Probiotics, Prebiotics and Synbiotics - A Review

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ABSTRACT

Probiotics, prebiotics and synbiotics are emerging as a fascinating field in medicine and dentistry. Probiotics are dietary supplements containing beneficial bacterias and yeast which play an important role to strengthen the immunity. Probiotics play a major role to strengthen the immunity and a important role in dentistry by creating a biofilm and helps in prevention of dental caries. Prebiotics are designed in a way to stimulate the number and activities of probiotics to improve health. Synbiotics refer to nutritional supplements combining pro and prebiotics that acts together in a synergistic manner.

Key words: Probiotics, Prebiotics, Synbiotics, Microorganisms, Oral health.

INTRODUCTION

The benefits of Probiotics have been recognized and explored for over a century.¹ Probiotic approach can be effective in selectively inhibiting oral pathogens or modulate the microbial composition of dental plaque.² Prebiotics are nondigestible dietary supplements.³ Prebiotics are designed to improve health by stimulating numbers and/or activities of probiotics like Bifidobacteria and Lactobacilli.¹ Prebiotics have been proved to be an aid to complement probiotics in the treatment of oral diseases.³ Their function is to enhance the growth and activity of beneficial organisms and simultaneously suppress the growth and activity of potentially deleterious bacteria.⁴ Synbiotics refer to nutritional supplements combining probiotics and prebiotics that are thought to act together; i.e. synergism. The potential benefits of synbiotic therapy are obvious, however, the great challenge, as is the case with probiotics and prebiotics alone, is to determine the best combination for each disease setting and each individual.¹ Probiotics and prebiotics that are thought to act together; i.e. synergism. It has been suggested that a combination of a probiotic and a prebiotic, i.e. Synbiotics might be more active than either a probiotic or prebiotic alone.¹

Probiotics

Probiotic is derived from Latin word “pro”- for and Greek word “biotic”- life.⁵ The role of fermented milk in human diet was known even in Vedic times. But, the scientific interest in this area boosted after the publication of the book entitled ‘The Prolongation of Life’ by Ellie Metchinkoff in 1908. He suggested that people should consume fermented milk containing lactobacilli to prolong their lives.⁴

At this time Henry Tissier, a French paediatrician, observed that children with diarrhoea had in their stools a low number of bacteria characterized by a peculiar, Y shaped morphology.
These bacteria were, on the contrary, abundant in healthy children (Tissier, 1906). He suggested that these bacteria could be administered to patients with diarrhoea to help restore a healthy gut flora. The works of Metchnikoff and Tissier were the first to make scientific suggestions about the probiotic use of bacteria, even if the word “probiotic” was not coined until 1960.6

The term Probiotic was first introduced by Lily and Stillwell (1965).7 The first probiotic bacteria studied were lactic acid bacteria (Fuller, 1991).8 Lactobacillae & Bifidobacterium are the main probiotics. Other probiotics are Escherichia, Enterococcus, Bacillus, Saccharomyces, Streptococcus and Propionibacteria. In 1984 Hull identified the first probiotic species, the lactobacillus acidophilus. Later in 1991, Holcombh identified bifidobacterium bifidum. WHO in 1994 described the probiotics as next most important in immune defense system following antibiotic resistance.9,10,11

### Definition of probiotics

<table>
<thead>
<tr>
<th>Author</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Lilly &amp; Stillwell, 1965</td>
<td>Substances produced by microorganisms that promote the growth of other microorganisms</td>
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<tr>
<td>Parker, 1974</td>
<td>Organisms and substances that contribute to intestinal microbial balance</td>
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<tr>
<td>Fuller, 1989</td>
<td>A live microbial feed supplement that beneficially affects the host animal by improving its intestinal microbial balance</td>
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<tr>
<td>Havenaar &amp; Huis Int</td>
<td>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</td>
</tr>
<tr>
<td>Veld, 1992</td>
<td>Living microorganisms that, upon ingestion in certain numbers, exert health benefits beyond inherent basic nutrition</td>
</tr>
<tr>
<td>Schaafsma, 1996</td>
<td>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.</td>
</tr>
<tr>
<td>Naidu et al, 1999</td>
<td>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</td>
</tr>
<tr>
<td>Schrezemeir &amp; De Vrese, 2001</td>
<td>Live microorganisms that, when administered in adequate amounts, confer a health benefit to the host</td>
</tr>
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### Composition of probiotics

