



# Probiotics - Do they have a Role in Medicine and Dentistry ?

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## Abstract

Probiotics are dietary supplements containing potentially beneficial bacteria or yeasts. They are administered in different quantities that allow for colon colonization. These products help in stimulating health promoting flora and also suppressing the pathologic colonization and disease spread.

The use of probiotic plays an important aspect in dentistry too ever since the oral infections occupied the prime space among the other infections effecting the humans. This concept of microbial ecologic change both for medical and dental changes has accumulated a lot of evidence in recent times. But to date, no substantial literature and use has been postulated.

There are claims that probiotics strengthen the immune system to combat allergies, stress, exposure to toxic substances and other diseases. There are reports of their beneficial use in HIV infection and cancers, mostly, the colo-rectal carcinomas. Their use in pre malignant and malignant oral disorders is yet to be probed.

Strains of genera lactobacillus and bifidobacterium are the most widely used probiotic bacteria.

This review is an attempt to discuss briefly the role of probiotics in medicine and dentistry.

## Introduction

The human gut contains 10 times more bacteria than cells elsewhere. The enormous biomass consists of over 400 known bacterial species that generate intense metabolic activity and are of key importance for human health. This eco-system gets disrupted when exposed to toxics in the form of polluted water and food as well as injudicious use of antibiotics.<sup>1,2,3</sup> This causes destruction of beneficial bacteria leaving the resistant ones, pathogenic. Of late it has been realized by health care professionals and prompted them to seek alternative therapeutic options. One such alternative is the use of beneficial bacteria, the probiotics, which stimulate health-promoting indigenous flora and reverting back the change.<sup>1,2,4</sup>

The concept of oral foci of infection, affecting the systemic health has been extensively researched.<sup>3,4</sup> Removal of these oral foci using probiotics in the oral cavity has tremendous improvement in general health of the individual. This proposed concept is reinforced by recent evidences that probiotics may play a vital role in oral ecology.<sup>4</sup>

## Definition

Probiotics are bacterial cultures or living microorganisms upon ingestion in certain quantity promote and enhance health benefits.<sup>3,4</sup> An International Life Science Institute Europe consensus document proposed a simple and widely accepted definition of probiotics as- 'Viable microbial food supplements which beneficially influence the health of human'. These bacteria

should belong to the natural flora in order to resist gastric secretion and survive during intestinal transit. They should also adhere to the intestinal mucosa and finally should have the ability to inhibit gut pathogens.<sup>2,3,4</sup>

Prebiotics are non digestible food ingredients such as fructo-oligosaccharides (FOS), lactulose and inulin that beneficially affect the host by selectively stimulating growth and/or increase activity of a limited number of probiotic like bacteria in a colon.<sup>1</sup>

## History

The dietary use of living microorganisms has a long history. Mention of cultured dairy products is found in the bible and the sacred books of Hinduism. Sacred milks and cultured dairy products such as *kefir*, *koumiss*, *liben* and *dahi*, were often used therapeutically before the existence of microorganisms was recognized.<sup>3</sup>

In 1907, Elie Metchnikoff postulated that consumption of Bulgarian yoghurt promotes good health. In 1950, a probiotics product was used as a drug for the treatment of scour among pigs. Lilley and Stillwell (1965) introduced the term probiotics. Mann and Spoering 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, Holcomb identified *bifidobacterium bifidum*. WHO in 1994 described the probiotics as next most important in immune defense system following antibiotic resistance. These incidences paved way for a new concept of probiotics in medicine and dentistry.<sup>4,5,6</sup>

Recently there are reports of usage of lactic acid bacteria in microbial infections and cancer due to their immunostimulatory properties.<sup>6,7</sup> These microorganisms can inhabit the bio-film and actually protect oral tissue from disease. They also have cariostatic activity; help in preventing candidal colonization and act as antioxidants.<sup>4</sup>

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## Species and Health Benefits

Probiotics can be varied. They can be yeast, bacteria or moulds. But most commonly, bacterial species are predominant. Some of the species are:<sup>1,4</sup>

