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REVIEW

Probiotics, prebiotics and synbiotics- a review

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Abstract The health benefits imparted by probiotics and prebiotics as well as synbiotics have been the subject of extensive research in the past few decades. These food supplements termed as functional foods have been demonstrated to alter, modify and reinstate the pre-existing intestinal flora. They also facilitate smooth functions of the intestinal environment. Most commonly used probiotic strains are: *Bifidobacterium, Lactobacilli, S. boulardii, B. coagulans.* Prebiotics like FOS, GOS, XOS, Inulin; fructans are the most commonly used fibers which when used together with probiotics are termed synbiotics and are able to improve the viability of the probiotics. Present review focuses on composition and roles of Probiotics, Prebiotics and Synbiotics in human health. Furthermore, additional health benefits like immune-modulation, cancer prevention, inflammatory bowel disease etc. are also discussed.

Keywords Probiotics · Prebiotics · Synbiotics · Intestinal disorders · Cancer · Cardiovascular diseases

Introduction

"Let food be thy medicine and medicine be thy food", the age old quote by Hippocrates is the ideology of today's health conscious population. Eli Metchnikoff, the Russian Nobel prize winner was the first one to recognize the beneficial role of select bacteria on gastrointestinal tract of humans. Subsequently the "Theory of Longevity" by Metchnikoff was correlated with prolonged youth and a healthy old age, observed largely in Balkan peasants of those times, who used cultured milks in their diet (Kaufmann 2008). Since then, the quest continues for understanding role of wide range of food components and nutrients in enhancing health or preventing chronic diseases. The research in this field has resulted in a plethora of new labels for foods that have indicated distinct benefits and such foods are termed as functional foods (Webb GP 2011). The concept of Functional foods emphasizes that food not only are vital for living but also play a role in the prevention and reduction of risk factors for several diseases and are also capable of enhancing certain vital physiological functions. Functional foods also provide the body with required amount of vitamins, fats, proteins, carbohydrates, etc. (Cencic and Chingwaru 2010)

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Probiotics

The term Probiotics is derived from a Greek word meaning "for life" and used to define living non-pathogenic organisms and their derived beneficial effects on hosts. The term "Probiotics" was first introduced by Vergin, when he was studying the detrimental effects of antibiotics and other microbial substances, on the gut microbial population. He observed that "probiotika" was favourable to the gut microflora. Probiotic were then redefined by Lilly and Stillwell as "A product produced by one microorganism stimulating the growth of another microorganism". Subsequently the term was further defined as "Non-pathogenic microorganisms which when ingested, exert a positive influence on host's health or physiology" by Fuller. The latest definition put forward by FDA and WHO jointly is "Live microorganisms which when administered in adequate amounts confer a health benefit to the host".

Some of the popularly used probiotic microorganisms are *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, bifidobacteria and certain strains of *Lactobacillus casei*, *Lactobacillus acidophilus*-group, *Bacillus coagulans, Escherichia coli* strain Nissle 1917, certain enterococci, especially *Enterococcus faecium*SF68, and the yeast *Saccharomyces boulardii*. Bacterial spore formers, mostly of the genus Bacillus dominate the scene. These probiotics are added to foods, particularly fermented milk products, either singly or in combinations. New genera and strains of probiotics are continuously emerging with more advanced and focused research efforts.

Probiotic products may contain either a single strain or a mixture of two or more strains. E.g. #VSL3 is a mixture of 8 different probiotic strains. Probiotic effects are very strain specific and cannot be generalized. A single strain may exhibit different benefits when used individually and in combination. The benefits of a probiotic formulation also differ with the patient group. Limited studies that have been performed have shown greater efficacy with multi-strain probiotics (Chapman et al. 2011).

Research on probiotics, in particular *Lactobacilli,* has grown exponentially during the last two decades as can be seen from the fact that compared to 180 research articles published during 1980–2000, more than 5700 research articles were published during 2000–2014 on "probiotic *Lactobacillus*" ("Probiotic Lactobacillus" PubMed 2014).

FAO and WHO have jointly put forward guidelines in order to set out a systematic approach for an effective evaluation of probiotics in foods to substantiate the health claims and benefits. Some of the pre-requisites of an ideal probiotic organism are depicted in Fig. 1. The FAO/WHO guidelines on Probiotics could be used as global standard for evaluating probiotics in food that could result in the substantiation of health claims. The guidelines make it necessary to perform the following activities:

1. Strain identification.
2. Functional characterization of the strain(s) for safety and probiotic attributes.
3. Validation of health benefits in human studies.
4. Honest, not misleading labelling of efficacy claims and content for the entire shelf life.

