

Review article:

Probiotics - A ray of hope

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Abstract:

Probiotics are a form of 'good bacteria' that provide health benefits for the host. For over 100 years, probiotics have been scientifically proven to be beneficial in a wide variety of health conditions. Yet it took generations to apply the benefits of probiotics to dental advantages. This article gives an insight to scientific literature going on in this upcoming field which holds great promises in the future of dentistry.

Keywords: Probiotics, Prebiotics

Introduction

Since centuries useful bacteria's are added to our food for their beneficial effects on human health. In recent year, the beneficial effects of probiotics are being increasingly promoted by health professionals. It has been reported that these probiotics can play an important role in immunological, digestive and respiratory functions and could have a significant effect in alleviating infectious disease in children and adults.⁽¹⁾ Application of 'health-promoting for therapeutic purposes is one of the strongest emerging fields.^(R22) "Probiotic" means that mechanisms are employed to selectively remove only the pathogen while leaving the remainder of the oral ecosystem intact.⁽²⁾ Probiotic is derived from Latin word 'pro' -for and Greek word "biotic" - life.⁽²⁾

Definitions

Probiotic by World Health Organization WHO (2001) is defined as " Probiotics are defined as living microorganisms which, when administered in adequate amounts, confer a health benefit on the host."⁽³⁾

Guarner et al defined probiotics as live microorganisms which when administered in adequate amounts, confer beneficial effect on the health of the host.⁽⁴⁾ Parker (1974) defined it as organisms and substances that contribute to intestinal microbial balance.⁽⁵⁾ Fuller (1989) defined it as a live microbial feed supplement that beneficially affects the host animal by improving its intestinal microbial balance.⁽⁶⁾ Havenaar&Huist Int Veld in 1992 defined it as a viable monoculture or mixed culture of microorganisms that, when applied to animal or human, beneficially affects the host by improving the properties of the indigenous microflora.⁽⁵⁾ Schaafsma in 1996 defined probiotics as living microorganisms that, upon ingestion in certain numbers, exert health benefits beyond inherent basic nutrition.⁽⁷⁾

A microbial dietary aduvant that beneficially affects the host physiology by modulating mucosal and systemic immunity as well as by improving nutritional and microbial balance in the intestinal tract.⁽⁹⁾

Schrezemeir& de Vrese in 2001 defined as a preparation of, or a product containing, viable,

defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and as such exert beneficial health effects in this host. ⁽⁹⁾

Live microorganisms that, when administered in adequate amounts, confer a health benefit to the host. (FAO/WHO report) Naidu et al in 1999 defined probiotics as a microbial dietary adjuvant that beneficially affects the host physiology by modulating mucosal and systemic immunity, as well as by improving nutritional and microbial balance in the intestinal tract. ⁽⁸⁾ According to Salminen, a probiotic is a "live microbial culture or cultured dairy product which beneficially influences the health and nutrition of the host." ⁽⁹⁾

History of probiotics-

In a Persian version of the Old Testament (Gn 18,8) it states that "Abraham owed his longevity to the consumption of sour milk" ⁽³⁾

Lilley & Stillwell (1965) introduced the term probiotics. They first used the term to describe "substances secreted by one microorganism which stimulates the growth of another" and thus was contrasted with the term antibiotic. ⁽³⁾ Fuller (1989) in order to point out the microbial nature of probiotics, redefined the word as "A live microbial feed supplement which beneficially affects the host animal by improving its intestinal balance." ⁽¹⁾

The term prebiotic was introduced by Gibson and Roberfroid who exchanged "pro" by "pre" which means "before" or "for". They defined prebiotics as a "non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon." ⁽⁹⁾ Ukrainian bacteriologist Metchnikof (1908) proposed a diet containing milk fermented by lactobacilli to prevent poisoning of body by bacteria. The concept of probiotic thus emerged opening new field of bacteriology. ⁽¹¹⁾

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.

In 1994, WHO described the probiotics as next most important in immune defence system following antibiotic resistance.