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 *Lactobacillus species* help in production of enzymes to digest and metabolize proteins and carbohydrates. They aid in synthesis of vit. B and vit.K and facilitates breakdown of bile salts. More than 100 species of *L. acidophilus*, *L. brevis*, *L. casei*, *L. rhamnosus*, *L. salivarius* has been identified. They are usually dispensed in gel, paste, powder and liquid forms. They enhance innate and acquired immunity as well as help in inhibition of pro-inflammatory mediators. More recently, a study demonstrated that long term consumption of milk caused a significant reduction in caries risk.<sup>4,7</sup>

*Bifidobacterium species* are strictly anaerobic and predominate the large intestines. Over 30 species had been identified. The benefits from these include metabolization of lactose, generate lactic ions from lactic acid and synthesize vitamins. They also ferment indigestible carbohydrates and produce beneficial short chain fatty acids. They are believed to be beneficial in reducing antibiotic associated diarrhea and traveller's diarrhea. They relieve constipation, alleviate inflammatory bowel disease and prevent DNA damage. Finally they may prevent or delay the onset of cancers.<sup>8,9</sup>

*Streptococcus thermophilus* and *Lactobacillus bulgaricus* are primary cultures used in yogurt production. Most noted benefits are to metabolize lactose, improve lactose intolerance and antimicrobial activity.<sup>9</sup>

*Saccharomyces boulardii*: It is a non colonizing lactic acid producing yeast. It prevents or treats antibiotic-associated diarrhea, *C. difficile* associated disorders, acute diarrhea, traveller's diarrhea in tube fed patients. They are also useful in AIDS related diarrhea and to prevent relapse of Crohn's disease. Most noted feature is that they secrete proteases and other substances that breakdown bacterial enterotoxins and inhibits their binding to intestinal receptors. They also help in immune function enhancement. Most of the beneficial species enhance vitamin production and reduce serum-cholesterol level and in anticarcinogenic activity.<sup>8,9</sup>

## Selection of Probiotics<sup>4</sup>

The criteria for considering certain product should be:

1. They should be non toxic and non pathogenic preparation.
2. Produce beneficial effect
3. Should withstand gastrointestinal juice
4. Should have good shelf life
5. Should replace and reinstate the intestinal microflora

Probiotics and prebiotics could affect the host in combination by synergistic action.

## Mechanism of Action of Probiotics on Immunity<sup>5</sup>

Regulatory T lymphocytes (Tregs) are thought to play a critical role in limiting inflammation in response to the nonpathogenic antigens, and defects in the T-cell subset have been implicated in the pathogenesis of few gastro-intestinal disorders. Recent studies suggest that Toll-like receptor pathways may mediate interactions between dendritic cells, T lymphocytes and mast cells, thus modulating allergic immune responses.

Toll-like receptor signaling triggers dendritic cell maturation, which primes naive T lymphocytes towards specific T helper cell types 1 and 2 immune responses. Although a T helper cell type 1/2 balance may be important in modulating allergic responses, T regulatory cells that suppress certain immune responses may be critical in immune regulation.

The effect is produced either by absorption of a soluble antigen or by translocation of 'lactobacilli' through the gut wall into the blood stream. Lactobacilli which adhere to human intestinal epithelial cells are capable of activating macrophages.

Another class of pharmacologic agents, the histone/protein deacetylase inhibitors (HDACs), has recently been shown to improve Treg function and increase Treg numbers in mice. HDACs regulate chromatin remodeling and affect gene expression by modifying histones via acetylation. HDAC inhibitor therapy increases the number of Tregs and diminishes DSS colitis in a Treg-dependent manner. These results suggest that HDACs may be an important target to alter Treg function, although more specific inhibitors may be necessary for safe use in humans.

## Interleukin-10

Murine models demonstrate an important role for IL-10 in Treg-mediated control of intestinal inflammation; however, the source of IL-10 may not be entirely Treg derived. In the T cell transfer model of colitis, IL-10-deficient CD4<sup>+</sup>CD25<sup>+</sup> Tregs were both able to prevent and cure established colitis. A model of innate immune cell-induced colitis achieved by infection of RAG-deficient mice with *Helicobacter hepaticus*, the requirement for IL-10 appears to be more stringent.