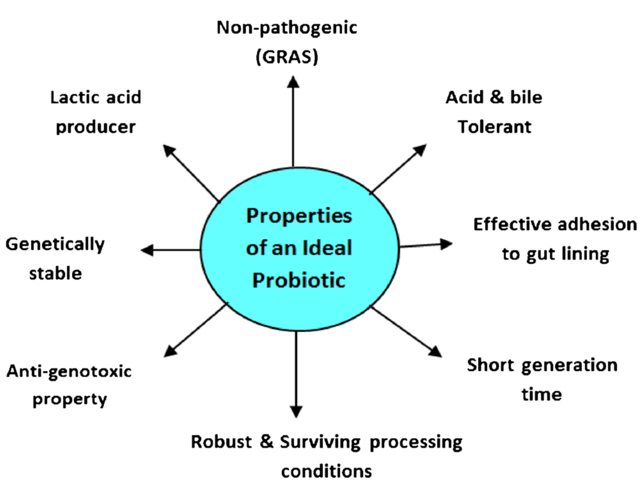

Fig. 1 Characteristics of an ideal probiotic strain

Prebiotics

Prebiotics are mostly fibers that are non-digestible food ingredients and beneficially affect the host's health by selectively stimulating the growth and/or activity of some genera of microorganisms in the colon, generally lactobacilli and bifidobacteria (DeVrese and Schrezenmeir 2008) An ideal prebiotic should be 1) Resistant to the actions of acids in the stomach, bile salts and other hydrolyzing enzymes in the intestine 2) Should not be absorbed in the upper gastrointestinal tract. 3) Be easily fermentable by the beneficial intestinal microflora (Kuo 2013).

FAO/WHO defines prebiotics as a non-viable food component that confer health benefit(s) on the host associated with modulation of the microbiota. Prebiotics form a group of diverse carbohydrate ingredients that are poorly understood with reference to their origin, fermentation profiles, and dosages required for health effects. Some of the sources of prebiotics include: breast milk, soybeans, inulin sources (like Jerusalem artichoke, chicory roots etc.), raw oats, unrefined wheat, unrefined barley, yacon, non-digestible carbohydrates, and in particular non-digestible oligosaccharides. However, among prebiotics only bifidogenic, non-digestible oligosaccharides (particularly inulin, its hydrolysis product oligofructose, and (trans) galacto-oligosaccharides (GOS), fulfil all the criteria for prebiotic classification (Pokusaeva et al. 2011).

Prebiotics like inulin and pectin exhibit several health benefits like Reducing the prevalence and duration of diarrhea, relief from inflammation and other symptoms associated with intestinal bowel disorder and protective effects to prevent colon cancer (Peña 2007). They are also implicated in enhancing the bioavailability and uptake of minerals, lowering of some risk factors of cardiovascular disease, and promoting satiety and weight loss thus preventing obesity (Pokusaeva et al. 2011). Some of the important properties of the oligosaccharides along with names of the widely used prebiotics are outlined in Table 1 (Swennen et al. 2006).

Recently several plant and bacterial sources have been explored for their benefits as prebiotics and probiotics. Some of the novel prebiotics and probiotics have been enlisted in

Table 1 Properties of an ideal prebiotic (Swennen et al. 2006)

Desirable attributes	Properties of oligosaccharides
Active at low dosage	Selectively and efficiently metabolized by *Bifidobacterium* and / or *Lactobacillus* sp.
Lack of side effects	Selectively and efficiently metabolized by beneficial bacteria without producing gas.
Persistence through the colon	Preferably high molecular weight
Varying viscosity	Available in different molecular weights and linkages
Acceptable storage and processing stability	Possess 1–6 linkages and pyranosyl sugar rings
Ability to control microflora modulation	Selectively metabolized by restricted microbial species.
Varying sweetness	Varying monosaccharide composition

Table 2. It is expected that this will remain an active area of research.

Synbiotics

When Gibson introduced the concept of prebiotics he speculated as to the additional benefits if prebiotics were combined with probiotics to form what he termed as Synbiotics (DeVrese and Schrezenmeir 2008). A synbiotic product beneficially affects the host in improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract by selectively stimulating the growth and/or activating the metabolism of one or a limited number of health-promoting bacteria. Because the word "synbiotics" alludes to synergism, this term should be reserved for products in which the prebiotic compound(s) selectively favor the probiotic organism(s) (Cencic and Chingwaru 2010). Synbiotics were developed to overcome possible survival difficulties for probiotics. It appears that the rationale to use synbiotics, is based on observations showing the improvement of survival of the probiotic bacteria during the passage through the upper intestinal tract. A more efficient implantation in the colon as well as a stimulating effect of the growth of probiotics and ubiquitous bacteria contribute to maintain the intestinal homeostasis and a healthy body (Peña 2007)

Several factors like pH, H_2O_2, organic acids, oxygen, moisture stress etc. have been claimed to affect the viability of probiotics especially in dairy products like yogurts (Romeo et al. 2010).

