. bifidum*, *B. dentium*, and *B. longum*. (Crociani *et al.*, 1996; Maukonen *et al.*, 2008; Beighton *et al.*, 2008). Culture-based studies suggest that *bifidobacteria* are among the first anaerobes in the oral cavity (Rotimi and Duerden, 1981). Both *lactobacilli* and *bifidobacterium* are present in the breast milk and hence are the first microorganisms to be exposed to oral cavity of an infant (Gueimonde *et al.*, 2007; Abrahamsson *et al.*, 2009).

Probiotic microorganisms and their administration vectors

The most common probiotic strains belong to the genera *lactobacillus* and *Bifidobacteria* (Parvez *et al.*, 2006). Table 1 demonstrates the list of the different probiotics which are being currently used. Lactic acid bacteria are gram-positive, acid tolerant, non-respiring bacteria that are characterized by their ability to ferment carbohydrates (like sucrose) to produce short chain carboxylic acids, which reduces the surrounding pH. Their cariogenic potential has attracted the interest of several researchers. The lowering of pH in the oral cavity dissolves the hard tissues such as enamel and dentine, promoting caries (Toi *et al.*, 2000). *L. rhamnosus* named after the discoverers, Sherwood Gorbach and Barry Goldin, has been shown to produce a substance with potential inhibitory activity against different bacterial species including carcinogenic *Streptococcus* species. (Meurman, 2006) Some of the popular probiotic foods are yoghurt, cheese, tempeh, miso soups, natto, sauerkraut and many pickles, kefir, cottage cheese, preserved vegetables and powdered drink mixes. Most probiotic foods are fermented atleast partially. The most common prebiotic foods include soyabeans, Jerusalem, regular artichokes, oats, honey, berries, asparagus, many fruits, and goat's milk. Figure 4 demonstrate some of the common probiotic vehicles (Famworth, 2003)

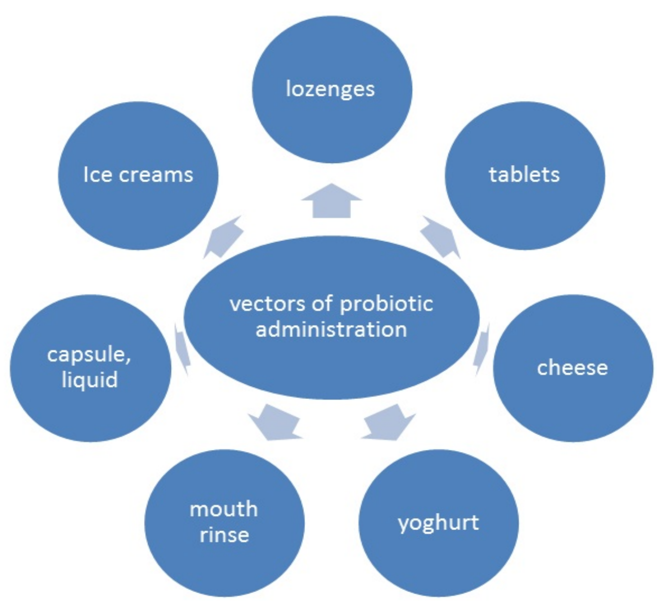


Fig. 4: Probiotic Administration Methods.

Table . 1: Currently used probiotic microorganisms in the treatment of oral diseases (Anuradha and Rajeshwari, 2005; Parvez *et al.*, 2006;).

Bacteria				**Yeasts and Molds**
***Lactobacilli* species**	***Bifidobacterium* species**	***Streptomyces* species**	**Other species**	
L. acidophilus, *L. rhamnosus,* *L. johnsonii,* *L. casei,* *L. gasseri,* *L. delbreuckii* ssp. *bulgaricus,* *L. fermentum,* *L. plantarum,* *L. brevis,* *L. lactis,* *L. reuteri,* *L. paracasei.*	*B. bifidum,* *B. longum,* *B. infantis,* *Bifidobacterium* DN-173 010 *B. adolescentis,* *B. animalis,* *B. thermophilum.*	*Streptococcus faecium,* *Streptococcus thermophilus.*	*S. salivarius,* *W. sibaria, Leuconostoc, Pediococcus,* *Propionibacterium.*	*C. albicans,* *Sacchromyces boulardii,* *A. niger,* *A. oryzae,* *c. pintolopesii,*