Definition of Prebiotics :

The term prebiotics was introduced by Gibson & Roberfroid who exchanged "pro" for "pre" which means "before" or "for". They also defined prebiotics as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon." ⁽¹²⁾

Definition of symbiotic : The term symbiotic is used when a product contains both probiotics and prebiotics. ⁽⁹⁾

Probiotics:

Probiotics can be varied. They can be yeast, bacteria or moulds.

1. Lactic acid producing bacteria (LAB):
lactobacillus, bifidobacterium,
streptococcus.
2. Non lactic acid producing bacterial species
: Bacillus, propionibacterium
3. Nonpathogenic yeasts : Saccharomyces
4. Non spore forming and nonflagellated rod
or coccobacilli.

Characteristics of ideal probiotics

Fuller in 1989 ⁽²⁾ stated following characteristics of ideal probiotics

1. It should be a strain, which is capable of exerting a beneficial effect on the host animal, e.g. increased growth or resistance to disease.
2. It should be non-pathogenic and non-toxic.
3. It should be present as viable cells, preferably in large numbers.

4. It should be capable of surviving and metabolizing in the gut environment e.g. resistance to low pH, organic acids and bile.
5. It should be stable under storage & field conditions.

Properties of the Probiotic to be used against dental disease are⁽⁹⁾

1. Binding to dental surface
2. Produce antimicrobial substances against pathogens
3. Alteration of ecological conditions of the mouth
4. Reduction of the inflammatory response.

Selection of probiotic

Probiotics must be able to exert their benefits on the host through growth and/or activity in the human body. (Collins et al, 1998; Morelli, 2000)⁽¹⁾ Svantetwetman et al 2008 enumerated following criteria for selection of Probiotics⁽¹³⁾

1. They should be non-toxic and non pathogenic to the host
2. They should be able to withstand the acidity of the GIT.
3. They should have a beneficial effect on the host
4. They should be able to replace and reinstate the intestinal microflora

5. They should have a good shelf life.

Micro-organisms commonly used as Probiotics in oral health

The organism capable of adhering to and colonize the surface of the oral cavity constitute 'Oral Probiotics'.⁽¹⁴⁾

Currently used probiotics in the treatment of oral diseases are (Anuradha&Rajeshwari, 2005, Parvez et al, 2006)⁽¹⁴⁾

Lactobacillus : L.Acidophilus, L. rhamnosus, L. johnsonii, L. Casei, L. gasseri, . Bulgaricus, L. Plantarum, L.Delbreukii, L.Bulgaricus, L.Reuteri, L. brevis, L. lactis, L. fermentum, L. salivarius, L. paracasei

Pediococcus: Pentosaceus

Saccharomyces: cerevisiae, Boulardii

Bifidobacterium species: B.bifidum, B.lactis, B. longum, B. infantis, B. adolescentis, B. animalis, B. thermophilum.

Streptomyces species: Streptococcus faecium, Streptococcus thermophiles.

Enterococcus species: faecium

Bacillus species: subtilis, Cereus, Coagulans, Licheniformis

Yeast and Molds: Aspergillusoryzae, A. niger, c.pintolopesii. C. albicans, Sacchromycesboulardii.

Others species: S. Salivarius, W.Sibaria, Leuconostoc, Peiococcus, Propionibacterium.

Difference between replacement therapy and probiotic therapy.⁽¹⁵⁾

Replacement therapy

1. Effector strain is not ingested, rather is applied directly on the site of infection.
 2. Involves dramatic and long-term change in the indigenous microbiota.
 3. Colonisation of the site by the effector strain is crucial.
 4. Has a minimal immunological impact.
- system

Probiotic therapy

1. Probiotics are generally dispensed as dietary supplements.
2. Hardly a dramatic and long-term change in the microbiota.
3. Probiotics are able to exert a beneficial effect even without permanently colonising the site.
4. Exerts beneficial effects by influencing the immune

Administration of Probiotic⁽¹⁶⁾

Different means of probiotic administration for oral health purpose are

- A culture concentrate added to a beverage or fruit (such as fruit juice)
- Inoculated into prebiotic fibers
- Inoculants into a milk-based food (diary products such as milk, milk drink, yoghurt)
- Yoghurt drink, cheese, kefir, biodrink
- As concentrated and dried cells packaged as dietary supplements (nondairy products)
- Such as powder, capsule, gelatin tablets.