The probiotic strains used in synbiotic formulations include *Lacbobacilli, Bifidobacteria spp*, *S. boulardii*, *B. coagulans* etc., while the major prebiotics used comprise of oligosaccharides like fructooligosaccharide (FOS), GOS and xyloseoligosaccharide (XOS), inulin, prebiotics from natural sources like chicory and yacon roots, etc. The health benefits claimed by synbiotics consumption by humans include: 1) Increased levels of lactobacilli and bifidobacteria and balanced gut microbiota, 2) Improvement of liver function in cirrhotic patients, 3) Improvement of immunomodulating ability, 4) Prevention of bacterial translocation and reduced incidences of nosocomial infections in surgical patients, etc. (Zhang et al. 2010).

Health benefits of probiotics, probiotics and synbiotics

The most important and documented beneficial effects of probiotics include the prevention of diarrhea, constipation, changes in bile salt conjugation, enhancement of anti-bacterial activity, anti-inflammatory. Furthermore, they also contribute to the synthesis of nutrients and improve their bioavailability; some probiotics are known to exert anti-oxidative activity in the form of intact cells or lysates. Probiotics have also demonstrated their inherent effects in alleviating symptoms of allergy, cancer, AIDS, respiratory and urinary tract

Table 2 Some novel prebiotics and probiotics (Saulnier et al. 2009)

Novel Prebiotics		Novel Probiotics
Prebiotic	Source	
A low-molecular-weight polysaccharide Ulvan	Agar and alginate of seaweed Gelidium CC2253 Green algae-Ulvarigida	*F. prausnitzii*
ß-glucans	Pleurotus sp. (pleuran) mushrooms	
Inulin-type fructans Oligosaccharide	Roots of traditional Chinese medicine *Morindaofficinalis* or Indian mulberry White and red-flesh pitayas (dragonfruit)	*L. plantarum*
Oligosaccharide	Yacon root	

infections. There are stray reports on their beneficial effects on aging, fatigue, autism, osteoporosis, obesity and type 2 diabetes (Harish and Varghese 2006).

As shown below a number of mechanisms are thought to be associated with probiotic beneficial effects:

1. Production of inhibitory substances like H_2O_2, bacteriocins, organic acids, etc.,
2. Blocking of adhesion sites for pathogenic bacteria.
3. Competition with the pathogenic bacteria for nutrients,
4. Degradation of toxins as well as the blocking of toxin receptors,
5. Modulation of immune responses.

Diarrhea

Diarrhea is defined by the World Health Organization as three or more loose or watery stools during 24-hour period. In the last 2 decades, several investigations on probiotic microorganisms by *in vitro* studies, animal experiments and appropriate well-designed clinical studies have validated the positive effects of probiotic consumption in arresting diarrhea of different types (Narayan et al. 2010).

a. Acute infantile diarrhea Acute infantile diarrhea caused by rotaviruses is most studied gastrointestinal condition and rapid oral rehydration is the primary treatment. Probiotics have been found to be useful as adjunct to rehydration therapy. Although limited data is available, it suggests the minimal effective dose in children is 10 billion CFU within the first 48 hours. (Szymański et al. 2006) A recent large trial with *C. difficile*-associated colitis demonstrated that *S. boulardii* prevented disease recurrence only in those individuals who had more than one *C. difficile* sequential infection. The yeast *S. boulardii* releases a protease that cleaves *C. difficile* toxins and blocks the toxin intestinal receptors. It is also found to stimulate specific intestinal antitoxin A immunoglobulin to combat the causative factor for diarrhea (Hord 2008 and McFarland 2006).

b. Antibiotic associated diarrhea: Disturbance/destruction of the indigenous microflora caused by antibiotic treatments often leads to diarrhea. The main mechanism by which antibiotics cause diarrhea is through impaired resistance to pathogens as a result of disruption of the gut microbial flora and subsequent alterations in the metabolism of carbohydrates, short-chain fatty acids, and bile acids (Bartlett 2002). Probiotics including various bacterial species like *L. acidophilus, L. rhamnosus GG, L. delbruckii, L. fermentum* etc. and the yeast *S. boulardii* are effective in reducing the incidence of antibiotic- induced diarrhea (McFarland 2006). However, it remains to be established by controlled clinical studies which probiotic is more effective and what dosage(s) are to be used. (Sudha and Bhonagiri 2012).

c. Traveller's diarrhea It is estimated that 20–60% of travellers around the world are affected by traveller's diarrhea. It particularly affects people who travel from industrialized to developing countries, especially tropical and semi-tropical regions. The most common causes are bacteria (60–85 % of cases) and most responsible bacterial pathogen is *Escherichia coli* followed by *Campylobacter jejuni*, *Shigella* spp. and *Salmonella* spp. Parasites account for about 10 % and viruses for balance 5 % of infections (Hill and Ryan 2008). It was observed that *S. boulardii* was found to be more effective on bacterial diarrhea and *Lactobacillus GG* showed effectiveness against viral and idiopathic diarrhea. *Lactobacilli, Bifidobacteria, Enterococci and Streptococci have* been used prophylactically to prevent traveller's diarrhea (McFarland 2007).