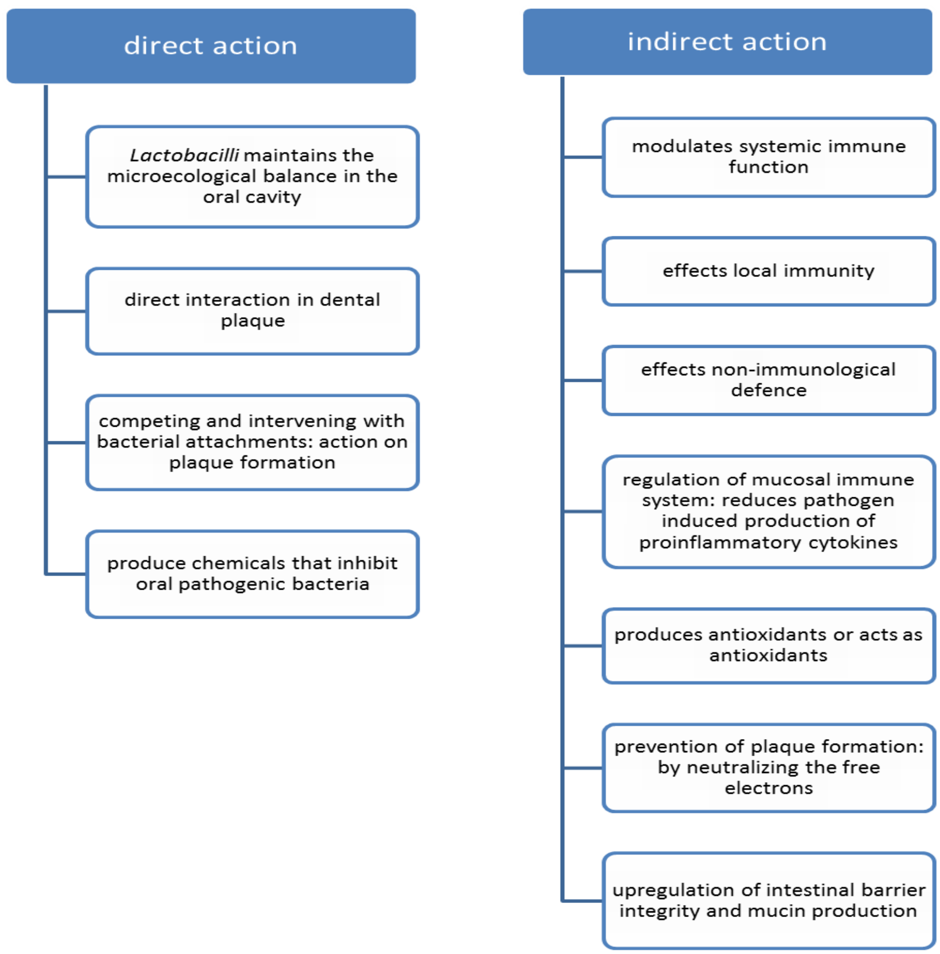


Fig. 5: Possible mechanism of probiotic action in the oral cavity. (Koll-Klais *et al*., 2006; Isolauri *et al*., 1993; Vanderhoof *et al*., 1999; Izumita, 2001; Minna *et al*., 2002; Suvarna and Boby, 2005; Meurman and Stamatota, 2007; Haukioja, 2010).

Hypothetical mechanism of probiotic action in the oral cavity

Probiotic bacteria guard the oral health by competing with the oral pathogens for nutrients, growth factors and site of adhesion. Once adhered to the oral cavity, probiotic bacteria aggregate and inhibit the adhesion of the harmful microorganisms by producing bacteriocins or other antimicrobial compounds such as acids or peroxides. Thus, Probiotics help to prevent the inflammation of oral cavity and the oral tissue destruction by oral pathogens (Strus *et al.*, 2001; Roberfroid, 2002). Probiotic first needs to adhere successfully to the surfaces of oral cavity in order to avoid or reduce its rapid exclusion from the oral cavity. Studies have shown that the pretreatment with lysozymes can increase adhesion properties of the lactobacilli without affecting its viability (Stomatova *et al.*, 2009). The lactobacilli adhesion mechanism involves hydrophobicity and surface charge in addition to specific carbohydrate and/or proteinaceous components. Another factor that needs to be considered while evaluating establishment of probiotics in the oral cavity is saliva-mediated aggregation. Those microorganisms that have the ability to co-aggregate may have greater advantage over non co-aggregating organisms which are easily removed from the mouth (He *et al.,* 2001; Lorca *et al.,* 2002; Carlen *et al.,* 2003; Nikawa *et al.,* 2004).