In this system, Treg-mediated suppression of colitis was prevented by the administration of anti-IL-10 receptor antibodies, and IL-10-deficient Tregs were unable to protect animals from colitis. It has recently been shown that deletion of IL-10 under the control of the FoxP3 promoter results in spontaneous colonic inflammation. Although there is no spontaneous disorder of the skin or lungs, the experimental animals demonstrated increased inflammation in these organs in hypersensitivity models. These data suggest that IL-10 secretion by Tregs is critical in the control of intestinal inflammation, but that non-Treg-derived IL-10 also significantly limits colitis. These data also highlight the unique importance of Treg-derived IL-10 in the control of mucosal inflammation, given that mice deficient for IL-10 exclusively in Tregs develop colitis and airway hypersensitivity, but do not develop the fatal systemic autoimmunity seen in FoxP3-deficient mice.

**Probiotics and HIV** : Recently it has been postulated that the probiotic bacteria may slow down AIDS progression. Lin Tao and his colleagues screened hundreds of bacteria taken from the saliva of volunteers. The results showed that some *Lactobacillus* strains had produced proteins capable of binding a particular type of sugar found on HIV envelope, called

mannose. The binding of the 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 configuration would immobilize any immune cells harboring HIV and prevent them from infecting other cells.<sup>10</sup>

## Probiotics and Cancer

The anticancer effects of probiotics were long recognized but evidence in literature is minimal. Recently, there has been growing interest in proving their interrelationship. Individuals who consume high amount of animal protein and fats apparently showed increased risk of colon cancer. The refined diet has also been implicated in causation of breast and prostate carcinoma. It has been postulated that microflora of GI tract are involved in inducing colorectal carcinoma. Evidence is cropping up that probiotics can interfere at various stages of cancer process, more so by interference with chromosomal and DNA damage. However more research is required to develop specific regulations on their consumption.<sup>8,9,14</sup>

## Probiotics in Colon Cancer Prevention<sup>11</sup>

In addition to their conventional use as gut modulators, probiotics are investigated for their role to prevent colon cancer. In-vivo and molecular studies have demonstrated encouraging outcomes, mainly attributed to its antimicrobial effects against carcinogen-producing microorganisms, antimutagenic properties, and alteration of the tumor differentiation processes.

Present studies have suggested that prebiotics also possess protective effect against colon carcinogenesis, mainly attributed to the production of short chain fatty acids upon its fermentation by gut microflora, and alteration of gene-expressions in tumor cells.

Ingestion of prebiotics results in a different spectrum of fermentation products, including the production of high concentrations of short-chain fatty acids. Gut flora, especially after the ingestion of resistant starch, induces the chemopreventive enzyme glutathione transferase in the colon. Together, these factors lead to a reduced load of genotoxic agents in the gut and to an increased production of agents that deactivate toxic components. Butyrate is one such protective agent. Butyrate may inhibit the genotoxic activity of nitrosamides and hydrogen peroxide in human colon cells.

Notably, some of the newer studies showed that short-lived metabolite mixtures isolated from milk that was fermented with strains of *Lactobacillus bulgaricus* and *Streptococcus thermophilus* are more effective in deactivating etiologic risk factors of colon carcinogenesis than are cellular components of microorganisms. In humans, the ingestion of probiotics leads to the excretion of urine with low concentrations of components that are genotoxic in human colon cells and high concentrations of components that induce oxidized DNA bases.

## Probiotics in Prevention of Clostridium Difficile Diarrhoea

Diarrhea is one of the most common adverse events associated with antibiotic use, and infection with *C difficile* accounts for 15% to 25% of cases of diarrhea related to the use of antibiotics.

Overall, up to one quarter of patients treated with antibiotics may develop diarrhea caused by *C difficile*. Diarrhea associated with *C difficile* is more common among older adults, and it usually develops 2 to 3 weeks after cessation of antibiotic therapy.