Some plausible mechanism(s) by which probiotics prevent or ameliorate diarrhea are a) Stimulation of the immune system, b) Competing for binding sites on intestinal epithelial cells (Hempel et al. 2012) or c) through the secretion of bacteriocins like nisin. However, such mechanisms are believed to be largely dependent on the nature and type of diarrhea (McFarland 2007).

Irritable bowel syndrome (IBS)

IBS is one of the most common functional gastrointestinal disorders and is a chronic condition characterized by recurrent bouts of abdominal discomfort and pain, bloating and a changeable bowel habit with an absence of any overt mucosal abnormality and flatulence. The multi-factorial pathophysiological factors for inducing IBS are: a) Psychological factors like stress and emotional status b) Social factors like upbringing and support systems and c) Biological factors like gut motility and visceral sensitivity, which interact in a complex way to exacerbate the symptoms (Tanaka et al. 2011).

VSL#3, a mixture of 8 probiotic strains and Lactobacillus *plantarum* decreased flatulence and relieved abdominal bloating (Chapman et al. 2011). Reduction in pain was observed with *L. rhamnosus*GG (Kim et al. 2005). Different studies in adults showed that *B. infantis*, *L. rhamnosus*GG and mixture of different probiotics such as *L. rhamnosus*GG, *L. rhamnosus*LC705, *B. breve*Bb99 and *Propionibacterium freudenreichii*JS were found to be effective in alleviating the symptoms (Hatakka et al. 2008). Consumption of *Bifidobacterium bifidum* MIMBb75 for 4 weeks effectively alleviated global IBS, as well as its related symptoms (Guglielmetti et al. 2011). Probiotic *Escherichia coli* Nissle 1917 has also been proved effective in IBS treatment, especially in patients with altered enteric microflora, e.g., after gastro-enterocolitis or administration of antibiotics (Kruis et al. 2012).

Soluble, non-viscous fibers as prebiotic may also be potentially useful in alleviating symptoms of inflammatory conditions, such as IBS. A good example is partially hydrolyzed guar gum which has been shown to mitigate the abdominal pain and bowel habits better than wheat bran and improve the qualitative scores of epithelial injury and inflammation (Hardy et al. 2013).

Inflammatory bowel disorder: (IBD)

IBD is chronic, relapsing, multi-factorial disorder causing inflammation of the gastro-intestinal tract that causes severe watery and bloody diarrhea accompanied by abdominal pain. IBD affects both -the colon and small intestine and includes Ulcerative colitis (UC), Crohn's Disease (CD) and pouchitis. The other reported factors involved in causing IBD are: genetic, environmental factors, dysregulation of immune system, type of intestinal microbes and oxidative stress (Moeinian et al. 2013). CD and UC both are chronic inflammatory autoimmune conditions of the gastrointestinal tract and probably are due to the lack of adaptation of the innate immune system to the environment and the "westernization" of civilization (Matsumoto et al. 2005). These diseases affect 1–5 of 1,000 individuals and represent a major burden on the national health systems of many countries on different continents. Other organs, such as the eyes, skin and joints are often affected. Recent advances in genetics and in the molecular mechanisms of the proteins coded by genes like NOD2 and CARD15 have assisted in better understanding of such complex disorder (Peña 2007).

a. Ulcerative colitis: (UC) UC like IBD mainly affects the lining of the large intestine and rectum. Long-standing UC is a risk factor for colon cancer. Use of various probiotic species like *S. boulardii*, *Lactobacillus casei* and *Bifidobacterium bifidum* has shown promising results (Kelesidis and Pothoulakis 2012). A pilot study suggested that fermented milk containing *B. breve, B. bifidum* and *L. acidophilus* was beneficial to induce mild degree remission in patients (Sheil et al. 2007).

b. Crohn's disease: (CD) Crohn's disease is a form of IBD which usually affects the intestine, but may occur anywhere from the mouth to the end of the rectum. CD causes ulceration and inflammation that affects the body's ability to digest food, absorb nutrients and eliminate waste in a healthy way. *Salmonella, Campylobacter jejuni, Clostridium difficile, Adenovirus,* and *Mycoplasma* have been identified as some of the common causative agents. There are reports suggesting the effectiveness of probiotics in countering the problems of CD (e.g.,: *E. coli Nissel*1917*, S. boulardii, Lactobacillus rhamnosus* strain *GG*, VSL#3, L. GG) in humans (Jonkers et al. 2012).