The Probiotics have a three step action mechanism -

i. Stimulates and modulates immune response,
ii. Normalize intestinal microflora
   - Ensures colonization resistance
   - Controls irritable bowel syndrome and other inflammatory bowel diseases.
iii. And also have the metabolic effects like-
   - Bile salt deconjugation and secretion,
   - Lactose hydrolysis,
   - Reduction in toxigenic and mutagenic reactions in gut.
   - Supply of nutrients to colon epithelium.

Probiotics first competes with the oral pathogens for adhesion site and then colonizes the oral surface. After the probiotics aggregate the oral surface, they compete with oral pathogens for nutrients, growth factors and also produce antimicrobial compounds, including organic acids, hydrogen peroxide, carbon peroxide, diacetyl, low molecular weight antimicrobial substances, bacteriocins, and adhesion inhibitors (Silva *et al.,* 1987; Ouwehand, 1998). Probiotics can also activate and modulate the immune system (Kato *et al*., 1983), and they have been shown to reinforce gut defence by immune exclusion, immune elimination, and immune regulation (Isolauri *et al.,* 2002). Fig. 5 demonstrates the hypothetical mechanism of probiotic action. Probiotics have been investigated for their role in the activation of oral immune inductive sites. The diffuse lymphoid aggregates of the waldeyer's ring contain the immune inductive sites in the oral cavity. Lingual and pharyngeal tonsils and adenoids contain most of the lymphatic tissue. Dendritic cells in the mucosal surfaces play vital role in antigen presentation and in activating T-cell responses. Depending on the signals from dendritic cells either immune tolerance or active immune response toward a specific antigen may occur (Meurman and Stamatova, 2007).

Acute otitis media and probiotic therapy

Acute otitis media is a common viral infection which becomes infected by bacteria in young children and is characterized by acute ear pain . Children with acute otitis media have been observed to harbour fewer α-hemolytic Streptococci in the nasopharynx than those resistant to acute otitis media (Bernstein *et al.,* 1993; Brook and Yocum, 1999; Fujimori *et al.,* 1996). The α-hemolytic stretococci interferes with the growth of pathogens causing acute otitis media (Tano *et al.,* 1999). After spraying α -hemolytic Stretococci into the nose of 108 otitis-prone children regularly for 10 days and the final administration of the 'booster dose' after 2 months, 42% (22 of 53) of the children in the placebo group remained healthy during follow-up period and had a normal tympanic membrane as compared with 22% (12 of 55) of the children in the placebo group. The spray was administered immediately after the antibiotic therapy and consisted of two *Streptococcus sanguinis* strains, two *Streptococcus mitis* strains and one *Streptococcus oralis* strain, in equal proportions (Roos *et al.,* 2001). Hatakka and coworkers examined the effect of probiotic capsules containing two *L. rhamnosus* strains, one *Bifidobacterium breve* strain, one *Propionibacterium freudenreichii* strains in otitis-prone children (Hatakka *et al.,* 2007). The probiotic treatment showed the tendency to decrease but not significantly reduce the occurrence of acute otitis media. Probiotic milk containing *L. rhamnosus* GG promoted the nasal colonization of *Staphylococcus aureus*, *Streptococcus pneumoniae* and β-hemolytic *Streptococci* (Gluck and Gebbers, 2003) and had initial effects on respiratory tract infections in children attending day care centers (Hatakka *et al.,* 2001).

Voice prostheses and probiotic therapy

A voice prosthesis is an artificial device, usually made up of silicone that is used to help the laryngectomized patients to speak. This device has a very short life time because of the excessive growth of the microorganisms, especially *Candida* species on its surface. As a result, there is improper closure of the valve of prostheses leading to leakage of food into the wind pipe, causing breathing troubles. Since yeast and bacterial colonization of esophageal side of prosthesis impedes fluent speech, respiration and swallowing (Izdebski *et al.,* 1987; Mahieu *et al.,* 1986; Neu *et al.,* 1993) because of either leakage or increased airflow resistance. Therefore, it is needed to replace the voice prostheses regularly, every 1-2 weeks to 3-4 months.

In a study, the buttermilk containing *Lactobacillus lactis* and *Lactococcus lactis ssp. cremoris* and a fermented milk drink containing *L. casei* Shirota were examined for their ability to decrease the amount of bacteria and yeast on voice prostheses in both in vitro and in vivo studies. The results showed that the consumption of fermented milk containing *L. casei* Shirota increased the lifetime of voice prostheses by four times (Schwandt *et al.,* 2005)

Residence time of Probiotics in oral cavity

Resident microbiota performs several functions and benefits health and shields the body from various pathogenic microorganisms (Fig.2). Caglar *et al*. (2006) studied the residence time of probiotics in oral cavity after withdrawal of probiotic treatment. Two-week use of a *L. reuteri* enriched yogurt showed a reduced *S. mutans* level in oral cavity. The effects were observed during use and for a few days after discontinuation. Wolf *et al*. (1995) observed the loss of *L. reuteri* colonization; two months after having probiotic use discontinued.

