Appraisal of Probiotics and Prebiotics in Gastrointestinal Infections

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Abstract

A probiotic is a viable microbial dietary supplement that beneficially affects the host through its effects in the gastrointestinal tract (GIT). Probiotics are widely used to prepare fermented dairy and non-dairy products. Several health-related effects associated with the intake of probiotics, including alleviation of lactose intolerance, immune enhancement, control of different kinds of diarrhea and colon cancer etc. have been reported in human studies. Prebiotics are nondigestible food ingredients that benefit the host by selectively stimulating the growth or activity of one or a limited number of microorganisms in the colon. Work with prebiotics has been limited, only several oligosaccharides and inulin-type fructans have generated some research-based effective data. However, the common understanding about the utility of prebiotics is that they benefit our intestinal ecosystem, improve immunity and overall health. At present, claims about reduction of disease risk are only tentative and further research is needed. The combination of probiotics and prebiotics in a synbiotic has not also been studied well. This combination might improve the survival of the bacteria crossing the upper part of GIT, thereby enhancing their effect in the large bowel. In addition, their effects might be additive or even synergistic. Several research groups are evolved in India to implement the age-old system into modern practice. Fundamental research with clinical trials is there with the growth of Probiotic market in India. Present trends of research hopefully will ensure the implementation of its potentials towards the benefit of life extensively.

Review

General Concept:

About a century ago, India won her first Noble prize by the work of Viswakavi Rabindranath Tagore in the year 1913. In his several novels, he mentioned about the curd or dahi or specially misti dahi and sketched a character of a curd peddler, in: Dakghar (Post office). Almost during the same period, Elie Metchnikoff received Noble prize for his discovery of phagocytosis in 1908, and devoted last decade of his life investigating means of increasing human longivity and advocating the consumption of lactic acid producing bacteria (Shruthy et al., 2011). Again our Vedic Sanskriti had recognized the role of diet in health and nutrition and now after several thousand of years, we are proving and improving the linkages among health, nutrition and diet with science based investigation. The usage of “panchamrit” in Hindu rituals is to be considered as the oldest functional food or synbiotic food in the history of mankind. The utility of curd has been described in Rig-Veda also. The Dadhi made out of cow’s milk has been described as a likeable food not only for the humans but of gods as well. The following mantra from Rig-Veda (10-179-3) aptly describes the nutritional qualities of “Dadhi” or curd (made from cow’s milk):

“Shratam manya oodh nishrat magnow sushraatam manye tadyate naviyah madhyen dinasaya sevanasya dadhana pivender vajrinpu rukunjushanah”.

However, lack of written documents and scientific evidence kept western world unaware and unnoticed until the publication of book, “Prolongation of life” in 1907 by Elie Metchnikoff.

Dahi or Dachi or Doi or Tahri or Perugu or Mosaru or Thayir are the acronyms for curd or yogurt in India. The Indian economy had been agriculture-based since the Vedic civilization. Cow and land were the sources of major economy. Almost all the oldest documents and mythological inscriptions were cow-centric. Right from the day of Lord Krishna to the modern age, milk, and thousands of milk-products like curd, cream, butter, lassi, paneer, sandesh, rasogolla, ksheer; sreekhand etc. are in common use regularly. Specially, curd is a very essential and regular food item in India with particular reference to south India. The curd is prepared in India by natural contamination and fermentation. Besides milk, other indigenous fermented foods have been prepared and consumed for thousands of years and are strongly linked to culture and tradition. In the Indian subcontinent,
making use of fermented food and beverages using local food crops and other biological resources are very common (Roy et al., 2004). But the nature of products and the base material vary from region to region. One can contemplate that people are using microorganisms, unknowingly for varied purposes. Further, such kind of undocumented knowledge of traditional systems is in the danger of extinction due to various causes. The contaminants may be yeast or/and bacteria. The fermented food and beverages contain microorganisms those may or may not be beneficial to health, but are generally regarded as safe (GRAS). Again, the beneficial microbes are called probiotics with special characteristics. The metabolic ingredients which support the growth of probiotics are termed as prebiotics. Together probiotics and prebiotics constitute the functional food, called synbiotics (Bagad et al., 2012).

The scientific understanding of probiotics and their potential for preventing and treating health conditions is moving ahead. The effectiveness of probiotics is strain-specific, and each strain may contribute to host health through different mechanisms. Pathogen inhibition by probiotics may provide significant human health benefits. Many reports indicate that probiotics can affect innate immunity and also protect against pathogens by decreasing pathogenic adherence or by production of acids or bacteriocins (Kumari et al., 2011). The most usual application of probiotic microorganisms is for the prevention or therapy of gastro intestinal disorders such as irritable bowel syndrome (Cui and Hu, 2012; Murakami et al., 2012), colitis (Rodrigues et al., 2012), colon cancer (Denipote et al., 2010; Wollowski et al., 2001) and most importantly diarrhoea (Boyle et al., 2006; Cremonini and Videlock, 2012). Several clinical trials have evaluated their effective use in the prevention and treatment of infectious gastro-intestinal (GI) diseases or disturbances happened in the normal micro-flora. The ideal probiotic is one that remains viable in sufficient number by adhering to the intestinal epithelium to confer a significant health benefit (Kumari et al., 2011). In the last three decades, scientists have gathered plenty of evidences of health and nutritional benefits of probiotics. As a result many global companies including India participated in the manufacturing of several different nutraceuticals and pharmaceuticals to offer health benefits to society.

2. Introduction to probiotics, prebiotics, synbiotics

“Let food be thy medicine and medicine thy food”, the age old quote by Hippocrates is certainly the tenet of today. The growing interest in understanding the role of food in human health has moved from the primary role of food as a source of energy to the more subtle action of biologically active food components on human health. ‘Probiotics’ has been defined by an expert committee as “living organisms, which upon ingestion exerts health benefits beyond inherent general nutrition”. FAO has defined it as “live microorganisms which when administered in adequate amounts confer a health benefit on the host”. Probiotics commonly stem from the category of Lactic acid bacteria (LAB). LAB are Gram positive, non-spore forming, catalase negative, acid tolerant and strictly fermentative with lactic acid as the major end product during sugar fermentation (homo- or hetero-fermentative). LAB with probiotic potentials are known to exert positive influence on host health and physiology. The physiological effects include the production of antibacterial substances, maintenance of healthy microflora, reduction of cholesterol level in the blood (Starovoitova et al., 2012), stimulation of immune functions and the removal of carcinogens (Boyle et al., 2006; Rupa and Mine, 2012). At present probiotic bacteria are widely used in human and animal nutrition because they beneficially influence the balance of the intestinal flora of the host (Kumari et al., 2011). Implementation of probiotics is intended to reduce the use of antibiotics, with a proven low risk of inducing or being associated with the etiology of disease (Szajewska, et al., 2006).

Mahatma Gandhi advocated the virtues of fermented milk and milk products in his book “The Diet Reform”. The therapeutic property of curd is due to the probiotic bacteria present in them. Promising probiotic microorganisms come under the genera Lactobacillus and Bifidobacterium. In general, LAB are food-grade organisms witnessing a long history of safe use and are categorised as GRAS for human consumption. But not all curd bacteria may have the probiotic potentials and may not be as good as it is labeled with yogurt. To address the fact that how far curds we consume are probiotic, we performed a study for two years which revealed that 10 of 20 samples (50%) had lactic acid bacteria and only two of LAB positive curds (10%) had the probiotic strains of Lactobacillus spp. Isolated strains showed several characteristics of being a good probiotic. Strains were acid resistant, bile salt tolerant, antibacterial, and antagonistic by slow acidification and antimicrobial production, and adherent (Shruthy et al., 2011).