The therapeutic effects of probiotic consumption on CD are reported to be due to competitive action with commensal, pathogenic flora and an influence on the immune response system (Van Immerseel et al. 2010). Probiotics also prevent IBD by restoring integrity of the "protective" intestinal mucosa (Peña 2007).

c. Pouchitis Pouchitis is another type of IBD where ileal pouch gets inflamed especially after colectomy and ileal pouch canal anastomosis. In different studies the VSL#3 probiotic mixture was found to be highly effective for maintaining remission of chronic pouchitis (Veerappan et al. 2012). The effective probiotic strains induce distinct mucosal cytokine profiles like IL-4 and IL-10. Probiotics may also influence the mucosal cell-cell interactions and cellular stability by enhancement of intestinal barrier function by modulating cytoskeletal and tight junctional protein phosphorylation, and also by producing anti-oxidant enzymes such as superoxide dismutase and catalase thus ameliorating the IBD symptoms (Howarth 2008).

Prebiotics also have been reported to play a beneficial role in controlling the IBD. A significant reduction in the number of bacteriodetes in faeces was reported in patients with chronic pouchitis treated with 24 g per day of inulin (Langen et al. 2009). In another study, 10 Crohn's Disease patients receiving 15 g of FOS demonstrated a reduced disease activity index (Lindsay et al. 2006). In another randomized study involving 103 Crohn's Disease patients who received FOS 15 g/day showed no clinical improvement but it was able to reduce IL-6 of lamina propria dendritic cells though no change in IL-12 was observed. There was also no significant number of Bifidobacteria and *F. prausnitzii* in faeces (Scaldaferri et al. 2013).

Several studies on both acute and chronic intestinal inflammation suggest that probiotics, prebiotics and/or synbiotics may be helpful in the management of inflammatory bowel disorder (Peña 2007).

Lactose intolerance

Lactose intolerance is most common type of carbohydrate intolerance and attributed to lack of digestion of lactose due to low levels of β galactosidase enzyme activity (Lactose Intolerance- Scientific status report 2011). Symptoms include abdominal distress like diarrhea, bloating, abdominal pain and flatulence. Two possible pharmacological interventions for lactose intolerance are: 1) Treatment with commercially available lactase (tablets) or 2) With probiotics such as *Lactobacillus bulgaricus* and *Streptococcus thermophiles*. It is also observed that consumption of milk containing *Bifidobacterium longum* and *L. acidophilus* cause significantly less hydrogen production and flatulence. The combination of *Lactobacillus casei*shirota and *Bifidobacterium breve* Yakult has shown better effect and improved the symptoms of lactose intolerance significantly (Vonk et al. 2012).

Immunomodulation

Probiotic bacteria have immunomodulatory effects, adjuvant like properties and anti-inflammatory activity and affect humoral as well as cell mediated immunity. Probiotic bacteria are known to secrete factors responsible for modulating immune responses. For instance, secreted factors from *L. reuteri* decrease NF-κB dependent gene expression, resulting in diminished cell proliferation and enhanced mitogen activated protein kinase, an important event for inducing apoptosis (Delcenserie et al. 2008). As fermented milk drinks are popular sources of probiotics, it is important to note that *L. helveticus* is capable of producing factors during milk fermentation which are responsible for increasing calcineurin expression, causing increased formation of mast and goblet cells in the mouse gastrointestinal tract (Isolauri et al. 2002). The ingestion of the probiotic culture VSL#3, however, slowed down regulation of such response by reducing IL-8 secretion, even in the presence of a pathogen *Salmonella dublin* (Hardy et al. 2013).

The mechanism for the beneficial effect of prebiotics on immune function in the gut has not been well established. However, some possible cellular events have been proposed: 1) Prebiotic fibers are able to down regulate hepatic lipogenic enzymes, through increased production of short chain fatty acids (SCFA) like propionate. 2) Production of SCFA from fiber fermentation especially Butyrate has been identified as a modulator of histone tail acetylation and consequently, increases the accessibility of many genes to transcriptional factors 3) Modulation of mucin production, 4) FOS and some other prebiotics have shown increased lymphocyte and/or leucocyte numbers in gut-associated lymphoid tissues (GALT) and peripheral blood, 5) Enhanced IgA secretion by the GALT is said to stimulate the phagocytic function of intraperitoneal macrophages (Schley and Field 2002). Experimental data in animals demonstrated that inulin supplementation increased SCFA in the caecum (Artiss et al. 2006).