Yli-Knuuttila *et al.* (2006) studied *L. rhamnosus* administration and oral cavity colonization and came to the conclusion that permanent colonization in oral cavity was unlikely in most cases. And therefore, regular use of probiotics was suggested. According to a study conducted by Haukioja *et al* (2006), binding strength of 17 *Lactobacillus* strains and 7

Bifidobacteria strains to saliva and oral mucous membrane was variable in different strains which caused an increased residence time of probiotic in oral cavity. Horz *et al*. (2007) assessed the Latency period of probiotic *S. salivarius* K12, 4 tablets/day for 3 days in several oral cavity areas in a 35-day follow-up. The results showed gradual reduction in *S. salivarius* level beginning 8 days after treatment withdrawal. However, probiotic may be found on oral mucous membrane, tongue and in stimulated saliva for more than 3 weeks.

Most of the studies on probiotics have been conducted in adults and none suggested permanent installation of probiotics in oral cavity. One of the chief reasons might be that adults already have an established microflora. It is, therefore, necessary to carry out further research on infants for it may increase the chances of permanent colonization of probiotic in oral cavity when a regular exposure of probiotics from early childhood is given.

Antagonistic activity of Probiotics against Dental Caries

Dental caries is a localized, progressive demineralization of the hard tissues of the crown and root surfaces of teeth. This occurs within a bacteria-laden gelatinous material called Dental plaque that adheres to tooth surfaces and becomes colonized by bacteria. *Streptococcus mutans* is the most destructive gram-positive bacterial strain in the mouth which ferments the sugar (carbohydrates) in the diet. This bacterial digestion of sugar produces lactic acid which destroys the enamel of teeth by creating an acidic environment around it. The initial microscopic damage gradually penetrates deeper through the layers of the tooth causing a cavity to form which leads to decay. *Streptococcus mutans* widely known as the main etiological agent of dental caries is a gram-positive bacteria which forms an insoluble glucan for adhesion, aggregation and biofilm formation. This glucan is synthesized from the glucose moiety of sucrose and plays an important role in the ability of *S. mutans* to potentiate the formation of dental caries. *Lactobacilli* and *Bifidobacteria* have been reported as promising bacteria for prevention of dental caries. Nase *et al*. inspired by the gastrointestinal benefits of *lactobacilli* and its *in vitro* inhibitory activity on a caries pathogen *Streptococcus sobrinus* (Meurman *et al.,* 1995), became the first researcher to investigate the inhibition of caries pathogens using *lactobacillus* strain, *L. rhamnosus* CG. Another reason for choosing *L. rhamnonus* was that they are not cariogenic as they cannot ferment sucrose or lactose (Homofermentive lactobacilli). The study examined the effects of long-term *L. rhamnonus* CG consumption on children's health (Hatakka *et al.,* 2001). A significantly reduced risk of dental caries was observed in the children of age 1-6 yrs on oral administration of *L. rhamnosus* for seven consecutive months. Ahola *et al*. (2002) compared the effects of cheese containing L. rhamnosus GG and L.rhamnosus LC 705 with the regular cheese. His hypothesis was based on the above study and on the positive effects of cheese on dental health. They found that *Lactobacillus gasseri* when ingested in the form of probiotic dairy product reduced the *Streptococcal mutans* count in saliva of adults and showed prevention of caries in children (Ahola *et al*, 2002). One of the obligate heterofermentative residents of human gastrointestinal tract, *L. reuteri* has also been investigated for its caries preventing effects. It was reported that eating *L. reuteri* containing yoghurt daily for 2 continuous weeks reduced the *S.mutans* levels in saliva by 0.5 $\log_{10}$ colony-forming units. The reduced *S. mutans* levels were maintained for atleast upto 2 weeks after discontinuing the consumption (Nikawa *et al.*, 2004).