Probiotics are encapsulated such that they rehydrate at specific sites, and encasing prebiotics in nano-aggregates that protect against stomach acid and deliver their payload when the pH reaches 7.4.⁽¹⁷⁾

Mode of action of probiotics :

Some of the hypothetical mechanism of probiotics action in the oral cavity is by⁽¹⁸⁾

Direct action :

1. Production of antimicrobial substances⁽¹⁹⁾(Silva et al , 1987, Ouwehand, 1998)⁽¹⁴⁾
 - a. Organic acids
 - b. Hydrogen peroxide
 - c. Bacteriocins
2. Binding in oral cavity⁽⁴⁾
 - a. Compete with pathogens for adhesion sites
 - b. Involvement in metabolism of substrates (competing with oral microorganism for substrates available)
3. Lactobacilli maintains the microecological balance in the oral cavity.

Indirect action :

1. Immunomodulatory⁽²⁰⁾(Kato et al, 1983)
 - a. Stimulate nonspecific immunity
 - b. Modulate humoral and cellular immune response
 - c. Effects local immunity
 - d. Regulation of mucosal immune system: reduces pathogen induced production of proinflammatory cytokines
 - e. Produces antioxidants or acts as antioxidants
2. Modify oral conditions
 - a. Modulating pH
 - b. Modification of oxidation reduction potential
 - c. Upregulation of intestinal barrier integrity and mucin production.

Probiotics and Oral health :

The oral cavity is a complex ecosystem, which has rich and diverse micro biota in it. The wide range of pH, nutrient availability, shedding and non shedding surfaces, salivary and crevicular fluids are the contributing elements. All these metabolic activity is in the state of homeostasis in normal condition. Any change in the environment disturb the homeostasis and lead to exogenous and endogenous infections.

More than 700 species of microflora are detected in the oral cavity. Tongue is densely populated with microbes. (Socransky&Haffajee, 2005; Kolenbrander et al 2006)⁽¹⁴⁾

Probiotics have many positive influences in creating better oral health.⁽²¹⁾ The probiotics can be used to prevent and cure various oral diseases due to its characteristic features such as its capacity to adhere to and colonize on various surfaces of the oral cavity.^(22,23) Sookkhee and colleagues⁽²⁴⁾ isolated 3790 strains of lactic acid bacteria from 130 individuals. They identified that bacteria such

as *Lactobacillus paracasei* ssp. *Paracasei* and *L. rhamnosus* can antagonize oral pathogens such as *Streptococcus mutans* and *Porphyromonas gingivalis*.

Probiotics and gingivitis-

Krasse and colleagues⁽²⁵⁾ assessed the beneficial effect of *L. reuteri* against gingivitis. After 14 days of ingesting the probiotic incorporated into chewing gums, the oral cavity of patients with a moderate to severe form of gingivitis had been reduced and the plaque index had been reduced. These results were suggested due to 3 plausible possibilities-*L. reuteri* is known to secrete 2 bacteriocins, reuterin and reutericyclin, that inhibit the growth of a wide variety of pathogens, second *L. reuteri* has a strong capacity to adhere to host tissues and thereby competing with pathogenic bacteria and third the recognized anti-inflammatory effects of *L. reuteri* on the intestinal mucosa, leading to inhibition of secretion of proinflammatory cytokines.

Probiotics and periodontitis-

P. gingivalis, *A. actinomycetemcomitans*, *T. denticola* and *T. forsythia* are the main periopathogens.

Riccia and colleagues recently studied the anti-inflammatory effects of *Lactobacillus brevis* in a group of patients with chronic periodontitis. The treatment for 4 days, led to improvement in the plaque index, gingival index, bleeding on probing for all patients. The authors suggested that the beneficial effect of *L. brevis* may be due to its capacity to prevent the production of nitric oxide and consequently, the release of PGE₂ and the activation of MMPs induced by the nitric oxide.⁽²⁶⁾ According to Koll-Klais et al, high levels of *Lactobacillus reuteri* and *Lactobacillus brevis* in microbiota caused an 82% and 65% inhibition in *Porphyromonas gingivalis* and *Prevotella intermedia* growth, respectively.⁽²⁷⁾