Synbiotics seems to be quite attractive proposition for enhancing the immune function. A combination of *B. coagulans* with inulin in diet for 6 weeks induced a significant reduction in the levels of C-reactive protein and also increased glutathione levels (Panda et al. 2006). Synbiotic supplementation of Lactobacillus, Bifidobacterium, and 10 % FOS in rats fed with high-fat, low-fiber diet suppressed intestinal and systemic inflammation and the effects were comparable to FOS supplementation (Delcenserie et al. 2008) Treatment of inflammation-prone HLA-B27 rats with similar synbiotics improved the histological changes due to inflammation (Erejuwa et al. 2014).

Cardiovascular diseases and lipid metabolism

Mann and Spoerry were the first to suggest the possible effects of probiotic consumption on lipid metabolism. They reported reduction in serum cholesterol levels in the Maasai people on consumption of fermented milk (Watson and Preedy 2010). This report created interest in the cholesterol lowering effects of fermented milks and lactic acid bacteria (Sudha et al. 2009). *L. bulgaricus, L. reuteri, B. coagulans* are some of the probiotic strains with reported hypocholerolemic effects. Studies in humans with *L. acidophilus* L1 milk, demonstrated a significant reduction in serum cholesterol. Consumption of low-fat yogurt containing *B. longum*BL1 in a trial involving 32 hypercholesterolemic patients, showed a significant decline in triglycerides, total serum and LDL cholesterol There was also 14.5 % increase in HDL cholesterol (Homayouni et al. 2012).

The hypocholesterolemic effect by probiotics could be due to 1) Decrease in hydroxyl-methyl-glutaryl-Coenzyme-A reductase in liver 2) A significant conversion of cholesterol into bile acids. Furthermore, enzymatic deconjugation of bile acids is also possible by the enzyme of probiotics. Once deconjugated, bile acids are easily absorbed by the intestine, leading to their elimination in the faeces and thus lowering of the serum cholesterol (Teitelbaum and Walker 2002), 3) Cholesterol may be removed by probiotics by incorporation into the cellular membranes during growth. *In vivo* studies are needed to verify such claims which are based on *in vitro* studies.

Prebiotics also seem to enhance the hypeprcholesterolemic activity as can be seen from the studies reported. One study in hamsters using inulin demonstrated a 29 and 63 % decrease in total cholesterol and triglycerides respectively (Nguyen et al. 2007). Another study using 40 male Sprague–Dawley rats showed a 27 % reduction in triglycerides with XOS as a prebiotic (Hsu et al. 2004). A chronic treatment of chicory inulin (20 g/day) for 3 weeks reduced serum triglycerides in men with hypercholesterolemia (Parnell and Reimer 2010).

Synbiotics have also shown promise in controlling lipid profile as borne out by one study wherein hypercholesterolemic male rats were fed with rice bran fermented with *L. acidophilus* (Oberreuther-Moschner et al. 2004). Twenty-four hypercholesterolemic male pigs were fed with a synbiotic formulation of *L. acidophilus* ATCC 4962, FOS, mannitol, and inulin for 8 weeks period and showed promising hypercholesterolemic activity (Liong et al. 2007).

Cancer

L. acidophilus is known to prolong the induction of colon tumors. It was demonstrated that feeding milk and colostrum fermented with *L. acidophilus* resulted in 16–41 % reduction in tumor proliferation (Andrews and Tan 2012). The other probiotic *L. bulgaricus* has also been reported to induce anti-tumor activity against sarcoma-180 and solid Ehrlich ascites tumors (Lee et al. 2012). The proposed mechanisms by which probiotics exert anti-tumor activity include: 1) Altering the immune functions associated with immune response 2) Anti-proliferative effects *via* regulation of apoptosis and cell differentiation. 3) Suppressing the production of enzymes like β-glucuronidase, urease, choloylglycine hydrolase, azedoreductase and nitro-reductase by bad bacteria especially entero-pathogens such as *E. coli and Clostridium perfringens*. Beta-glucosidase and urease convert pro-carcinogens in to proximate carcinogens. *Propionibacterium freudenreichii* was shown to induce cell death of human colon and gastric cancer cell lines through secretion of SCFAs in to culture media (Lee et al. 2012). Bifidobacteria probiotics reduced colon carcinogenesis induced by 1, 2-dimethylhydrazine in mice when used with FOS and inhibited liver and mammary tumors in rats (Fotiadis et al. 2008).

GOS consumption in humans resulted in reduced activity of nitroreductase which is involved in producing genotoxic metabolites, indicating the potential of prebiotics and probiotics to reduce or prevent carcinogenesis (Macfarlane et al. 2006).