L.reuteri has been reported to produce water-soluble, broad-spectrum antimicrobial compounds that exhibit antagonistic activity such as reuterin (Talarico *et al.,* 1988) and reutericyclin (Ganzle *et al.,* 2000). These compounds are resistant to proteolytic and lipolytic enzymes (El and Debevere, 1998) and are active over a wide range of pH. Caglar *et al*. (2005) examined the effect of *L.reuteri* ATCC 55730 on the level of *S.mutans* and *lactobacilli* in saliva of adults (21-24 years of age). One hundred and twenty healthy adults were randomly divided into four groups. Group A drank 200ml of water through a *L.reuteri* ATCC 55730 containing straw (once daily for 3 weeks), group B drank 200 ml of water through a placebo straw (once daily for 3 weeks), Group C consumed *L.reuteri* ATCC 55730 tablets (once daily for 3 weeks), While group D was given placebo tablets without bacteria (once daily for 3 weeks). Probiotic consumption in straw or tablet form recorded a significant reduction in *S.mutans* levels (Caglar *et al.*, 2005). Caglar and his co-workers also studied the effects of *bifidobacteria* on oral health of 21 healthy individuals (21-24 years of age) consuming *bifidobacterium*-containing yoghurt for four consecutive time periods (period 1,2,3 and 4). The subjects were given a daily dose of 200gms of yoghurt containing either *bifidobacterium* DN-173010 ($7x10^7$ Colony forming units/gram) or no *bifidobacteria* (control) for 2 weeks during the period 2 & 4. Period 1 and 3 were run-ins and washout periods of 1 and 4 weeks, respectively (Caglar *et al.,* 2006). A semi-quantitative diagnostic kit determining the salivary count of *S. mutans* and *lactobacilli* showed a decrease in salivary *S. mutans* count in the *bifidobacterium* containing yoghurt with no effect on *lactobacillus* count.

Although lactic acid bacteria have cariogenic potential but there are evidences that *lactobacilli* are much more related to caries progression than to the initiation of a caries lesion (Edwardsson, 1974; Maltz *et al.,* 2002).

An artificial caries model showed that caries lesions formed by *S. mutans* and *Actinomyces isrealii* are much deeper than those produced by *lactobacilli* although in the presence of *L. acidophilus*, the growth of *S.mutans* and *A. israelli* showed synergistic effect (Shen *et al.,* 2004). *Lactobacilli* strains are naturally found in the oral microbiota of healthy individuals. Sookkhee and coworkers screened 3790 lactic acid bacteria for their ability to inhibit the *in vitro* growth of various oral pathogens. *L. paracasei* and *L. rhamnosus* were found to have potent antimicrobial activity against a number of oral pathogens (Sookkhee *et al.,* 2001).

Milk and milk products are the most popular carriers of probiotics. Milk contains calcium, calcium lactate and other organic and inorganic compounds with known anti-cariogenic properties (Gedalia *et al*.,1991; Kashket and Yaskell, 1997). Thus, they prevent the colonization of oral pathogens in oral cavity (Schupbach *et al.,* 1996). After 1 week of daily consumption of 250 grams of yoghurt, containing *L. rhamnosus* CG, *lactobacilli* was found to harbour the saliva for upto 2 weeks after discontinuing the consumption of yoghurt (Nase *et al.,* 2001). A similar experiment using fruit juice containing *L. rhamnosus* GG for 2 weeks, detected *L. rhamnosus* GG in the saliva for upto one week after discontinuation of the fruit juice.

Hillman and co-workers have isolated a *S. mutans* strains from the oral cavity of a healthy adult which is capable of inhibiting many of the other *S. mutans* strains naturally found in the oral cavity by producing a bacteriocin called mutacin 1140 (Hillman *et al.,* 1987). Mutants capable of producing threefold elevated amounts of mutacin 1140 were found to displace the resident microbiota and colonize the oral cavity (Hillman *et al.,* 1985; Hillman *et al.,* 1987).