Dahi or curd is a regular food component of South India and has been documented well for its beneficial effects. It is the semisolid product obtained from pasteurized or boiled cow/buffalo milk by souring natural or otherwise by a harmless lactic acid or other
bacterial culture. Unlike yoghurt which involves the use of specific symbiotic/mixed culture of *Lactobacillus bulgaricus* and *Streptococcus thermophilus*, curd contains a mixture various strains of LAB or yeast or combination of both. Thus the quality of dahi may vary with the type of starter culture used. Otherwise the mode of preparation is almost similar to yoghurt. Poor quality milk, unhygienic practices associated with the preparation and the use of wild type of starter culture give rise to poor grade dahi having less shelf-life. They may not have the probiotic potentials and may not be as good as yoghurt.

### 2.1. Probiotics

Probiotics can be bacteria, moulds or yeast. But most probiotics are lactic acid bacteria consist of a number of heterogenous bacterial genera within the phylum Firmicutes. The genera *Carnobacterium*, *Enterococcus*, *Lactobacillus*, *Lactococcus*, *Lactosphaera*, *Leuconostoc*, *Melissococcus*, *Oenococcus*, *Pediooccus*, *Streptococcus*, *Tetragenococcus*, *Vagococcus* and *Weissella* are recognized as LAB. Depending on the organism, metabolic pathways differ when glucose is the main carbon source: homofermentative bacteria such as *Lactococcus* and *Streptococcus* yield two lactates from one glucose molecule (Embden-Meyerhof-Parnas pathway), whereas the heterofermentative (ie. *Leuconostoc* and *Weissella*) transform a glucose molecule into lactate, ethanol and carbon dioxide (pentose phosphate pathway) (Sonomoto and Yokota, 2011). In addition, LAB produces small organic compounds that give the aroma and flavor to the fermented product. All probiotic bacteria are LAB but all LAB are not probiotic. We observed also the same phenomenon in our study (Shruthy et al., 2011). LAB has been cited to be part of human and animal microbiota. LAB constitutes an integral part of the healthy gastrointestinal (GI) microecology and is involved in the host metabolism. LAB and gut microbiota ferment various substrates like lactose, biogenic amines (Stadnik and Dolatowski, 2012) and allergenic compounds and convert into short chain fatty acids (SCFA), organic acids, gases and also synthesise enzymes, vitamins (Rossi et al., 2011), antioxidants (Gowri and Ghosh, 2011; Achuthan et al., 2012) and bacteriocins (Lasta et al., 2012). With these properties, intestinal LAB constitutes an important mechanism for the metabolism and detoxification of foreign substances entering the body. Table 1 shows the use of several microorganisms with probiotic potentials.

### Table 1

**Commonly used microorganisms as probiotics**

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**See Illustration 1**

#### 2.1.1. Characterisation of lactic acid bacteria

Phenotypic characterisation includes identification of colony morphology, gram staining, fermentation patterns or a combination of these methods. With the developing technology, molecular typing is getting more reliable to identify and differentiate bacterial strains. Many of these techniques are based on the polymerase chain reaction (PCR) using oligonucleotide primers to amplify targeted DNA fragments, to different taxonomical levels, from genus-specific differentiation, to the species-specific level, to sub-species level and also further to the strain-level. In a separate study, we isolated probiotic LAB from fermented non-milk food and characterized both phenotypically and genotypically and identified using 16S rDNA where we reported a strain, *Pediococcus sp.* (GS4), *Pom4* (Gowri and Ghosh, 2010a). In addition, PCR based Pulse-Field Gel Electrophoresis (PFGE) (De Baets et al., 2009; Strus et al., 2012) techniques, Denaturing gradient gel electrophoresis (DGGE) (Dalmacio et al., 2011) and temperature gradient gel electrophoresis (TGGE) (McCartney, 2002) analysis of faecal 16S rDNA (Gowri and Ghosh, 2010; Kumaret al, 2012) gene and its rRNA amplicons have shown to be powerful approaches in determining and monitoring the probiotic community.

#### 2.1.2. Selection criteria for probiotics

There is considerable interest in probiotics for a variety of medical conditions, and millions of people around the world consume probiotics daily for perceived health benefits. The probiotic must be able to survive extremely harsh condition found in the digestive tract of the host. This involves the ability to survive the high acidity of the stomach as well as the concentrated bile found in the small proximal of the intestine. It should persist, albeit for short periods in the gastro-intestinal tract influencing metabolic activities like cholesterol assimilation, lactase activity and vitamin production. They need to avoid the effects of peristalsis, which tend to flush out bacteria with food. The survival of probiotic organisms in the gut depends on the colonization factors they possess, organelles which enable them to resist the antibacterial mechanisms that operate in the gut. In addition to these biological criteria, probiotic intended for human use must also be commercially feasible and technologically compatible with the food manufacturing process. Thus they must be mass producible, remain viable on storage and maintain the characteristic sensory attributes of the traditional food. General biological criteria for probiotics include: acid tolerance; bile salt tolerance;
adherence to the gut mucosa; -galactosidase activity; antibiotic resistance; and antimicrobial potential.

2.1.2.1. Acid tolerance

Bacteria used as probiotic adjuncts are commonly delivered in a food system and therefore begin their journey to the lower intestinal tract via mouth. It was reported that the duration of acidic stress from entrance to release from the stomach to be 90 min which can cause cellular damage at Low pH of 1.5. However, many of the Lactobacilli isolated from the ileal samples performed well and could successfully transit the stomach and capable of reaching the intestinal environment and function effectively. The mechanism involved in acid tolerance is not known, however studies in mice models have inferred that genes induced upon exposure to acid was identified to play a role in survival of Lactobacillus strain under acidic conditions.

2.1.2.2. Bile tolerance

Bile acids are synthesised in the liver from cholesterol and are secreted from the gall bladder into the duodenum in the conjugated form (500–700 mL/d). Microbial activity in the colon brings about extensive chemical modifications (deconjugation, dehydroxylation, dehydrogenation, and deglucuronidation) to the secreted bile acids (He et al., 2012). In vitro studies have shown that both conjugated and deconjugated bile acids exhibit antibacterial activity. Several studies have shown the involvement of gene activation due to membrane stress or oxidative damage upon exposure to bile acids. Research has shown that the permeability of L. acidophilus cells was increased in the presence of bile. Increased permeability allows more substrate to enter cells so that the -galactosidase activity of the whole cell is increased.

2.1.2.3. Adhesion to the gut mucosa

Attachment is considered as a necessary first step in the colonisation of the host mucosal surfaces. HT-29 and Caco-2 cells are human intestinal cell lines expressing morphologic and physiologic characteristics of normal human enterocytes that have been exploited to elucidate the mechanisms mediating adhesion. And it explains that mechanism of adhesion is not unique for all Lactobacilli. Most Lactobacilli have been shown to adhere via binding to collagen type I and a few strains to other proteins such as fibronectin, fibrinogen and lactoferrin.

2.1.2.4. -galactosidase activity

-Galactosidase reduces lactose intolerance and is an important therapeutic property of probiotic bacteria. The prevalence of lactose intolerance varies depending on ethnic origin and is caused by the deficiency in ? Galactosidase, resulting in the inability to digest the disaccharide lactose. On reaching the large bowel, the undigested lactose is degraded by bacterial enzymes, leading to osmotic diarrhoea. Lactose intolerant individuals develop diarrhoea, flatulence and abdominal pain after consumption of milk. LAB with probiotic potential contain the ? Galactosidase enzyme which aids in lactose digestion in the small intestine after being released from bacterial cells upon exposure to bile acids (Zarate and Chaia, 2011).