Probiotics, which are regulated as dietary supplements and foods, consist of yeast or bacteria. They are available as capsules, gels, pastes, tablets, packets, liquids, or powders, and are contained in various fermented foods, most commonly yogurt or dairy drinks. Probiotic products may contain a single microorganism or a mixture of several species. Probiotics can be bacteria, moulds, yeast. But most probiotics are bacteria. Among bacteria, lactic acid bacteria are more popular.18

### Criteria for probiotics

Fuller in 1989 listed the following as features of a good probiotic.

1) A strain, which is capable of exerting a beneficial effect on the host animal, e.g. increased growth or resistance to disease.
2) Non-pathogenic and non-toxic.
3) Present as viable cells, preferably in large numbers.
4) Stable and capable of remaining viable for
Currently used probiotics

Bacteria
- Lactobacillus: acidophilus, sporogenes, plantarum, rhamnosum, delbrueck, reuteri, fermentum, lactus, cellubiosus, brevis
- Bifidobacterium: bifidum, infantis, longum, thermophilum, animalis
- Streptococcus: lactis, cremoris, alivarius, intermedius
- Leuconostoc
- Pediococcus
- Propionibacterium
- Bacillus
- Enterococcus
- E. Faecium

Yeast and moulds
- cerevisiae
- niger
- oryzue
- Pintolopesii
- Sacharomyces boulardii

Therapeutic actions of probiotics
1. Reduces progression of AIDS.
2. Enhancement of calcium absorption.
3. Competition against harmful microorganisms including Candida, preventing colonisation of pathogens through the production of inhibitory substances including acids and hydrogen peroxide and natural antibiotics.
4. Reduction in liver toxicity.
5. Enhancement of peristalsis, digestion, regularity and re-absorption of nutrients, in infants, promotion of healthy digestive tract colonisation.
6. Enhancement and balance of oestrogen levels, prevention of osteoporosis through increased calcium uptake.
7. Enhancement of vitamin status (B, K), digestion of proteins, fats, carbohydrates.
8. Increased resistance to infectious diseases (Perdigon et al, 1995; Arunachalam et al, 2000)
11. Reduction in blood pressure and regulation of hypertension, serum cholesterol concentration (Fuller, 1997)
12. Reduction in allergy (Bengmark, 2000), respiratory infections (Hatakka et al, 2001)

Probiotic products
- A culture concentrate added to a beverage or food (such as a fruit juice).
- Inoculated into prebiotic fibers.
- Inoculants into a milk-based food (dairy products such as milk, milk drink, yoghurt).
- As concentrated and dried cells packaged as dietary supplements (non-dairy products).

Mechanism of action of probiotics
Possible modes of action of probiotic

Suppression of viable count by
(a) Production of antibacterial compounds
(b) Competition for nutrients
(c) Competition for adhesion sites

Alteration of microbial metabolism
(a) Increased enzyme activity
(b) Decreased enzyme activity

Stimulation of immunity
(a) Increased antibody levels
(b) Increased macrophage activity

Role of probiotics in dentistry
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:
· Direct interaction in dental plaque
· Involvement in binding of oral microorganisms 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

Side effects and safety aspects of probiotics
Probiotics may theoretically be responsible for four types of side effects: systemic infections, deleterious metabolic activities, excessive immune stimulation in susceptible individuals, and gene transfer. Cases of infection due to lactobacilli and bifidobacterium are extremely rare and are estimated to represent 0.05 - 0.4% of cases of infective endocarditis and bacteraemia.

In general gas & bloating is one of the side effects of eating probiotic supplement. Probiotic can heighten & stimulate the immune system. So there is a great chance that people with underlying health issues can catch infections caused by probiotics. 

Till date no pathogenic or virulence properties have been found for Lactobacilli, Bifidobacterium or Lactococci (Aguirre & Collins 1993).