A study on 23 dairy bacterial strains reported two strains, namely, *Streptococcus thermophilus* and *Lactococcus lactis* with the ability to incorporate into the biofilm similar to the dental plaque and grow along with five other strains of oral bacterial species associated with supragingival plaque. *Lactobacillus lactis* was reported to modulate the growth of oral microflora, eliminating the colonization of *Streptococcus oralis, Veillonela dispar, Actinomyces* and carcinogenic *Strep. sobrinus* (Comelli *et al.,* 2002). Till now the probiotics were consumed in liquid form. The difference between probiotics intake in liquid and capsule forms on *S. mutans* count was observed by a study using probiotic bacteria *Lactobacillus sporogens, Lactobacillus bifidum, L. casei, L. termophilus, L. acidophilus, L. bulgarius, L. rhamnosus*. The *S.mutans* count increased irrespective of the fact whether the probiotics were ingested in liquid or in capsular form (Montalto *et al.,* 2004). Koll-Klais *et al.* (2005) studied various strains of lactobacilli and found inhibitory action of 69% strains on the growth of *S. mutans* and 82% strains inhibited the growth of *P. gingivalis.* Strahnic *et al*. (2007) conducted a study on antagonistic activity of probiotic strains *L.salivarius* and *L. fermentum* and found both the strains to be antagonistic to the growth of *S.mutan* and *Streptococcus pneumonia*. *L.salivarius* survived the low pH produced by the increased count of *S. mutans*. Stamatova *et al*. (2007) stated that *L. rhamnosus* and *Lactobacillus bulgarius* produced inhibitory effects against *P. gingivali, Fusobacterium nucleatum* and *Streptococcal* species.*Bifidobacterium* compete with some black pigmented anaerobes for vitamin k, an essential growth factor. (Hojo *et al.,* 2007). Daily ingestion of *L. salivarius* in tablet form displayed the inhibition of *Porphyromonas gingivalis, Prevotella intermedium,* and *Prevotella nigrescens.* (Ishikawa *et al.,* 2003). Van *et al*. (2009) reported the inhibitory action of *Bdellovibrio bacteriovorus* on *A. actinomycetemcommitans* and suggested the scope of using *B. bacteriovorus* in prevention and treatment of periodontitis. The oral administration of *Lactobacillus salivarius*, in tablet form resulted in a reduced Plaque index and probing pocket depth in patients who were smokers as compared to a placebo group. (Shimauchi *et al.,* 2008). The LGG bacteria showed inability to ferment lactose or sucrose. Hence, the probiotic LGG bacteria are expected to be beneficial for oral health. (Stamatova *et al.,* 2009)

Antagonistic activity of Probiotics against Periodontal diseases

Periodontal disease is inflammation of dental support tissues which comprises of our gums, outer layer of the roots of our teeth, the bony socket that anchors our teeth, and the associated connective tissue. Periodontal disease is initiated by plaque formation. Probiotics have proved to inhibit plaque formation by lowering the salivary pH and producing antioxidants which utilize the free electrons required for mineralization of plaque. Plaque associated bacteria is unable to form the plaque in the above conditions. Therefore, Probiotics, indirectly, helps to prevent periodontal diseases. Various studies investigating the use of Probiotics for the treatment of gingivitis, plaque level, periodontitis have shown very encouraging results. A significant reduction in the number of periodontopathogens in plaque has been reported. The present knowledge of plaque-related periodontontitis considers three factors to be responsible for the occurrence of disease. These factors are- presence of a susceptible host, presence of a pathogen and low proportion or absence of beneficial microbiota (Socransky and Haffajee, 1992; Slots and Rams, 1991; Wolff *et al.,* 1994). Probiotics increase the number of beneficial microflora, competes with the pathogenic species to inhibit its growth and to prevent the occurrence of a disease (Roberts and Darveau, 2002).

Periodontal surgery (Haffajee *et al.,* 2003) to reduce the depth of the periodontal pockets alters the subgingival flora. The microflora is now characterized by high proportion of gram-positive aerobic species. Recolonization by less pathogenic bacteria occurred within 1-2 weeks (Goodson *et al.,* 1991; Harper and Robinson, 1987; Magnusson *et al.,* 1984). However, subgingival flora grows rapidly to resume its form and number within weeks to months (Magnusson *et al.,* 1984; Mousques *et al.,* 1980; Quirynen *et al.,* 2005; Van *et al.,* 1988; Wade *et al.,* 1992). The re-establishment of subgingival microbiota depended on many factors viz. the level of oral hygiene, the efficacy of the subgingival debridement and the residual probing depth (Magnusson *et al.,* 1984; Pedrazzoli *et al.,* 1991; Petersilka *et al.,* 2002; Sbordone, 1969; Van *et al.,* 1988).

Subgingival plaque samples of patients with localized juvenile periodontitis and patients with refractory periodontitis were found to lack some of the bacterial species otherwise found in the subgingival plaque samples of the healthy patients. These bacterial species were identified as *Streptococcus sanguinis* (Truper and De Clari, 1997) and *streptococcus uberis*. These bacterial species were found to inhibit the growth of *Aggregatibacter actinomycetemcomitans* (Norskov-Lauritsen and Kilian, 2006) and other periodontal pathogens (Hillman and Socransky, 1982; Hillman *et al.,* 1985) by producing hydrogen peroxide (Hillman and Shivers, 1988). *In vitro* study of *L. salivarius* TI 2711 behaviour isolated from a healthy human volunteer showed inhibitory action on *P. gingivalis*, *Prevotella intermedia* and *Prevotella nigrescens* after 6-12 hrs coculturing (Ishikawa *et al.,* 2003).