2.1.2.5. Antibiotic resistance

One of the most important safety aspects of LAB is their resistance to antimicrobial drugs that might be transferred to other possible, pathogenic bacteria. Moreover, the resistance profile of LAB to antibiotics will enable to clarify their potential in minimizing the negative effects of antibiotic therapy on the host bacterial ecosystem. The Lactobacillus species have been found susceptible to many cell wall synthesis inhibitors like penicillin and ampicillin, however resistance to vancomycin has been demonstrated being intrinsic.

2.1.2.6. Antimicrobial potential

Probiotics have the ability to produce antimicrobial compounds against pathogenic and carcinogenic bacteria and also to adhere to and colonise the intestinal gut mucosa. LAB is known to produce bioactive molecules such as organic acids (Lactic, acetic and propionic acid), Carbon dioxide, H2O2, low molecular weight substances as well as protein-like antimicrobials called Bacteriocins (Gomes et al., 2012). Inhibition of the growth of pathogenic bacteria because of antimicrobials is biologically significant as it is thought to be that of amensalism, a means of one bacterium gaining advantage over another competing bacterium. In our study, several of our probiotic isolate have shown to produce bacteriocin like Pediocin from Pediococcus spp. GS4 with molecular weight of 9.9 kDa that inhibits the growth of Staphylococcus aureus (ATCC 25923), Listeria monocytogenes (ATCC 15313) and diarrhoeagenic bacteria including Shigella dysenteriae type1, S. sonnei, Salmonella typhimurium, Vibrio cholerae O1 and O139 (Gowri and Ghosh, 2010; Gowri and Ghosh, 2010a; Shruthy et al., 2011).

2.1.2.7. Organic acids

LAB is characterised by the accumulation of organic acids and the accompanying reduction in pH. It has been proposed that the low external pH causes acidification of the cell cytoplasm, while the
undissociated acid, being lipophilic, can diffuse passively across the membrane (Schellenberg et al., 2012). The undissociated acid acts by collapsing the electrochemical proton gradient, or by altering the cell membrane permeability which results in disruption of substrate transport systems. One among the organic acids is the lactic acid, a major metabolite of LAB fermentation. It is in equilibrium with its undissociated and dissociated forms, and the extent of the dissociation depends on pH. Different microorganisms vary considerably in their sensitivity to lactic acid. Heterofermentative LAB strains are known to produce acetic and propionic acids in addition to lactic acid through metabolic pathways. These acids interact with the cell membrane and cause intracellular acidification and protein denaturation.

2.1.2.8. Hydrogen peroxide

H₂O₂ is produced as a result of the action of flavoprotein oxidases or nicotinamide adenine dihydroxy nucleotide (NADH) peroxidase in the presence of oxygen. It has been reported that the production of H₂O₂ by Lactobacillus and Lactococcus strains inhibited Staphylococcus aureus, Pseudomonas spp. and various psychrotrophic microorganisms in foods. The antimicrobial activity of H₂O₂ may result from the oxidation of sulphhydryl groups thereby causing denaturation of a number of enzymes, as well as the increased membrane permeability as a result of peroxidation of membrane lipids (Schellenberg et al., 2012). This may cause DNA damage through the production of bactericidal free radicals such as superoxide (O₂⁻) and hydroxyl (OH) radicals with H₂O₂ serving as a precursor for the free radical cascade. In raw milk, H₂O₂ activates the lactoperoxidase system, producing hypothiocyanate (OSC₅N), higher oxycacids (O₂SCN⁻ and O₃SCN⁻) and intermediate oxidation products that are inhibitory to a wide spectrum of Gram-positive and Gram-negative bacteria.

2.1.2.9. Carbon dioxide

Carbon dioxide is also one of the end products of heterofermentative metabolism. CO₂ has effectively inhibited the growth of many food spoilage microorganisms, especially Gram-negative psychrotrophic bacteria. With CO₂ at 10% lowering the total bacterial counts by 50% and at 20-50% exhibited strong antifungal activity. CO₂ could play a role in creating an anaerobic environment which inhibits enzymatic decarboxylation reaction and the accumulation of CO₂ in the membrane lipid bilayer may cause a malfunction in permeability.

2.1.2.10. Aroma compounds

Diacetyl is produced by strains within all genera of LAB by citrate fermentation (Gallardo-Escamilla et al., 2005). The antimicrobial effect of diacetyl has been known since the 1930s. It inhibits the growth of Gram-negative bacteria by reacting with the arginine-binding protein, thus affecting the arginine utilisation. Acetaldehyde is another aroma compound produced by L. delbrueckii subspecies bulgaricus by the action of a threonine aldolase, which cleaves threonine into acetaldehyde and glycine. It can accumulate in the product at a concentration of about 25 ppm. It was shown experimentally that Staphylococcus aureus, Salmonella typhimurium and E. coli in dairy products are completely inhibited by acetaldehyde at a concentration of 10-100 ppm.

2.1.2.11. Fatty acids

Some Lactobacilli and Lactococci possessing lipolytic activities produce significant amounts of fatty acids with antimicrobial potential under specific conditions. The unsaturated fatty acids are active against Gram-positive bacteria, and the antifungal activity of fatty acids is dependent on chain length, concentration, and pH of the medium. Reuterin is produced during the anaerobic growth of Lb. reuteri by the action of glycerol dehydratase, a heterofermentative species inhabiting the gastrointestinal tract of humans and animals which has been chemically identified to be 3-hydroxypropanal (1-hydroxypropionaldehyde), a highly soluble pH-neutral compound which is in equilibrium with its hydrated monomeric and cyclic dimeric forms. Reuterin exhibits a broad spectrum of antimicrobial activity against certain pathogenic Gram-positive and Gram-negative bacteria, yeast, fungi and protozoa (Schaefer et al., 2010).

2.1.3. Bacteriocins as antimicrobials

Some LAB strains ribosomally synthesise antimicrobial peptides, or bacteriocins, targeted to inhibit other Gram-positive bacteria (Gomes et al., 2012). Bacteriocins permeate the outer membrane of Gram-negative bacteria and induced the inactivation in conjunction with other enhancing antimicrobial environmental factors, such as low temperature, organic acid and detergents. Bacteriocins produced by LAB are classified into three main groups, lantibiotics (Class I), non lantibiotics, small heat-stable peptides (Class II) and large heat-labile protein (Class III) The lantibiotic nisin naturally produced by Lactococcus lactis ssp. lactis is commercially available as food additive E234. Besides the production of bacteriocins, some LAB is able to synthesise other antimicrobial peptides including low-molecular-mass metabolites, and/or cyclic
dipeptides.

2.1.4. Role of probiotics in human health

Attempt has been made to unify the hypothesis for health benefits achieved using probiotics (Heineman et al., 2012). Several results include lowering the frequency and duration of antibiotics-associated clostridial diarrhea, rotaviral infection, chemotherapy and Travellers' diarrhea; stimulation of immunity and decrease in unfavourable metabolites like ammonia and procarcinogenic enzymes in the colon. Some more benefits have been experienced over the recent times which specify the i) reduction of Helicobacter pylori infection (Baryshnikova, 2012), ii) reduction of allergic symptoms (Matsuda et al., 2012), iii) relief from constipation (Liu, 2011; Malaguarnera et al., 2012), iv) relief from irritable bowel syndrome (Thomson et al., 2012), v) beneficial effects on mineral metabolism (Lamberti et al., 2011; Rossi et al., 2011), vi) cancer prevention (Escamilla et al., 2012; Maroof et al., 2012), and vii) reduction of cholesterol and triacylglycerol plasma concentrations (Wang et al., 2012).

The role of probiotic organisms as alternative or complementary therapy in combating a large number of disorders, especially gastrointestinal and their ability to enhance immune response has attracted global attention. A brief outline has been drawn here to introduce the some health benefits of probiotics.