Synbiotic treatment prevented azoxymethane-induced suppression of NK-cell activity in Peyer's patches, an effect not observed in the individual pro- and prebiotic treatments (Saulnier et al. 2009). Dietary administration of *B. longum* and oligofructose and inulin inhibits the formation of pre-neoplastic lesions. In addition *B. longum* suppressed mammary and colon cancer (Kaur and Gupta 2002). Overall, studies *in vitro* systems and in a wide range of animal models provide considerable evidence that probiotics, prebiotics and synbiotics exert anti-neoplastic effects. (Fotiadis et al. 2008).

Additional benefits of prebiotics

Obesity

A breakthrough paper published in Nature reported that microbial population present in the gut is different for obese and lean people, and that when obese people lost weight their microflora resembled to that of lean people. Diets containing high fibers typically have lower degrees of fat and energy density, and helpful for reducing the risk of obesity by promoting satiety and weight loss (Ley et al. 2006). This is further supported by experimental studies which demonstrated that in the lean and obese mice, gut microbiota affects energy balance by influencing the efficiency of calorie harvested from the diet, as well as utilization and storage of harvested energy (Stienstra et al. 2012). Recent study on overweight adults with wheat dextrin, demonstrated a progressive and significant increase in satiety, and decrease in hunger feeling (Erejuwa et al. 2014).

Bioavailability and uptake of minerals

Minerals like Ca, Mg, Fe, K etc. are the macronutrients required for the smooth functioning of the body. Studies have demonstrated enhancement of Ca absorption with prebiotic intake, mainly fructans. A 12-month study of 100 adolescents ingesting 8 g/day short- and long-chain inulin fructans showed a significant increase in Ca absorption and improved greater bone mineral density (Abrams et al. 2005). Ovariectomized rats were fed with Inulin and FOS. They showed higher Ca absorption, although the results depended upon the Ca:FOS ratio in the diet (Web 2011). However, daily consumption of cereal containing a combination of short- and long-chain fructo-oligosaccharides (9 g/day) as part of a controlled diet did not benefit calcium absorption or retention in adolescent girls (Whisner et al. 2013)

It is postulated that in the colon the fiber, undergoes fermentation by the intestinal microflora resulting in the formation of SCFA which lowers the luminal pH. The insoluble, unabsorbed calcium is converted to the ionic form in the acidic medium. Both, low pH and SCFAs result in the hypertrophy of the mucosal cells, leading to an enlargement of the surface area of the intestine and thus enhanced calcium absorption. Prebiotic intake also promotes mucin production which contributes to the lower incidence of bacterial translocation across the gut barrier. It is hypothesized that non-digestible oligosaccharides enhance the permeability of the tight junctions of the ileum (Schley and Field 2002). Thus, increased calcium absorption is most likely mediated by its increased solubility within the colon owing to fermentation of the prebiotic and the subsequent decrease in intraluminal pH (Cashman 2003).

Laxation and regularization

It is well recognized that fiber is important for normal laxation. This is primarily due to the ability of fibers to increase stool weight due to its physical presence, water retained by the fiber, and increased bacterial mass from fermentation. Larger and softer stools increase the ease of defecation and reduce transit time through the intestinal tract, which may help to prevent or relieve constipation. In general, cereal fibers are the most effective at increasing stool weight. Wheat bran is considered the gold standard when it comes to fecal bulking, Inulin, although extensively fermented, has little effect on stool weight, (Bonnema et al. 2010). Not all fibers have the same effect on gastrointestinal tolerance; FOS can cause symptoms with low doses (10 g) while other fibers, such as poly-dextrose and resistant starch have been consumed at doses up to 50 g without symptoms (Kaur and Gupta 2002).

The soluble fibers have a broader effect on the gastrointestinal tract. They tend to be fermented extensively and are sometimes metabolized quantitatively to hydrogen, methane, carbon dioxide and SCFAs. SCFAs reduce the intraluminal pH which favors the growth of bifidogenic and other lactic acid bacteria. SCFAs also stimulate water and electrolyte absorption in the intestine and hence reduce the risk of diarrhea and dehydration. They also increase colonocyte proliferation and metabolic energy production (Van den Abbeele et al. 2010).

Synbiotics have also been suggested to alter the composition of the colonic microbiota, reduce inflammatory processes in the gut mucosa and have ability to induce remission in IBD as well as prevention of travellers' diarrhea and improved the overall quality of life in patients. (Romeo et al. 2010, Pokusaeva et al. 2011).