Krasse and coworkers (2005) performed a double blind, placebo- controlled study on randomly selected 59 patients with modern-to-severe gingivitis to evaluate the oral benefits of two different strains of *L. reuteri*. Experiment began with the plaque removal pretreatment of all the patients. He divided the patients into three groups viz. placebo group (with 18 patients) who consumed a chewing gum twice daily for 2 weeks, probiotic A group (with 20 patients) were instructed to consume a chewing gum with *L. reuteri* strain A twice daily for 2 weeks and probiotic B group (with 21 patients) consumed a chewing gum with strain B of *L. reuteri* twice daily for 2 weeks. The results showed a significant reduction in plaque scores for both the probiotic groups with no reduction in the plaque scores for placebo group (Krasse *et al.,* 2005).

Probiotic mouth wash has been demonstrated to reduce the incidence of plaque formation and gingivitis in 6-8 year old children (Harini and Anegundi, 2010). The presence of two species, *Streptococcus oralis* and *S. uberis* has proved to inhibit both *in vitro* and *in vivo* growth of periodontopathogens. Their presence has been demonstrated as an indicator of good periodontal health (Hillman *et al.,* 1985). Riccia and coworkers (2007) studied a group of patients with chronic periodontitis and found the anti-inflammatory effects of *Lactobacillus brevis*. He also showed the possibility of *L. brevis* being antagonistic, leading to reduced plaque formation and gingival index. The influence of *Lactobacilli* in the oral cavity is evident from the research findings that demonstrate the inhibition of the growth of periodontopathogens in the presence of *Lactobacilli* (Sookkhee *et al.,* 2001; Ishikawa *et al.,* 2003; Koll-Klais *et al.,* 2005). Periodontal destruction and inflammation are closely associated with decreased level of certain lactic acid bacteria (Koll-Klais *et al.,* 2005). The presence of homofermentative *lactobacilli*, especially *Lactobacillus gasseri* results in lower risk of dental plaque and inflammation. *Lactobacillus gasseri* and *L. fermentum* were found more prevalent in the oral cavity of healthy individuals as compared to those with chronic periodontosis (Koll-Klais *et al.,* 2005). Kang and coworkers isolated *Weissella cibaria* from children's saliva and tested its ability to reduce dental plaque. *W. cibaria* is a gram-positive, non-spore forming, non-motile, heterofermentative *lactobacilli* which can be easily isolated from the fermented foods. The results proved the ability of *W. cibaria* to inhibit the biofilm formation, both *in vitro* and *in vivo* (Kang *et al.,* 2006). Teughal and coworkers examined the effect of seven different bacterial strains on the colonization of hard surfaces and epithelial cells by *A. actinomycetemcomitans, P. gingivalis, P. intermedia* and *Tannerella forsythia* (Teughal *et al.,* 2007; Van *et al.,* 2007).

The *in vitro* analysis concluded that *S. sanguinis* KTH- 4, *S. salivarius* TOVE and *S. mitis* BMS are the most potent inhibitors of periodontal pathogens. Hence, probiotics are capable of inducing physical and chemical changes in the microbial flora of oral cavity (Teughal *et al.,* 2007). Probiotics can compete with the resident microbiota for essential nutrients (Sanders, 1969), inhibit the growth of pathogens (Wilson, 2005) and they can generate immune response against the virulence factors of pathogens (Yasul *et al.,* 1999).

Antagonistic activity of Probiotics against Halitosis

Halitosis or Bad Breath is the condition when the breath has unpleasant odor. Halitosis is not only a dental problem but also an embarrassing social problem. It is a bacterial disorder of mouth. Food debris adhere to the posterior portion of the tongue which is the most common site for bacteria to colonize and produce malodorous substances such as volatile sulphur compounds (VSCs). VSCs are the by-products of microbial degradation of proteins, blood, mucins found in saliva, and the traces of food retained in the oral cavity. Although there are various reasons for halitosis like respiratory tract infections, metabolic disorders and consumption of some particular foods but the most common reason for halitosis is the imbalance of the normal microflora of the oral cavity (Scrully and Greenman, 2008).

A study on the bacterial species isolated from the tongue of a halitosis sufferer and then compared with the subjects that are considered healthy found *Atopobium parvulum, Eubacterium sulci, Fusobacterium periodonticum* to be mostly associated with halitosis and *Streptococcus salivarius* to be most prevalent in the healthy subjects. *S. salivarius* being capable of producing bacteriocins contributes to the reduction of bacterial species producing VSCs that produces foul smell. It is therefore, known as the commensal probiotic of oral cavity (Kazor *et al.,* 2003).