2.1.4.1. Lactose intolerance

Most of the world’s population (60-90% of non-caucasians and 6-12% of Caucasians) become lactose intolerant after weaning, this stems from a 90-95% decline in the production of lactase. The presence of lactase alters the osmotic balance in the colonic lumen and develops symptoms including abdominal bloating, cramping, flatulence and diarrhea. The contribution of lactase by the bacterial cultures used to manufacture the probiotic curd (yoghurt) is thought to mediate enhanced lactose digestion. In general, results have indicated that probiotics effectively improve the digestion of lactose and this effect seems to be more cell-density dependent than strain specific.

2.1.4.2. Cholesterol reduction

The WHO has predicted recently that by 2030, cardiovascular diseases will remain leading causes of death, affecting approximately 23.6 million people around the World. The risk of heart attack is three times higher in those with hypercholesterolemia, compared to those who have normal blood lipid profiles. The cholesterol-lowering activity of certain fermented milk and dairy products with some species of Lactobacillus, Bifidobacterium, Enterococcus, and Streptococcus has been demonstrated in rats, hamsters, and pigs. A human strain with similar cholesterol assimilating properties has been discovered. L. acidophilus designated strain NCFM had an appreciable ability to assimilate cholesterol. The in vitro studies have evaluated a number of mechanisms proposed for the cholesterol-lowering effects of probiotics and prebiotics. One of the mechanisms includes enzymatic deconjugation of bile acids by bile-salt hydrolase of probiotics. Once deconjugated, bile acids are less soluble and absorbed by the intestines, converted to coprostanol, leading to their elimination in the faeces.

2.1.4.3. Irritable bowel syndrome

Irritable Bowel Syndrome (IBS) is the most common functional gastrointestinal disorder with a reported prevalence in the general population between 12%–22%. IBS is characterised by a collection of functional gastrointestinal symptoms such as abdominal pain, defecatory frequency and/or constipation. The etiology of IBS is still not clear and numerous factors are involved in the damage to the mucosa, including microorganisms, psychological factors and nutritional habits. In addition, the gut-associated immune system is up regulated as evidenced by increased inflammatory cytokines such as interleukin 1, 6, and 10. The upregulated gastrointestinal (GI) associated immune tissue is known to stimulate discharge of enterochromaffin cells and other cells, which release serotonin and/or histamine resulting in GI symptoms. The type of colonising microflora may play an important role in regulating immunity. IBS patients host an intestinal microflora containing few Lactobacilli and a decrease in Bifidobacteria faecal concentration. In normal conditions, an immunologic tolerance is maintained toward the commensal enteric bacteria which prevent intestinal inflammation. This controlled homeostatic response is lost in susceptible individuals that develop chronic aggressive cellular immune response at the intestinal level. Oral administration of L. rhamnosus GG (LGG) in patients with Crohn’s disease resulted in the promotion of the intestinal IgA immune response, reduction in the pain and severity scores in patients. Positive role of probiotics in IBS are convincing but a trend to the beneficial effect of bacterial supplementation as an adjunct to treatment is emerging.

2.1.4.4. Colon cancer

Colorectal cancer is one of the leading causes of cancer morbidity and mortality in many countries and it is thought to be caused by an interaction between
dietary factors and genetic predisposition. Diet is estimated to be responsible for 30 to 60 percent of all cancers. Genotoxic carcinogens including heterocyclic aromatic amines, which are formed during the cooking of meat, increase the potential risk factor of colon cancer in high-meat consumers. Epidemiological studies have shown that consumption of fermented milk products, especially those containing probiotic bacteria, may help reduce the risk of cancer at a number of sites. Lactobacillus acidophilus, Lactobacillus casei Shirota strain and LGG have been shown to have inhibitory properties on chemically induced tumours in animals. There is some evidence that probiotics can interfere at various stages of the cancer process, such as prevention of DNA damage in the colon by live bacteria, suppression of pre-neoplastic changes in the colon and suppression of colon tumours in animals. Preliminary studies on the effect of probiotic consumption on cancer appear to be promising. However further studies are needed before the beneficial effects of probiotics in the prevention of human colon cancer can be confirmed.

### 2.1.4.5. Probiotics and dental health

Probiotics may be beneficial for the oral microflora by preventing the growth of harmful bacteria such as Streptococcus mutans. A few studies are available on the dental effects of LAB and fermented products. Russian Scientists have reported that probiotic Bifidobacterium spp. can reduce gingival and periodontal inflammation. Lactobacillus GG (ATCC 53103) has been studied for the colonising properties in the oral cavity. In healthy volunteers, it was observed to colonise oral mucosa for up to two weeks after completion of the oral intake. Some of the hypothetical mechanisms of probiotics action in the oral cavity include binding of oral micro-organisms to proteins, action on plaque formation and on its complex ecosystem by competing and intervening with bacterial attachments and involvement in metabolism of substrate, production of chemicals that inhibit oral bacteria like antioxidants (Gowri and Ghosh, 2011).

### 2.1.5. Features of probiotics to develop a functional product

An effective probiotic is required to function under various environmental conditions and has to survive in many different forms. The candidate probiotic should possess some characteristics:

1. Acid tolerance and tolerance to human gastric juice.
2. Bile tolerance (an important property for survival in the small intestine)
3. Adherence to epithelial surfaces and persistence in human GI tract.
4. Immuno-stimulation,
5. Antagonistic activity against pathogens such as, *Helicobacter pylori*, *Salmonella typhimurium*, *Listeria monocytogens* and *Clostridium difficile*.
6. Antimutagenic and anticarcinogenic properties.
7. Should maintain viability and activity in the carrier food for long periods under storage and field conditions (industrial scale) before consumption.

### 2.2. Prebiotics

Prebiotic is a non-digestable food ingredient that confers benefits on the host by selectively stimulating the growth and/or the activity of one bacterium or a group of bacteria in the colon and thus improves host health (Gibson and Roberfroid, 1995; Ooi and Liong, 2010; Gourineni et al., 2011; Salvini et al., 2011; Yeo et al., 2009) and promotes the growth of certain probiotics. Thus, the prebiotic approach advocates the administration of non-viable entities. Dietary carbohydrates, such as fibres, are candidate prebiotics, but most promise has been realized with non-digestible oligosaccharides, because of their selective metabolism. As prebiotics exploit non-viable food ingredients, their applicability in diets is wide ranging. Prebiotics could also be termed as “Colonic foods”, i.e., food that enter the large intestine (colon) and which serve as substrates for endogenous and autochthonous colonic bacteria, thereby indirectly providing the host with energy, metabolic substrates and essential nutrients. Resistant starch and non-starch polysaccharides (NPS) are classified as colonic foods but not as Prebiotics, as they are not metabolized by a limited number of beneficial bacteria. However, some non-digestible oligo-saccharides are classified as both colonic foods as well as Prebiotics. Fructo-oligosaccharides (FOS), transgalactosylated disaccharides (TOS/GOS) and soybean oligosaccharides (SO) are the only products recognized widely and are used as food ingredients that meet all the requisites of probiotic classification. Besides these, xyl-o-oligosaccharides (XOS), lactulose and lactitol are also considered as Prebiotics. The prebiotic activity of FOS has been confirmed in both laboratory and human trials. This is because these carbohydrates have a specific colonic fermentation directed towards bifidobacteria. *Bifidobacteria* are able to break down and utilize fructo-oligosaccharides due to their possession of a β-fructofuranosidase enzyme, providing a competitive advantage in a mixed culture environment like the human gut. XOS are used as food ingredients owing to their technological properties and healthy effects. Xylo-oligosaccharides (degree of polymerization; DP=2) is considered a member of
XOS with beneficial effect in GI tract. Results obtained in vivo using rats proved the administration of XOS resulted in increased amounts of *Bifidobacterium spp.* with the increase of SCFA. It has been observed that ingested X2 is not excreted in feces or in urine in the 24h following oral administration. Since X2 cannot be hydrolysed either by saliva, pancreatin, gastric juice, or intestinal mucosa homogenate, suggest X2 is utilized by intestinal microflora. GOS are another class of prebiotics that are manufactured and marketed in Europe and Japan. These consist of a lactose core with one or more galactosyl residues linked via ?1?3, ?1?4 and ?1?6 linkages. They have found application in infant formula foods. Table 2 shows the classification and sources of Prebiotics.