Hillman et al reported *S. oralis* and *S. uberis* to inhibit growth of pathogens in laboratory and animal models. They suggested that in the absence of these bacteria, periodontal tissues become prone to several periodontal diseases. Shimazaki and colleagues used epidemiological data to assess the relationship between periodontal health and the consumption of dairy products such as cheese, milk and yoghurt. They found that individuals who consumed yoghurt and beverages high in lactic acid exhibited lower probing depths and less loss of clinical attachment than individuals who consumed few of these dairy products.⁽²⁸⁾

Teughels et al reported that the subgingival application of bacterial mixture of *Streptococcus sanguinis*, *S. Salivarius* and *S. mitis* significantly suppressed the recolonization of *Porphyromonas* and *Prevotella intermedia*.⁽²⁹⁾ Harini and Aneundi, 2010 reported that use of probiotic mouth was reduced the incidence of plaque formation and gingivitis in 6-8 year old children.⁽¹⁴⁾ Grudianov et al applied a periodontal dressing comprised of collagen and *L. casei* in periodontally treated patients. They reported that probiotics were effective in normalisation of microbiota in periodontitis and gingivitis patients when compared with a control group.⁽³⁰⁾

Probiotics and halitosis-

Halitosis (bad breath) is believed to affect a large proportion of the population. Reports of its occurrence date back to ancient times. Documentation of early Egyptian and other cultures indicate that people were aware of this problem and sweetening their breath with various herbs and spices, a practice that continues to this day.⁽³¹⁾ It has a significant socio-economic impact and may reveal an underlying disease.⁽³²⁾

According to Scully and Greenman 2008,⁽¹⁴⁾ the most common reason for halitosis is the imbalance of the normal microflora of the oral cavity. Kazor

et al reported that *L. salivarius* was the most predominant species detected in healthy subjects, where it was detected in only one of the subjects with halitosis at very low levels.⁽³²⁾

Halitosis is caused by a number of volatiles and most of its etiological factors are present in oropharynx. *F. nucleatum*, *P. intermedia*, *P. gingivalis* and *T. denticola* are shown to produce "Volatile Sulphur Compunds" responsible for halitosis.⁽²⁾ *Streptococcus salivarius* is frequently detected in oral cavity of individuals without halitosis and is therefore considered as a commensal bacterium of the oral cavity. These bacteria's produce bacteriocins which contribute in reducing the no. of bacterias producing Volatile sulphur compounds (VSC) diagnosed with halitosis.

Kang et al reported that *W. cibaria* has the capacity to coaggregate with *F. nucleatum*. It sticks on to epithelial cells and produce hydrogen peroxide as well as bacteriocin which inhibits the production of *F. nucleatum*.⁽³³⁾ Burton et al reported that reduction of oral VSCs levels were seen after administration of *S. salivarius* K12. They had administered the probiotics in form of lozenge for 3 days after chlorhexidine mouthrinse.⁽³⁴⁾

Probiotics and dental caries-

Dental caries is characterized with loss of enamel (demineralization) due to bacterial processes.⁽³⁵⁾ This leads to the formation of cavities on the surface of the tooth. It is multifactorial disease. In caries, there is an increase in acidogenic. Changes in pH leads to changes in the oral microflora results in an overgrowth of various bacteria including *Streptococcus sorbinus*, *Streptococcus mutans* and *Porphyromonas gingivalis* which are recognized as the primary cause of dental caries.

Dental caries is one of the most common disease in the world- second only to common cold⁽³⁶⁾ and can lead to pain, tooth loss & infection.