How to assess the safety of probiotic products?
Three approaches can be used to assess the safety:
1) Studies on the intrinsic properties of the strain.
2) Studies on the pharmacokinetics of the strain.
3) Studies searching for interactions between the strain and the host.

Disadvantages of probiotics
Liquid preparations like yogurt have some major disadvantages

i) short shelf- life,
ii) bacteria damaged by pasteurization and/or centrifugation
iii) use of additives and preservatives
iv) difficult transport and storage because of its bulky nature
v) use of normally only one or more strains of bacteria (multiple strains probiotics are more potent)
vi) damage by stomach acidity
vii) refrigeration requirement.

### Different means of probiotic administration for oral health purposes

<table>
<thead>
<tr>
<th>Author</th>
<th>Vehicle</th>
<th>Strain</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caglar E et al., 2005</td>
<td>Straw, tablet</td>
<td>L. reuteri ATCC 55</td>
<td>S. mutans level reduction</td>
</tr>
<tr>
<td>J.P. Burton et al., 2006</td>
<td>Lozenge</td>
<td>S. salivarius</td>
<td>Reduces oral VSC (Volatile sulphur compounds) levels</td>
</tr>
<tr>
<td>K. Hatakka et al., 2007</td>
<td>Cheese</td>
<td>L. rhamnosus GG; Prorionibacterium JS</td>
<td>Reduced risk of high yeast counts and Hyposalivation</td>
</tr>
<tr>
<td>Kang et al., 2005</td>
<td>Rinse solution</td>
<td>W. cibaria</td>
<td>Reduction of VSC</td>
</tr>
<tr>
<td>Montalto M et al., 2004</td>
<td>Capsule, liquid</td>
<td>L. sporogenes, L. bulgaricus, L. thermophilus, L. acidophilus, L. casei</td>
<td>Increased salivary counts of lactobacilli without significant decrease in S. mutans counts</td>
</tr>
<tr>
<td>Yli-Knuuttila H et al., 2006</td>
<td>Yogurt drink</td>
<td>L. rhamnosus GG</td>
<td>Temporary oral cavity colonization</td>
</tr>
</tbody>
</table>
Freeze dried powder probiotics have some disadvantages such as i) bacteria damage by freeze drying ii) short powder shelf life iii) upon absorption of water by powder, bacteria become activated and die iv) poor adherence, colonization and survival in the gut due to damage caused by freeze drying v) Probiotics may become weakened due to addition of stabilizers and preservatives.

Prebiotics

The bacterial population of the human gastrointestinal tract constitutes an enormously complex ecosystem. Most of these organisms are beneficial (e.g. bifidobacterium and lactobacillus) but some are harmful (e.g. Salmonella species, Helicobacter pylori, Clostridium perfringens). Some dietary substances, the so-called prebiotics can favor the growth of these beneficial bacteria over that of harmful ones. 

Prebiotics are defined as non-digestible or low-digestible food ingredients that benefit the host organism by selectively stimulating the growth or activity of one or a limited number of probiotic bacteria in the colon (Crittenden & Playne, 1996; Dimer & Gibson, 1998; Zimmer & Gibson, 1998; Manning & Gibson, 2004).32

Classification of prebiotics

Based on the number of monomers linked together, prebiotics can be classified:
- Disaccharides
- Oligosaccharides (3-10 monomers)
- Polysaccharides

Commonly used prebiotics

Lactulose, galacto-oligosaccharides, fructo-oligosaccharides, inulin and its hydrolysates, malto-oligosaccharides, and transgalacto-oligosaccharides. The main end products of carbohydrate metabolism are short-chained fatty acids, namely acetate, butyrate and propionate, which are further used by the host organism as an energy source.32

Prebiotic products

Prebiotic oligosaccharides can be produced in three different ways: by extraction from plant materials, microbiological synthesis or enzymatic synthesis, and enzymatic hydrolysis of polysaccharides (Crittenden & Playne, 1996; Gulewicz et al., 2003).3 Prebiotics are naturally found plenty in certain fruits like bananas, asparagus, garlic, tomato and onion wheat.