### Table 2

#### Classification and sources of Prebiotics

*See Illustration 2*

Prebiotics are with following characteristics: i) they are parts of edible plants; ii) they are carbohydrates that are composed of mixture of oligosaccharides/ and polysaccharides (degree of polymerization differs); iii) resist hydrolysis by human digestive enzymes; iv) do not appear to be significantly absorbed in the small intestine (exception remains with very short chain oligosaccharides); v) they are not metabolized by the host; and vi) they are excreted as such in the urine. However, the dietary intake of OS is difficult to estimate, but it may reach 3-13 g/day per person. Certain studies indicate that daily intake of 5-20 g of Inulin and FOS selectively promotes the growth of *Bifidobacteria*. Such studies are not available in India.

A large number of beautiful and excellent review articles are available to gain interesting information about pro- and pre-biotics. However, the common understanding about the utility of Prebiotics is that they benefit our intestinal ecosystem, improve immunity and overall health. Probiotics along with Prebiotics have been significantly used for the clinical benefit in the prevention and management of gastrointestinal and non-gastrointestinal conditions(Sazawal et al., 2010; O’Donnell et al., 2011) like necrotizing enterocolitis, Traveller’s diarrhea, allergic colitis, inflammatory bowel diseases and in pediatrics’ gastrointestinal disorders, by increasing biomass of probiotics and stool bulking.

### 2.3. Synbiotics

A further approach is synbiotics, where probiotics and prebiotics are combined. Synbiotics are preparations that contain probiotics as well as prebiotics. Synbiotics further improve the efficacy of the probiotic and prebiotic when used individually. This occurs because the prebiotic boosts the growth of the surviving probiotic once it reaches the area of the intestine where it would multiply. The symbiotic concept combines efficacious probiotic strains with specific probiotic compounds in a single product (Zhang et al., 2010; Fotiadis et al., 2008; Bengmark, 2012; Martin et al., 2012). Synbiotic is defined as “a mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and implementation of live microbial dietary supplement in the GI tract.

Synbiotics are mostly prepared by adding prebiotic ingredients / dietary fibre or value added ingredients along with probiotics having some intention of health advantage. More than 350 products have been approved under Food for specific health use (FOSHU) as on 1st April,2011 with a claim to control GI functions (helps to maintain good GI condition and to improve bowel movement), which include oligosaccharides, *Lactobacillus*, *Bifidobacteria*, dietary fibres/ non-digestible oligosaccharides. Several synbiotic formulations have been reported in literature. Among all, preparation with cassava starch or inulin, milk and three different LAB; lactulose, inulin with *L. acidophilus* LA-5 and *B. bifidum* BB-12; inulin, FOS and honey with *L. acidophilus*; sugar with inulin and probiotics; raftiline, raftilose with honey, milk and LAB are worth mentioning. In our study, we prepared several formulations (capsule) for delivery of probiotics (our strains *Pediococcus sp.GS4, L. lactis* and *L. gasseri*) for health benefits. Our preparations contain several different Prebiotics as excipients which include XOS, FOS, inulin, skim milk, dulcitol, xylitol, lactitol, honey, ascorbic acid in permutation and combination. It is also reported that Prebiotics products are available in the form of tablet or powder and mint wafers, which contains inulin and calcium (500 mg), manufactured by the company, “Naturally Vitamines” under brand name of *Inuflora™* and Inu-Lean respectively. Stonyfield Company, sells synbiotic products in blended flavoured *yoghurt* form containing six live active culture and inulin. A large number of scientific literatures are there to claim its use in different clinical gastrointestinal (GI) conditions as displayed in Table 3.

### Table 3

#### Clinical applications of Synbiotics in several GI conditions

*See Illustration 3*

3. **Mechanisms of action of synbiotics on mucosal surface of GIT**

Gastrointestinal tract (GIT) represents a complex ecosystem in which a delicate balance exists between...
the intestinal microflora and host. It comprised of 95% obligate anaerobes including *Bifidobacterium, Clostridium, Eubacterium, Fusobacterium, Peptococcus, Peptostreptococcus, Bacteroides* and others. About 1-10% of intestinal population is composed of facultative anaerobes including *Lactobacillus, Escherichia coli, Klebsiella, Streptococcus, Staphylococcus*. Aerobic microorganisms are not present in the GIT. The distribution of these hosekeeping bacteria differ from oral cavity to anus. The load of microbiota vary from $10^2$ to $10^{10}$ colony forming unit (cfu) per gram of aspirate or stool and vary also with age, gastric acid secretion, diet, life style and time feeding. In general, we the *Homo sapiens sapiens* possess 10 times more microbiota than our cells content ($10^{13}$). In the small intestine, jejunum and ileum contain no more than $10^4$ - $10^6$, whereas the terminal ileal content increases by 10-100 folds. On opening into the gut, the microbial load increases by million fold and reaches to $10^{12}$ to $10^{13}$ cfu gram of stool. Each individual has a rather unique colonic flora that remains constant over long periods of time, with minor variations conditioned by frequency of bowel movement and diet. Uniquely, the morphology of gut is governed by the microbiota and maintains the homeostasis of the host (Marik, 2012).

The therapeutic applications with probiotics, prebiotics, and synbiotics are moving fast in the recent decade. The effectiveness of probiotics is strain-specific, and each strain may contribute to host health through different mechanisms. Many reports indicate that probiotics can affect innate immunity and also protect against pathogens by decreasing pathogenic adherence or by production of acids, H$_2$O$_2$, bacteriocins or several surface active molecules which are inhibitory to pathogens in gastro-intestinal tract.

Probiotics have been found to control intestinal disorders, partially due to immunomodulating the innate pattern-recognition receptors such as TLRs, NLRs and CLR and because of serum antibodies IgG, and secretory IgA and IgM enhancing immune response. Certain strains can intermittently translocate across the intestinal mucosa without causing infection, thus influencing systemic immune events. Evidence has been presented that some *Lactobacilli* can directly stimulate the immune system on the gut mucosal surface via localised GI tract lymphoid cell foci. In a recent study, potential of twenty seven lactobacilli and sixteen bifidobacteria strains were compared to stimulate bone-marrow derived dendritic cells. Most of them induced strong production of IL-12 and TNF-? (D'Souza et al., 2012).

A number of mechanisms work to prevent harmful bacteria from growing on and attaching to the intestinal epithelium: production and secretion of antimicrobial agents such as bacteriocins and organic acids, adherence via competition for the binding sites and steric hindrance and barriers interfering with pathogens and hence promote the elimination of harmful bacteria. The probiotic exert multiple potential to confer health benefit to the host following several mechanisms which include (1) competition for dietary ingredients as growth substrates, (2) bioconversion of, for example, sugars into fermentation products with inhibitory properties, (3) production of growth substrates, like exopolysaccharides or vitamins, for other bacteria, (4) direct antagonism by bacteriocins, (5) competitive exclusion for binding sites, (6) improved barrier function, (7) reduction of inflammation, thus altering intestinal properties for colonisation and persistence within, and (8) stimulation of innate immune response. A summary has been drawn to demonstrate the possible mechanisms of actions offered by probiotics-prebiotics or symbiotics to enhance the health benefit to humans with special reference to GI conditions as in Table 4.