Dental caries affects the majority of adults and 60-90% of school children.⁽³⁷⁾ First randomized, double blind, placebo-controlled intervention study for examining the effect of milk containing *L. rhamnosus* GG on caries was conducted and found to reduce *S. mutans* count at the end of the trial. Calgar et al in 2006 investigated effect of probiotic bacterium *L. reuteri* and found reduced levels of salivary mutans streptococci in young adults.⁽⁶⁾ Comelli et al found that *L. lactis* was able to modulate the growth of the oral bacteria, and in particular to diminish the colonization of *Streptococcus oralis*, *Veillonelladispar*, *Actinomycesnaeslundii* and of the cariogenic *S. sobrinus*.⁽²⁹⁾

Montalto et al administered a probiotic preparation containing seven live probiotic lactobacilli in capsule or liquid form and found a statistically significant increase in the salivary counts of lactobacilli compared to baseline, while the counts of *S. mutans* remained unaffected. This is the only clinical trial presenting lack of probiotic effect on *S. mutans* level. This may be due to the competition for binding sites in oral biofilms.⁽³⁸⁾

Kang et al (2006) found that a *Weissellacibaria* produced water-soluble polymer from sucrose which inhibits the formation of *S. mutans* biofilm.⁽³³⁾ Calgar et al (2007) evaluated the effect of xylitol and probiotic chewing gums on salivary mutans streptococci and lactobacilli and concluded that daily chewing on gums containing xylitol and probiotics reduced the levels of salivary mutans streptococci and lactobacilli.⁽³⁹⁾ Nase et al administered *L. rhamnosus* GG via milk for 7 months and found lower incidence of dental caries and lower *S. mutans* levels.⁽⁴⁰⁾

Ahola et al studied the incidence of caries and levels of *S. mutans* after administration of *L. rhamnosus* GG and *L. rhamnosus* LC 705 through cheese for 3 weeks. Their study showed lower

reduction of the *S. mutans* level and caries risk reduction. ⁽⁴¹⁾Chung et al, 2004 studied effect of *L. fermentum* which was found in the saliva of healthy children. They found that this strain significantly inhibited the formation of the insoluble glucan produced by *S. mutans*. It did not affect the multiplication of this pathogenic strain, but inhibited the adherence onto the walls. ⁽⁴²⁾

Nikawa et al examined the effects of *L. reuteri* containing yogurt in a group of 40 dental hygienist. *L. reuteri* is an obligate heterofermentative resident in the GIT reported to produce compounds that exhibit antagonistic activity such as reuterin⁽⁴³⁾ and reutericyclin⁽⁴⁴⁾ which are water soluble, broad spectrum antimicrobials, effective over a wide pH range. They found that consuming *L. reuteri* containing yogurt daily for 2 weeks significantly reduced the *S. mutans* levels in saliva by 0.5 log 10 colony forming units. These results were found atleast upto 2 weeks after discontinuing the consumption. ⁽⁴⁵⁾

Probiotics and orthodontics-

Fixed appliances have always been blamed to harbour pathogens leading to increase incidences of periodontal diseases and white spot lesions. Ahn SJ et al in their prevalence study using PCR found higher incidence of cariogenic streptococci strain on the brackets bonded on the incisors. ⁽⁴⁶⁾

Research are undertaken to study the effect of probiotic consumption in orthodontic patients.

Cildir SK et al studied the changes in microbial flora during daily consumption of yoghurt containing probiotic bacteria in 24 healthy adolescent patients undergoing orthodontic treatment and found lowered count of salivary *mutans streptococci* which may than lead to lower risk of white lesion formation. ⁽⁴⁷⁾

ChontiraSaetang et al studied the effect of powdered milk containing *Lactobacillus paracasei* on salivary *mutans streptococci* in the

orthodontically treated Cleft patients. They found statistically lowered salivary levels of *mutans streptococci*. ⁽⁴⁸⁾

Probiotic dosage

The dosage of probiotics (No. of micro-organisms) to be ingested for adequate beneficial effects has yet not been clear. Typically, a probiotic should contain several billion microorganisms. Probiotics in the form of gelatin capsules, powder or suspensions can be administered orally. Usually a combination of prebiotics and probiotics is administered. 0.48 billion spores of *Lactobacillus bifidum*, *Streptococcus thermophiles* and 0.10 billion spores of *Saccharomyces boulardi* along with 300 mg of fructo-oligosaccharides, is given as single daily dose.