Future emerging areas of research

1. Concerted research efforts are being directed to establish the probiotic effects on cardiovascular disorders like myocardial infarction, atherosclerosis etc.(Loscalzo 2011)
2. Neuro-gastroenterologist Dr. Gershon's working hypothesis postulates the existence of an enteric nervous system, its role and its participation in gut's physiology and other associated gut disorders (Gershon 1998). The afore mentioned hypothesis can be addressed by understanding the role of "Microbial endocrinology"- Probiotics synthesize as well as respond to the neuroactive compounds (Roshchina 2010).

Challenge for probiotic formulations

Inappropriate use of the term "probiotic" and failure to recognize the importance of the strain specificity and dose specificity is a concern today. Probiotics when produced as nutritional supplements, not drugs, undergo less regulatory scrutiny as it is not mandatory for the manufacturer to substantiate claims of efficacy or safety of foods and nutraceutical supplements. This is a main reason for poor to non-existent efficacy and safety information on most commercial products.

The challenge for experts working on the medical aspect of functional foods and probiotics, prebiotics, synbiotics and novel foods is to apply the new knowledge generated by basic scientists in the field of intestinal flora. Peña (2007) has suggested that probiotic research stands today at the intersection of gastroenterology, immunology and microbiology and is highly dynamic in both the basic and the clinical field. Further understanding of the complex molecular mechanisms leading to the effectiveness of probiotics will also spur the development of more successful probiotic formulations.

The pitfalls and inherent defects of commercial probiotic products and remedial measure are delivery of inadequate quantity of probiotics to the lower gastrointestinal tract - specifically the acidic environment of the stomach (Pathak 2011). Therefore, a more specific target delivery system along with appropriate dosage needs to be evolved. Additional developments required are: 1) The probiotic formulation should have an enhanced shelf life and should deliver live active probiotic cells even after prolonged storage 2). Evaluation methods need to be established to make sure that the formulation actually contains clinically proven viable probiotics bacteria (Both et al. 2012).

Limitations of probiotic research

Our understanding of mechanisms involved in beneficial effects of probiotics, probiotics as well as synbiotics is rather superficial. Incomplete information about probiotic dosages required for particular clinical effects adds to the need for molecular characterization of probiotics for establishment of health claims. Direct evidences are still limited for understanding the immune mechanisms by which probiotics are able to exert the beneficial effects. Formulations like #VSL-3 containing a cocktail of probiotic strains have not been studied for the probiotic interactions between those strains. This remains the grey area which needs to be explored (Boyle et al. 2006). In designed clinical trials and validation studies with larger sample size there is a need to understand the interactions between the microbiota, the host and the prebiotic component.

In the realm of manufacturing process and subsequent formulation there is very limited published literature and lot needs to be done to improve the survival of strains during formulation and storage. There is a requirement for more properly.

Debated roles of probiotics and prebiotics

Occurrences of probiotic(s) causing harm are rare, but the most commonly encountered side effect is gastrointestinal distress like bloating. *S. boulardii* and *Lactobacillus GG* have been reported to accelerate the complications in specific patient groups especially the immune-compromised subjects (Szajewska et al. 2010). Pregnant women, newborns and elderly people are at higher risk of potential probiotic infection because they are immune-compromized. Several Lactobacillus strains are naturally resistant to vancomycin, this raises concerns regarding the possible transfer of such resistance to more pathogenic organisms in the gut *milieu* (Saulnier et al. 2009).

Fermentation of FOS in the colon leads to production of hydrogen and carbon dioxide which can cause discomfort to people. Excessive intake of prebiotics especially oligosaccharides like FOS, GOS etc. causes abdominal discomfort like bloating and distension, as well as significant levels of flatulence (Niittynen et al. 2007).

Conclusions

Overall in this review probiotics, prebiotics and synbiotics have been discussed with respect to the systemic effects they exert on the host's health, metabolism and immune system. Probiotics, probiotics and synbiotics have systemic effects on the host's health metabolism and immune system. Utilization of prebiotics by probiotics should be a pre-requisite for symbiotic selection, in order to maintain a good synergy between the two and maximize the beneficial effects. By establishing the underlying mechanisms of probiosis and prebiosis, scientists would be able to design enhanced functional foods to improve host health. The ability to regulate the composition of the microbiota by prebiotic dietary substances and probiotic microorganisms is an interesting approach in the control and treatment of some major diseases. The recent advances in technology have enabled the deep sequencing and analysis of the unexpected diversity of the microorganisms in the GIT and it should be able to prevent the diseases and also facilitate to maintain a better health.

There are many published reports on the use of probiotics in humans but information on prebiotics and synbiotics is rather scanty. Furthermore, the health claims made needs to be substantiated and firmly established by properly designed large scale clinical trials. The ability to target specific organisms in the large intestine for defined, health-promoting purposes would be of great value. There are considerable differences in bacterial carbohydrate utilization patterns among the different strains as well as species, which is to be kept in mind for developing new synbiotics.

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