A variety of controlled trials, case series, and case reports have evaluated probiotics to treat first or recurrent episodes of CDAD. In addition, a study conducted a meta-analysis to determine the role of probiotics in CDAD. Most of them have shown favorable results with *Lactobacillus rhamnosus* GG or *Saccharomyces boulardii*. However, other reports have shown lack of benefit. Literature showed that these probiotics may be useful in treating or preventing recurrences of CDAD. Nonetheless, the heterogeneity of the studies makes definite conclusions difficult. In addition, incidences of bacteremia or fungemia associated with probiotic use have been reported, particularly in the last decade, mostly in immunosuppressed. Unfortunately, these are also the patients more likely to have severe CDAD or are at risk for recurrences. Given the potential for complications in debilitated and immunosuppressed patients, the risks may outweigh benefits, and rational antibiotic use may be a better option to prevent a first episode or recurrence of CDAD.<sup>12</sup>

## Probiotic Usage in Functional Gastrointestinal Disorders in Children and Adults

Chronic constipation is one of the most frequent complaints in childhood. Although there is evidence that gastrointestinal flora is important in gut motility, there is little evidence that gut flora is abnormal in constipation. Lactobacilli and bifidobacteria increase stool frequency and decrease consistency in normal individuals. But, according to several reviews, the evidence of probiotics for efficacy in constipation is limited. Fiber supplements, lactose-free diets, and lactobacillus supplementation are effective in the management of children with recurrent abdominal pain and irritable bowel syndrome. Several studies with *Lactobacillus* GG in children showed negative results in children with chronic constipation. *Bifidobacterium animalis* DN-173 010 has been shown to be effective in adults with constipation-predominant irritable bowel syndrome. Recent studies have shown that the fermented dairy product containing *Bifidobacterium lactis* strain DN-173 010 is effective in increasing stool frequency in constipation-predominant irritable bowel syndrome patients with a defecation frequency > 3/week and in constipated women with a defecation frequency < 3/week. A double-blind, placebo-controlled randomised multicentre trial in which 160 constipated children (age 3-16 years) with a defecation frequency < 3/week were randomly allocated to consume a fermented dairy product containing *Bifidobacterium lactis* DN-173 010 or a control product, twice a day, for 3 weeks. Results showed that the fermented dairy product containing *Bifidobacterium lactis* strain DN-173 010 is effective in increasing stool frequency after 3 weeks of product consumption in children with functional constipation and a defecation frequency < 3/weeks.<sup>13</sup>

## Probiotics and Calcium Absorption

Milk is considered to be abundant with calcium apart from other dietary sources. Individuals with lactose intolerance may probably develop osteoporosis due to decreased consumption of milk containing diet. Calcium absorption is favored in acidic pH. So if probiotics are fed to lactose intolerance patients, then milk lactose is hydrolyzed by probiotic strains and favors calcium absorption.<sup>4,14</sup>

## Probiotics in Veterinary Practice

Probiotics have been developed in an attempt to help the body re-establish a balanced intestinal bacterial environment (microflora). They are marketed as either pastes or powders and are commonly given to young foals, horses being trailered or in competition, and horses in many other situations. These products are commonly defined as live microbial feed supplements.

Colitis in horses caused by Clostridia bacteria or by Salmonella organisms can be helped by probiotic use as part of a comprehensive and aggressive treatment plan. Probiotics have been advocated for the treatment and prevention of diarrhea in young foals and have been effective against rotaviral infections. Because some probiotics react with antigens in the intestine, researchers felt these products might be useful in the treatment of food allergies and that probiotic use might reduce cases of colic, ulceration, and malabsorption.

## Probiotics and Oral Health

Mouth represents the first part of the gastrointestinal tract. Probiotics have been successful for treating digestive related diseases. These can be introduced into the oral cavity at much higher concentration with minimal loss in number. Many of the beneficial bacteria are destroyed by the hydrochloric acid in the stomach. The way to avoid this pitfall is to freeze the bacteria and put them in a pill.<sup>7</sup>

It should also be noted that as most probiotics are in dairy forms containing high calcium, possibly reducing demineralization of teeth. It is possible that these act at bio-film to keep pathogens away and occupy a space that might otherwise be occupied by a pathogen. Probiotics should adhere to dental tissues to establish a cariostatic effect and thus should be a part of the bio-film to fight the cariogenic bacteria. The duration of their stay locally also is important for beneficial effect. Ideal vehicles of probiotics installation are yogurt, milk and cheese. Some of the hypothetical mechanism of probiotics action in the oral cavity is by:<sup>1-4,7,15,16</sup>

- Direct interaction in dental plaque
- Involvement in binding of oral micro-organisms to proteins
- Action on plaque formation and on its complex ecosystem by competing and intervening with bacterial attachments.
- Involvement in metabolism of substrate and production of chemicals that inhibit oral bacteria

Indirect probiotic actions are also featured such as

1. Modulating systemic immune function.
2. Effect on local immunity.
3. Effect on non-immunologic defense mechanisms.
4. Regulation of mucosal permeability.
5. Probiotics as antioxidants and produce antioxidants.
6. Prevent plaque formation by neutralizing the free electrons.