Probiotics are marketed for the treatment of both mouth and gut associated halitosis. The administration of probiotic bacteria have been found to suppress the odor producing bacteria, resulting in a decrease in the foul smelling gases arising in the mouth. A study on the patients of halitosis reported reduced levels of volatile sulphur compounds after consumption of gum or lozenges containing *S. salivarius* K12 (Burton *et al,* 2006).

Kang and colleagues (2006) studied the ability of various strains of *Weilonella cibaria* to inhibit the production of volatile sulphur compounds by *F. nucleatum*. Results showed that *W. cibaria* produces hydrogen peroxide which inhibited the growth of *F. nucleatum*. When a probiotic solution containing *W. cibaria* was used for gargling, there was a marked reduction in the production of hydrogen sulphide and methanethiol and hence, reduction in foul smell (Kang *et al.,* 2006).

Probiotics and *Candida species*

Candida species specially, *C. albicans* is a leading cause of fungal infection in oral cavity; it is particularly common in the elderly and in immunocompromised patients. The intake of probiotics in cheese containing *L. rhamnosus* GG and *Propionibacterium freudenreichii* resulted in reduced risk of *C. albicans* infections (Hatakka *et al.,* 2007).

On assessing the effects of various *Lactobacillus* strains in oral cavity *Koll et al.* (2008) found that most strains suppressed the growth of periodontal pathogens, including *Actinomycetemcomitans* (60 out of 67 tested strains); *Porphyromona gingivalis* (35 out of 42 strains), *P. intermedia* (26 out of 42 strains), and cariogenic *S. mutans* (37 out of 67 strains). No inhibition was found, however, for *C. albicans* growth.

Hasslof *et al*. (2010) investigated the inhibitory action of those *Lactobacilli* strains which are used in commercially available probiotic products on growth of oral *Streptococci mutans* and *C. albicans* by agar overlay method. The results obtained showed that at concentrations ranging from 10^9 to 10^5 CFU/ml, all *lactobacilli* strains inhibited the growth of the *Streptococci mutans* completely with the exception of *L. acidophilus* La5 that executed only a slight inhibition of some strains at concentrations corresponding to 10^7 and 10^5 CFU/ml. Although *Candida* growth was reduced by all the *lactobacilli* strains tested but the effect was weaker than for *Streptococci mutans*. The strongest inhibition on *Candida albicans* was displayed by *L. reuteri* and two *L. plantarum* strains. Elahi and coworkers (2005) compared the *C. candida* count in mice fed with *L. acidophilus* to the control group and discovered the ability of *L. acidophilus* to control oral candidiasis. However, no observable delay in *C. albicans* colonization was noted when heat killed *L. casei* and *L. acidophilus* were given to the immunocompromised mice (Wagner *et al*., 2000).

Probiotics and HIV

Recently the role of probiotics to slow down the progression of AIDS (Acquired immunodeficiency syndrome) has been postulated by Lin Tao and colleagues (2008). A screening of saliva taken from hundreds of volunteers showed that some *Lactobacillus* strains produced proteins capable of binding a particular type of sugar, called mannose, found on HIV envelope. The binding of the sugar enables the bacteria to stick to the mucosal lining of the mouth and digestive tract and colonize them. One of the strain showed abundant mannose-binding protein particles into its surroundings which binded to the sugar coating and hence neutralized HIV. They also observed that immune cells trapped by *lactobacilli* formed a clump. This configuration would immobilize any immune cells harboring HIV and prevent them from infecting other cells.

Future Prospectives

Many researchers have reported significant benefits in oral health on administration of Probiotics. Genetic engineering and the recombinant DNA technology can further improve the probiotic characteristics. Lactic acid production by acidogenic bacteria has been considered to be the major cause for the production of caries lesion. The probiotic acidogenic bacteria can be engineered genetically to prevent dental caries. Mutations can be induced to create the mutants with increased bacteriocin production. Such mutant strains displace the indigenous strains and colonize the oral cavity. Still many *in vitro* and *in vivo* tests for the presence of the desirable characteristics must be carried out and various random trials need to be performed to find out the most potent probiotics organisms for oral health and the most effective ways of their administration.

CONCLUSION

Probiotics are an emerging field of microbiology with immense potential. Probiotic organisms being identical to the natural microflora of human body are safe, easily acceptable by the body, devoid of side-effects. They are of great interest to the researchers and its application as therapeutic agent is a topic of extensive research to the scientists of the world. Probiotics have been analyzed for treatment and prevention of various diseases and disorders of human body and the results obtained are very encouraging. Probiotics have turned out to be very promising in ensuring oral health and wellbeing.

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