Criteria for prebiotics33

1) Neither hydrolyzed nor absorbed in the upper part of the gastrointestinal tract
2) A selective substrate for one or a limited number of beneficial bacteria commensal to the colon, which are stimulated to grow and/or are metabolically activated
3) Consequently, be able to alter the colonic flora in favour of a healthier composition
4) Induce luminal or systemic effects that are beneficial to the host health.

Therapeutic actions of prebiotics35

The positive effects of prebiotics include antimicrobial, anticarcinogenic, hypolipidemic, glucosemodulatory and anti-osteoporotic activities. They may be used for the treatment of constipation, hepatic encephalopathy and inflammatory bowel disease. They can protect against some intestinal pathogens and may exert favourable lipid effects as well as have some benefit in diabetes mellitus. Besides, prebiotics also have a very important role in improving mineral absorption and balance, for instance, they may enhance the colonic absorption of some minerals.

Benefits of prebiotic supplemented formulas3

Clearly, breast milk is the “gold standard” for neonatal and infant nutrition and is recommended by the American Academy of Pediatrics as the nutrition. Use of prebiotic-supplemented infant formulas may have benefits for the infant who does not receive mother’s milk. The benefits are,

1) Higher counts of Bifidobacteria by 4 weeks of age. An increased number of Bifidobacteria is associated with lower numbers of intestinal pathogens.
2) The pattern of bifidobacterial sub-species is similar to the pattern of the breast-fed infant.
3) Prebiotic formulas result in stool pH and short-chain fatty acid patterns similar to the breast-fed infant.
4) Stool frequency and consistency is more like the breast-fed infant.
5) Reduced allergic reaction (atopic dermatitis) and reduced URI in the first year of life.
6) Fewer episodes of acute diarrhoea.
7) Prebiotic-supplemented formula is easily tolerated, with no difference in growth patterns.

### Studies using prebiotic-supplemented formulas

<table>
<thead>
<tr>
<th>Study</th>
<th>Prebiotic &amp; quantity</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Bruzzese et al 2006</td>
<td>GOS/FOS or control</td>
<td>Infants on prebiotic formula had fewer episodes of acute diarrhea, fewer upper respiratory infections</td>
</tr>
<tr>
<td>Moro et al 2006</td>
<td>0.8 g/dL of GOS, FOS and control hydrolysed protein formula</td>
<td>Incidence of atopic dermatitis significantly reduced in the infant fed prebiotic formula</td>
</tr>
<tr>
<td>Costalos et al 2007</td>
<td>0.4 g/dL of GOS and FOS and control</td>
<td>Prebiotic formula well tolerated, normal growth trend toward higher percentage of Bifidobacterium and lower percentage of E. coli in stool, suppresses Clostridium in stool</td>
</tr>
<tr>
<td>Ziegler et al 2007</td>
<td>0.4 g/dL PDX,GOS or 0.8 g/dL PDX,GOS and LOS or control</td>
<td>Looser stools on either prebiotic formula, more adverse events: diarrhoea, eczema, in supplemented groups</td>
</tr>
<tr>
<td>Scholtens et al 2008</td>
<td>0.6 g/dL FOS and GOS</td>
<td>At 27 weeks the concentration of secretory IgA was higher in prebiotic group than control, also Bifidobacterium percentage higher than control and Clostridium lower</td>
</tr>
<tr>
<td>Arslonaglu et al 2008</td>
<td>0.8 g/dL GOS/FOS</td>
<td>Formula fed for first six months; follow up for 2 years. Prebiotic group had significantly lower allergic symptoms – atopic dermatitis, wheezing, urticaria, fewer upper respiratory infections than controls during the first 2 years</td>
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</tbody>
</table>

FAGA—full-term appropriate for gestational age; GOS—galacto-oligosaccharides; FOS—fructo-oligosaccharides; PDX—Polydextrose; LOS—Lactulose.