Some of the literature review showed only few studies available on the prevalence, role and effects of probiotic bacteria in the mouth.

A study by Sookhee et al with 3790 lactic acid bacterial strains, showed about 5 species expressed inhibitory effect against other microorganism, including candida. Antimicrobial potentials of bacteria are affected by pH, catalase, proteolytic enzymes and temperature. The study also paved way for recognition of *L.paracasei* and *L. rhamnous* strains prompting for further study.

Another study by Nase et al showed marked reduction in caries risk with administration of probiotic milk from coded containers for 5 day/week for 7 months.<sup>17</sup> Ahola's study showed inhibitory effect on salivary counts of Strepto. Mutans and yeast by using a combination of LGG and Bifidobacteria. A Specially manufactured cheese was used as the vehicle of administration for 3 weeks. Eating cheese also enhanced remineralization and prevents demineralization of hard tissues in saliva.<sup>18</sup>

Lactic acid bacteria are considered detrimental to dental health because they ferment sugars and lower pH of these bacteria. When lactic acid bacteria are consumed in milk products, the buffering capacity of milk influences the acidity. The presence of calcium and other constituents may also protect tooth surfaces and inhibit the adherence of dental pathogens. Russian scientists have reported that probiotic bifidobacterium sp. reduce gingival and periodontal inflammation.<sup>7,16,19</sup>

Even though there is good number of studies indicating anticarcinogenic effect in intestines, there are no studies done over the effect of probiotics on premalignant and malignant conditions of oral cavity.<sup>20,21</sup>

### Methodological bias in studies with probiotics

It has been proposed that probiotics can favorably influence the course of critically ill patients. To address this question, a limited systematic review was undertaken to identify randomized, controlled trials that compared a group of critically ill patients taking probiotics with a group that did not. Ten such trials, mostly with high risks of methodologic bias, were identified. When the data were combined, the probiotics did not appear to influence mortality or duration of hospitalization. However, the recipients of the probiotics had fewer infectious episodes. Unfortunately, methodologic shortcomings could have introduced biases into the trials. Probiotics also appeared to reduce the incidence of antibiotic-associated diarrhea in hospitalized patients, although the study did not specifically focus only on those who were critically ill. In summary, it is not clear that probiotics are beneficial in the critically ill patient group.<sup>22</sup>

## Status of Probiotics in India

In India, Sporolac, *Saccharomyces boulardii* and yogurt (*L. bulgaricus* + *L. thermophilus*) are the most common ones used. Sporolac is manufactured using *Sporolactobacilli*. Lactobacilli solution is an example of a probiotic, usually given to pediatric patients. The latest and recent addition to the list of probiotics in India is made up of genetically modified *Bacillus mesentericus* which act as an alternate to B-complex capsules. Only sporulating lactobacilli are used with some of the antibiotic preparations.<sup>1,4</sup>

## Conclusion

Probiotics are emerging as a fascinating field in oral medicine. This concept prompts a new horizon on the relationship between diet and oral health. Clinical trails should be directed to assess the method of probiotic administration in oral cavity and dosages for different therapeutic uses. Research should be directed towards the action of probiotics on oral cavity and also on its pathological conditions.

## Future Trends

Probiotics can be used as passive local immunization against dental caries. High titers of antibodies can also be directed against human cariogenic bacteria produced in bovine colostrum

over the vehicle of fermented milk. Early mucosal colonization with E.coli bacteria in newborn stimulates mucosal immune system to produce specific antibodies as well nonspecific secretory immunoglobulins. Research is directed at the reduction of severity and occurrence of mucosal lesions, specifically aphthous ulcers.<sup>7,8</sup>

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