**Table 4**

**Summary of mechanisms of action of probiotics and the impact on health including GI Tract.**

See Illustration 4

**4. Mechanisms of beneficial effects**

The origin of cultured dairy products dates back to the dawn of civilization and mention of them is found in the Bible and the sacred books of Hinduism. However, the association between these products and human health was not realized until 1900s. During the same period of Metchnikoff, Cohendy observed that human subjects administered with sour milk containing *L. bulgaricus* were with reduced putrefaction, while Henry Tissier observed that children with diarrhea had in their stools a low number of *Bifidobacteria*, on the contrary, abundant in healthy children and suggested that these bacteria could be administered to patients with diarrhea to help restore a healthy gut flora in 1906. In the early 1920s, Rettger and Cheplin (1922) documented that *L. acidophilus* milk had therapeutic effects, in particular, a settling effect on digestion. They believed that colonisation and growth in the gut were essential for efficacy, and therefore, advocated the use of intestinal isolates. This kindled further interest in understanding the survival and colonisation of *Lactobacillus* spp. Since then yoghurts were in common use and were found efficacious in maintaining the balance of the gut flora or to prevent...
conditions, such as, diarrhoea, constipation, dyspepsia, cystitis, mucous colitis, chronic ulcerative colitis and dermatitis. Shirota focused his research on selecting strains of intestinal bacteria that could survive passage through the gut and on the use of such strains L. acidophilus Shirota (subsequently named L. casei Shirota) (Dong et al., 2010; Hori et al., 2002) was the basis for the establishment of the Yakult Company. Gordon and colleagues noted that the success of therapy using Lactobacillus was depended on certain criteria: it was essential to use a non-pathogenic organism which is a normal inhabitant of the intestine and capable of establishing itself in the gut and that a large number of viable cells \((10^5 - 10^9)\) were essential for the establishment of a beneficial flora. The co-administration of a diet with high milk or lactose content or the growth factors required by Lactobacilli was also considered as a key factor for successful bacterial therapy. The scientific basis of probiotics and the health benefits related to the consumption of food containing viable LAB has branched from this history and opened many new avenues for exploiting optimal benefits from these microbes. The probiotics has the best potential to be the best therapeutics for all sorts of diseases and disorders, the Panacea in near future (Martin et al., 2012).

Lactobacillus and Bifidobacterium species originating from human microflora have been a matter of interest. Hence Probiotics are sometimes called colonic foods. Lactobacilli have a long history of safe use in foods and dairy products. Lactobacilli are normal inhabitants of the intestinal ecosystem and vagina but variable amounts are found among people (ranging from 0 to \(10^6\) cfu/g faeces). The therapeutic roles of some Lactobacillus spp. have been demonstrated. Lactobacillus rhamnosus GG (LGG) was the first probiotic which received most clinical attention to date (Vandenplas et al., 2007). The Lactobacillus strain used traditionally for fermentation by the dairy industry was unable to implant to the gut so, LGG was discovered in 1985 by developing a list of ideal qualities for probiotics, as mentioned earlier. LGG has proven beneficial effects on the intestinal immunity. It increases the number of IgA and other immunoglobulin secreting cell in the intestinal mucosa, stimulates the local release of interferons, facilitates antigen transport to underlying lymphoid cells which severs to increase antigen uptake in the Peyer’s patches.

Bifidobacteria are also part of the human and animal microflora, but species differ according to age: newborns are readily colonised by Bifidobacterium breve and B. infantis and colonisation is favored in breast-fed compared to bottle-fed infants, whereas adults more often host B. adolescentis, B. bifidum and B. longum. Presently there are about 30 species included in the genus Bifidobacterium, 10 of which are from human sources and 17 from intestinal tracts of animal or rumen. Of these, six species from human origin, B. adolescentis, B. breve, B. bifidum, B. lactis, B. infantis and B. longum have been used in dairy products. It has now been conclusively demonstrated that some Bifidobacterium strains can survive intestinal transit and persist transiently within the colon. The therapeutic roles of Bifidobacteria in animal model and in human are due to four major mechanisms including modulation of the host immune system, resistance to infectious diseases such as against rotavirus diarrhoea and enteropathogens, control of inflammatory bowel disease such as Crohn’s disease, ulcerative colitis and pouchitis and prevention of cancer. Persistance of ingested Bifidobacterium in the digestive tract is dependent on the contribution of host genotype to the dominant microbial diversity suggesting specific interactions between microbes and humans. On the other hand, microflora establishment and maintenance is highly dependent on the food intake and style of diet. Among the other probiotics, Enterococcus faecium SF68 strain has been used in the management of diarrhoeal illnesses. Non-pathogenic probiotic yeast, Saccharomyces boulardii has also shown beneficial effect in the treatment of diarrhea associated with antibiotic use.

### 5. Clinical studies of probiotics in diarrheal disease and other GI infections

In India, about 59% of prescriptions for the treatment of diarrhoea were fixed dose combinations of an antibacterial and an antiprotozoal. Such combination has risks of adverse drug reactions and also increases the chances of drug resistance. Physicians in India are influenced by socio economic factors and so a cheap way for the management of diarrhoea is necessary (Reid et al., 2003; Preidis et al., 2011). Probiotics may be seen as a natural alternative to traditional drugs, and thus patients may regard probiotics as safer, more effective, and less likely to pose significant health risks. Probiotic therapy is preferable to traditional drugs because it involve a more holistic approach to the management of disease, are readily available and do not require the additional costs of a physician visit.

Diarrhoea is the second fatal disease in India and a common problem of other developing countries. It has been estimated that there may be 4 billion cases of acute diarrhoea each year worldwide. All kinds infectious diarrhea including Cholera, shigellosis and other infections lead to stunt and slow growth in
children below five years. Intake of curd has been found beneficial in a study in India (Saran, 2002). The balanced normal microbiota may become aberrant on infection and synbiotics repair the physiological and immunological processes to maintain the homeostasis. Diarrhoea is caused by infections, antibiotic therapy, and tube feeding. Infectious diarrhea is caused by more than 50 different pathogens including virus, bacteria, fungus and protozoa and it affects all age-groups. It is the major cause of high mortality and morbidity, as seen especially in India. In developing countries, bacterial enteropathogens, particularly enterotoxigenic *Escherichia coli* (ETEC) cause just under half of the cases of endemic paediatric diarrhoea and majority of all cases of Traveller’s diarrhoea (Ghosh et al., 1996). Probiotics have been best researched as therapeutics for the management of acute infantile diarrhoea. Rotavirus and enteropathogenic *E. coli* (EPEC) are leading cause of this condition worldwide. At least three systematic reviews have shown that use of probiotics achieves overall reductions in the duration of diarrhoea ranging from 17 to 30 hours. Many mechanisms of action explaining how lactobacilli reduce the duration of rotavirus-induced diarrhoea have been proposed (Reid et al., 2003; Reid et al., 2008; Preidis et al., 2011). These include competitive blockage of receptor sites when lactobacilli bind to receptors; signal(s) from lactobacilli regulating secretory and motility defences designed to remove perceived noxious substances; enhancement of the immune response; and production by lactobacilli of substances that inactivate the viral particles. However, it is not clear whether the routine use of probiotics in acute diarrhoeal illnesses is justified, as most acute diarrhoeal illnesses are self limited.