### Relationship between prebiotics and probiotics

Prebiotics when combined with probiotics have many advantages. Basically, prebiotics selectively stimulate the growth of probiotics, which is dose and strain dependent. Prebiotics serve as a selective growth substrate for the probiotics strain during fermentation, during the period of storage, or during its passage through the gut. These two combinations implant live microbial dietary supplements and create a congenial environment for their survival in gut flora. Thereby, this environment in gut flora improves healthy microbial balance. So, the combination of prebiotics and probiotics may have additive and synergistic effect in providing better oral health conditions. An essential requirement for a microorganism to be an oral probiotic is its ability to adhere to and colonize surfaces in the oral cavity. Microorganisms generally considered as probiotics may not have oral cavity as their inherent habitat and, subsequently, their possibility to confer benefit on oral health is then questionable. Probiotics and
Mode of action of prebiotics and health benefits in humans and animals

**Consumption of a prebiotic compound/food/feed additive**
- Resistance to digestion in the upper GI tract
- Entry to the colon
- Selective fermentation by beneficial microbiota
- Increased numbers of beneficial bacteria, reduced numbers of pathogens/putrefactive bacteria

**Production of short chain fatty acids**
- Effects on bowel function
- Increased resistance to infections
- Increased mineral bioavailability
- Effects on satiety/appetite in humans

**Immunomodulatory effects**
- Reduced risk of colon cancer
- Improved gut and bone health
- Reduced risk of obesity/metabolic syndrome in humans
- Reduced risk of obesity/metabolic syndrome in humans

**Comparison of Probiotics Vs Prebiotics**
- Probiotics:
  - Specific bifidobacteria and lactobacilli
  - Bifidobacteria directly help promote a balanced intestinal flora similar to breastfed infants
  - Supports gut barrier function
- Prebiotics:
  - Fructo-oligosaccharides
  - Galacto-oligosaccharides
  - Indirectly stimulates growth of multiple bacterial species including some bifidobacteria, if already present
  - Supports gut barrier function in the colon, may support and modulate immune function
prebiotics could affect the host in combination by synergistic action.\textsuperscript{42}

**Synbiotics**

A synbiotic has been defined as ‘a mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and implantation of live microbial dietary supplements in the GI tract, by selectively stimulating the growth and/or activating the metabolism of one or a limited number of health-promoting bacteria, and thus improving host welfare’ (Gibson & Roberfroid, 1995).\textsuperscript{28}

The main reason for using a synbiotic is that a true probiotic, without its prebiotic food, does not survive well in the digestive system. Without the necessary food source for the probiotic, it will have a greater intolerance for oxygen, low pH, and temperature. As prebiotics provides a great place for probiotics to thrive, the population of these good bacteria is known to preserve. Studies have shown that by harnessing both the benefits of these prebiotics and probiotics into synergy, the number of good bacteria in the digestive systems increased many folds for the betterment of our health.\textsuperscript{31}

Synbiotics work in two ways i) by improving the viability of probiotics and ii) by delivering specific health benefits.\textsuperscript{31} The intake of a synbiotic food leads to a modulation of the gut metabolic activities with a maintenance of the gut biostructure. In particular, the significant increase of short chain fatty acids, ketones, carbon disulfide and methyl acetate following the feeding period suggested potential health promoting effects of the synbiotic food.\textsuperscript{43}

**Therapeutic actions of synbiotics**

For therapeutic efficacy, the desirable characteristics of synbiotics include antimicrobial and anticarcinogenic qualities, antidiarrheal aspects, antiallergenic qualities, osteoporosis prevention, reduction in serum fats and blood sugars, regulation of the immune system, and treating liver-related brain dysfunction.\textsuperscript{4}

**CONCLUSION**

The use of probiotics for use in oral care applications is gaining momentum. There is increasing evidence that the use of existing probiotic strains can deliver oral health benefits. Further work will be needed to fully optimise and quantify the extent of this benefit. In parallel, the potential of prebiotics to maintain and enhance the benefits provided by the resident oral microbiota will be investigated. However, whether considering probiotics or prebiotics, it will be essential to develop an understanding of the broad ecological changes induced in the mouth by their ingestion and the long-term consequences of their use on oral health and disease.\textsuperscript{44}

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