The best means of administering probiotics is yet to be studied and will need randomized controlled trails. The dosage of probiotic administration in each indication needs to be defined. ⁽³¹⁾

Probiotic stay in the oral cavity:

Most of the studies on probiotics have been conducted in adults and none suggested permanent installation of probiotics in oral cavity. It is therefore, necessary to carry out further research on infants. Horz et al (2007) ⁽¹⁴⁾ assessed the Latency period of probiotic *S. salivarius* in several oral cavity areas in a 35 day follow up. His study showed that after 8 days of treatment withdrawal there was gradual reduction in *S. salivarius*. However they were found in oral cavity for more than 3 weeks.

Side effects of probiotics.

Probiotics like *Lactobacilli*, *bifidobacteria* and *lactococci* have generally been regarded as safe. There are other probiotic organisms, such as *Enterococcus*, *Bacillus*, and other spore forming bacteria, as well as *streptococci*, that are not generally regarded as safe. ⁽⁴⁹⁾

It appears that most people do not experience side effects from probiotics or have only mild gastrointestinal side effects such as gas. But there have been some case reports of serious adverse effects and research on safety is ongoing. However, the data on safety, particularly long-term safety, are limited, and the risk of serious side effects may be greater in people who have underlying health conditions.

The issue of safety is of special concern during the past few years due to increased probiotic supplementation in different food products. The most important area of concern with probiotic use is the risk of sepsis. Any viable microorganism is capable of causing bacteraemia, especially in patients with severe underlying disease or in those in an immunocompromised state⁽⁵⁰⁾ or infants.^(51,52)

Finally, safety issues are of paramount importance with any kind of bacteriotherapy.

Mackay et al reported a case of 67 years old male on daily dose of probiotic capsule, where development of *L. rhamnosus* endocarditis after a dental extraction with mitral regurgitation was seen.⁽⁵³⁾

Probiotic products may contain different types of probiotic bacteria and have different effects in the human body. The effects also may vary from person to person. Our understanding of probiotics is work in progress. FDA has not approved any health claims for probiotics. Before using probiotics, knowledge is must. Anyone with serious underlying health problems should be monitored closely for potential negative side effects while taking probiotics.⁽⁵⁴⁾

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.⁽⁵⁵⁾

Future research in the probiotics area⁽⁵⁶⁾

- Determine the physiological role, mechanisms of action, and extent of influence of probiotics in human health using human feeding studies. Studies on high-risk human populations for colon cancer or cancer recurrence would be a possible target for some studies.
- Validate biomarkers used for assessing probiotic function. Testing of predictions based on biomarker studies with actual results in human clinical evaluations is needed. Biomarker validation in the areas of immune system, cancer, and gut microecology is especially important. Once validated, biomarkers will be useful tools to assess dose-dependence and strain-specific responses. Biomarkers commonly used to select strains for probiotic use (adherence in tissue cultures, cholesterol assimilation, competitive exclusion of pathogens in tissue culture, inhibitor [bacteriocins, organic acids] production, lactase activity) have never been tested in controlled studies to determine if mutants without the characteristic perform any differently in clinical evaluations.
- Assess effects of probiotics on populations and activity of gut microbes. The application of gene based methods holds much promise in this field.

- Determine the role of probiotics as part of a whole food compared to isolated component.
- Improve reliability and ease of taxonomic classification of probiotic bacteria. Improve strain performance and activity.
- Conduct studies with consumers to understand how best to communicate the concept of probiotics and to determine favorable probiotic formats.
- Conduct research to improve product formats, consumer acceptance, stability, and efficacy of

probiotic-containing products.

Conclusion:

Use of probiotics for health maintenance is since long a proven fact. Probiotic has become a fascinating field opening new corridors. Science specifically dentistry is shifting from surgical approaches in the past to interceptive approaches in the present. Research on use of probiotics in dentistry is undertaken in large number in recent days. Development in this field gives hope of bringing preventive approaches in the future a reality. Hope we all with the help of good microbes (probiotics) lead the human kind to a disease free oral cavity via a natural and non invasive way.

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