There is not much information indicating whether probiotics reduce the serious complications of diarrhoeal illnesses (Yan and Polk, 2006). Furthermore, the data do not provide a clear understanding of the type, dose, or duration of probiotic treatment required for achieving clinical benefit. Limited data suggest that the minimal effective dose in children is 10 billion colony-forming units given within the first 48 hours. Another study evaluated the use of LGG as a prophylactic agent against diarrhoea in children. The regular administration of a daily dose of LGG, 6 days a week for 15 months, achieved a low rate of diarrhoea, but only in non–breast-fed infants.

Persistent diarrhoea is defined as a diarrhoeal episode that starts acutely but lasts for 14 days or more, and it is an important cause of morbidity and mortality in children under five years old in developing countries throughout the world. The cause of persistent diarrhoea is not completely understood but is likely to be complex; this in turn makes management of the condition difficult. In a separate study, four clinical trials involving children with persistent diarrhea were reviewed in 2010 (Sazawal et al., 2010). Two studies with a combined total of 324 showed that probiotics shorten the duration of diarrhoea and reduce the stool frequency on day 5. One study with 235 hospitalised children suggested that probiotics reduced the hospital stay. Three out of four trials reported that no adverse events occurred. The report was satisfactory but not overwhelming as every study is limited by few trials with small number of participants, and therefore may not represent a reliable estimate of probiotics’ effect.

Diarrhoea associated with antibiotic use and caused by *Clostridium difficile* is a complication of treatment with antimicrobial agents and occurs in about 5-25% of patients. *C. difficile* is responsible for around 15-25% of all cases of diarrhoea associated with antibiotic use, most occurring in older patients, usually in the two to three weeks after cessation of antibiotic treatment. *Lactobacilli*, *Bifidobacteria*, and *Streptococcus* species have all been evaluated for the prevention or treatment of diarrhoea associated with antibiotic use and found to be safe. In another study conducted in 2007 showed that consumption of a readily available probiotic drink containing *Lactobacillus casei*, *L. bulgaricus*, and *Streptococcus thermophilus*, twice a day during a course of antibiotics and for one week afterwards, reduced the incidence of diarrhoea associated with antibiotic use and *C. difficile*.

Two recent hospital-based studies in 2011, reported reduction in diarrhoea duration when *S. boulardii* was given to 186 children between 6-48 months, within 72 hours after the onset of acute diarrhea. The result suggests a complementary treatment of acute diarrhea in infants with daily oral doses of *S. boulardii*. In a separate randomized clinical trial, a total of 111 diarrhoeic children with median age of 40 months were treated with synbiotics containing *S. thermophilus*, *L. rhamnosus*, *L. acidophilus*, *Bifido lactis* with FOS. The duration of diarrhoeal episodes were one day shorter than placebo group.

The use of probiotics as prophylaxis against diarrhoea is an interesting concept that remains unproven (Culligan et al., 2009; Gratz et al., 2010). The data on the use of probiotics to manage adults with infective diarrhoea are limited and mixed. Twenty three research papers were on the treatment of infectious diarrhoea with probiotics and concluded that they appear to be a useful adjunct to rehydration therapy when managing both adults and children (Allen et al.,
6. Products marketed by Indian firms

A large number of research results on probiotics, prebiotics and synbiotics have been translated into industrial products. Due to its wide-acclaimed acceptability and simple formulation with dietary utility, probiotic market has brighter future to safeguard human lives. The market of functional food or designer food like synbiotics is governed by several factors specially the cultural base, geographical location, demography, economy, level of education in the society, government interests and others. Properly formulated probiotic-containing foods having the potential to promote health benefits offer consumers a low risk and low cost dietary component. Although the worldwide market for probiotics or/and synbiotics is growing fast and Japan, USA, Europe took the leadership, however, in India, the market has just started to conceive with leading companies like Amul, Nestle, Mother Dairy and Aavin making the first move. In India, these companies have come up with their probiotic products, which are very popular. Some of these are presented in Table 5.

Table 5

Indian company in the Probiotics market

See Illustration 5

Yakult-DANONE India, is the first Indian company with 50:50 joint venture of Japanese global probiotics leader, Yakult, with the French food major, Group DANONE, has entered the Indian probiotics market with launching of their product ‘Yakult’, a probiotic curd in December 2008. At least 39 probiotic drug brands, mainly in the area of gastroenterology, from 30 major Indian companies have already created a probiotics drug market in India worth Rs 80 crore. Major players in the probiotics drug market in India include companies like Ranbaxy (Binifit), Dr. Reddy’s Laboratories, which has four probiotic brands, Zydus Cadila, Unichem, JB Chem, and Glaxo SmithKline.

Many Indian research institutes are working on the probiotic technologies (Probiotic curd - Punjab Agricultural University, Ludhiana, Punjab; Probiotic ice cream - National Dairy Research Institute (NDRI), Karnal, Haryana; Cereal based probiotic foods – Haryana Agricultural University, Haryana, etc.). National Research Development Corporation, a Govt. of India enterprise under Ministry of Science and Technology, has also taken active role in commercialization of the probiotic technologies developed in various Indian research institutes and laboratories for popularization of this new concept.

India has a long tradition in using foods for their health-promoting or functional properties, influenced by Ayurvedic medicine. These functional foods can include herbal extracts, spices, fruits and other ingredients for fortification and enhanced health benefit. Increasing health-awareness of synbiotics is further raising demand for diet foods and fortified natural foods. Nine out of ten urban Indian consumers have been reported to generally choose foods based on health and wellness benefits.

Concluding Remarks

The concept of synbiotics is based on the knowledge of providing therapeutic benefit to human beings reducing or elimination the risk of gastrointestinal disorders. Increasing evidences in scientific literature point out that the consumption of synbiotics (Bio-yoghurt), particularly containing L. acidophilus and Bifdobacterium species offers considerable health benefits through different mechanisms to consumers. In addition to the nutritional favour there is a need for a sustained effect to combine the skills of the microbiology, food technologist and clinician. Undoubtedly, gut flora can protect the host against several intestinal diseases. Once the prophylaxis of probiotics are well established with respect to the claimed health benefits, probiotics are sure to gain firm footing in the health food sector of the market and well certainly be the major portion of functional food sector. The probiotic dairy foods such as probiotic ice cream, kulfi, yoghurt drink and dietetic yoghurt could be commercialized through the organized dairy for the benefit of common people.

The role of probiotic organisms as alternative or complementary therapy in combating a large number of disorders, especially gastrointestinal and their ability to enhance immune response has attracted global attention. A number of health related effects have been suggested and partially established but some can be considered reasonably well established and clinically well documented. It is hoped that the simplest formulation will be discovered soon like oral rehydration solution (ORS) to support the global health and economy. The potentials with synbiotics ensure to be a solution to those people where doctors never visit for the cause of health. It will be very friendly to ameliorate the public health in near future. The increase in metabolic activity of probiotics is fundamental to many of the currently proposed mechanisms of health promotion by prebiotics. Synergistic approach in synbiotics will add more
values to the mitigation, reduction or elimination of many existing diseases and many more diseases yet to be enlisted in the era of globalization. Truly, synbiotics has potentials to be panacea of all earthly diseases.

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References


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Molecular Science 10, 3517–3530.
Illustrations

Illustration 1

Commonly used microorganisms as probiotics

<table>
<thead>
<tr>
<th>Lactobacillus species</th>
<th>Bifidobacterium species</th>
<th>Other bacterial species</th>
</tr>
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<tbody>
<tr>
<td>L. acidophilus</td>
<td>B. bifidum</td>
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<td>Enterococcus faecalis</td>
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<td>L. casei</td>
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<td></td>
<td>S. thermophilus</td>
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Illustration 2

Classification and sources of Prebiotics

<table>
<thead>
<tr>
<th>Classification</th>
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<tr>
<td><strong>Polyols</strong></td>
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<td>Fructo-oligosaccharides (FOS)</td>
<td>Legumes, vegetables, cereals</td>
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<td>Soybean oligosaccharides (SO)</td>
<td>Soybean</td>
<td>Extraction/ hydrolysis</td>
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<td>(Trans) Galacto-oligosaccharides (TOS)/ (GOS)</td>
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<td>Compound</td>
<td>Source</td>
<td>Process</td>
</tr>
<tr>
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<td>-------------------------------------</td>
<td>--------------------------------</td>
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<td>Raffinose</td>
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<td>Fermentation</td>
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<td>Palatinose</td>
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<td>Iso-malto-oligosaccharides</td>
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<tr>
<td>Resistant starches</td>
<td>Legumes, vegetables, cereals</td>
<td>Extraction/ hydrolysis</td>
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Illustration 3

Clinical applications of Synbiotics in several GI conditions

<table>
<thead>
<tr>
<th>1. Rota virus diarrhea</th>
<th>11. Inflammatory bowel disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Antibiotic-associated diarrhoea</td>
<td>12. Pancreatis</td>
</tr>
<tr>
<td>1. Traveller’s diarrhea</td>
<td>13. Pouchitis</td>
</tr>
<tr>
<td>1. Diarrhea of various origin</td>
<td>15. Food allergies and lactose intolerance</td>
</tr>
<tr>
<td>1. Nosocomial diarrhea</td>
<td>16. Small bowel bacterial outgrowth</td>
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<tr>
<td>1. AIDS diarrhea</td>
<td>17. Dental caries</td>
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<tr>
<td>1. Gastroenterites</td>
<td>18. Cystic fibrosis</td>
</tr>
<tr>
<td>1. H. pylori infection</td>
<td>19. Enhancement of oral vaccine</td>
</tr>
<tr>
<td>1. Irritable bowel syndrome</td>
<td>20. Liver-gut-brain syndrome</td>
</tr>
</tbody>
</table>
Illustration 4

Summary of mechanisms of action of probiotics and the impact on health including GI Tract.

<table>
<thead>
<tr>
<th>Health Benefit</th>
<th>Mechanisms of actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Resistance to enteric infections</td>
<td>- Alteration of intestinal conditions to be less favourable of pathogenicity (pH, short chain fatty acids, bacteriocins)</td>
</tr>
<tr>
<td>2. Secretary immune effect</td>
<td>- Alteration of toxin binding sites to enterocytes.</td>
</tr>
<tr>
<td></td>
<td>- Influence on gut flora populations.</td>
</tr>
<tr>
<td></td>
<td>- Adherence to intestinal mucosa, interfering with pathogen adherence.</td>
</tr>
<tr>
<td></td>
<td>- Upregulation of intestinal mucin production</td>
</tr>
<tr>
<td></td>
<td>- Immunomodulation of pro-inflammatory (IFNγ, TNF-α) and anti-inflammatory (IL-10) cytokines.</td>
</tr>
<tr>
<td>1. Small Bowel decreasing bacterial infections</td>
<td>- Influence on activity of overgrown flora, toxic metabolite production</td>
</tr>
<tr>
<td>1. Urogenital infections</td>
<td>- Adhesion to urinary tract and vaginal tract cells colonization resistance</td>
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<tr>
<td>1. Infection caused by <em>Helicobacter pylori</em></td>
<td>-Inhibitor production (H₂O₂, Lactic acid, bacteriocins)</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>1. Promotion of lactose digestion</td>
<td>-production of bacterial lactase to hydrolyse lactose</td>
</tr>
<tr>
<td>1. Immune system modulation</td>
<td>-strengthening of non-specific defense against infection and tumours by production of IL-12 and TNF-α.</td>
</tr>
<tr>
<td></td>
<td>-adjuvant effect in antigen-specific immune responses</td>
</tr>
<tr>
<td></td>
<td>-Enhancement of secretory IgA production</td>
</tr>
<tr>
<td></td>
<td>-conjugated linoleic acid (CLA) of the probiotics upregulate the PPARγ to reduce inflammation and colon carcinogenesis</td>
</tr>
<tr>
<td>1. Hepatic encephalopathy</td>
<td>-Inhibition of urease-producing gut flora</td>
</tr>
<tr>
<td>1. Anti-colon cancer effect</td>
<td>-Mutagen binding carcinogen deactivation</td>
</tr>
<tr>
<td>1. Inhibition of carcinogen producing amines and enzymes of colonic microbes</td>
<td>-Antagonism</td>
</tr>
</tbody>
</table>
1. Effect of allergic states
   - Improves immune response
   - Influence on secondary bile salt concentration
   - Prevention of antigen translocation into bloodstream

1. Effect on blood lipids and heart disease
   - Assimilation of cholesterol within bacterial cell
   - Increased excretion of bile salts due to deconjugation by bile salt hydrolase

1. Antihypertensive
   - Antioxidative effect
   - Peptidase action on milk protein yields tripeptides which inhibit angiotensin-I converting enzyme.
   - Cell wall components act as ACE inhibitors
Illustration 5

Indian company in the Probiotics market

<table>
<thead>
<tr>
<th>Probiotics Products</th>
<th>Strains used</th>
<th>Company Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dairy products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probiotic curd</td>
<td></td>
<td>Heritage Foods(India) ltd</td>
</tr>
<tr>
<td>‘b-Activ’ Probiotic Dahi</td>
<td><em>L.acidophilus</em> and <em>B.lactis</em> strain BB12</td>
<td>Mother Dairy</td>
</tr>
<tr>
<td>‘Nesvita’ Probiotic yoghurt</td>
<td><em>L.acidophilus</em></td>
<td>Nestle (India)</td>
</tr>
<tr>
<td>Probiotic Ice-cream ‘Amul Prolife’</td>
<td>-</td>
<td>Amul Dairy (India)</td>
</tr>
<tr>
<td>Yakult</td>
<td><em>L.casei strain shirota</em></td>
<td>Yakult Danone India Private Ltd.</td>
</tr>
<tr>
<td>Pharmaceutical products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTIGUT</td>
<td>*L.acidophilus, L.rhamnosus,B.bifidus, B.longam, S.houardii, Fructooligosaccharides</td>
<td>Alembic</td>
</tr>
<tr>
<td>BINIFIT</td>
<td><em>S.faecalis, C.butyricum, Bacillus mesentericus, L.sporogenes.</em></td>
<td>Ranbaxy</td>
</tr>
<tr>
<td>BECELAC</td>
<td><em>L.acidophilus,Vit-B6, Vit-C,Folic acid.</em></td>
<td>Dr.Reddy’s Laboratories</td>
</tr>
<tr>
<td>Product</td>
<td>Ingredients</td>
<td>Manufacturer</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>BFILIN</td>
<td><em>L. acidophilus</em>, <em>L. rhamnosus</em>, <em>B. bifidum</em>, <em>B. longum</em>, <em>S. thermophilus</em>, <em>Fructooligosaccharides</em></td>
<td>Cipla</td>
</tr>
</tbody>
</table>
| EQUIPRO   | *L. acidophilus*, *S. Faecalis*  
*Clostridium butyricum*,  
*Bacillus mesentericus* | Cadila Pharma     |
| ECONOVA   | *L. Reuteri* RC-14  
*L. Rhamnosus* GR-1 | Glenmark          |
| GUTRITE   | *L. acidophilus*, *L. rhamnosus*, *B. longum*,  
*B. bifidum*, *S. bouardii*, *S. thermophilus*, *Fructooligosaccharides* | FDC              |
| GUTPROCAPS| *S. faecalis*,  
Clostridium butyricum  
*B. mesentericus*,  
*L. sporogenes* | Jb Chem           |
| PROBIZA D | *L. sporogenes*,  
*Fructooligosaccharides* | Zydus Cadila     |
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