Pre- and Probiotics: Using Functional Foods in the Fight Against Microbial Resistance to Antibiotics

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Abstract

Functional foods such as prebiotics, dietary fibers, and probiotic microorganisms have several beneficial effects on the human body. Probiotic microorganisms are reported to produce and enhance the absorption of vitamins and minerals, short-chain fatty acids, amino acids, and organic acids, resulting in the enhancement of the host immune system. Generally, lactic acid bacteria and yeasts are used as probiotics. Prebiotics are nonabsorbable polysaccharides/oligosaccharides such as fructooligosaccharides, inulin, and human milk oligosaccharides and have positive effects on host health, maintaining the balance of the gut microbiome, as well as stimulating immunomodulatory activity. Prebiotics are not metabolized by digestive enzymes, allowing them to reach the colon unaltered, where they can be fermented by probiotics. They also promote mineral absorption and act as a fertilizer for gut microflora. These prebiotics can act in synergy with probiotics (synbiotics) and can thus be even more effective if used wisely, selectively stimulating the growth of specific microorganisms. As these synbiotics can directly inhibit the growth and colonization of pathogens and regulate the immune system, they can be developed as an alternative strategy for combating antibiotic resistance in pathogens.

Keywords

Probiotic · Prebiotic · Synbiotic · Antibiotic resistance · Gut microflora

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1 Introduction

The health benefits of the indigenous microflora of the human body are evident, and the effects on mucosal immunology have recently received considerable attention. This has led to a resurgence of focus on maintaining the gut microbial balance, and in the use of prebiotics and probiotics. Probiotics are live microbial supplements that beneficially affect colon health by improving microbial colonization. Prebiotics, on the other hand, are indigestible food ingredients, such as oligosaccharides, which act by selectively increasing the growth of beneficial microorganisms in the colon, such as *Bifidobacteria* and *Lactobacilli*, eventually improving host health. A synbiotic is a combination of prebiotics and probiotics that work synergistically by improving the colonization and survival of beneficial microflora inside the GI tract. The intestinal mucosa forms a first line of defense, acting as a barrier to pathogens and toxins. Further inhibition of pathogens by the intestinal microbiota occurs due to their barrier effect, microbial interference, antagonism, colonization resistance, and competitive exclusion of harmful microorganisms. As gut immunity is directly affected by available nutrients and the resident microbial community, it can be targeted by therapeutic approaches in order to treat various diseases.

2 Probiotics

Probiotics (meaning "for life") are microorganisms which have health-promoting effects in humans and animals (Marteau et al. 2001). Schrezenmeir and de Vrese (2001) defined the term "probiotic" as "a preparation of or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial health effects in this host." These beneficial microorganisms are utilized to alter the indigenous microflora, "the usually complex mixture of bacterial population that colonizes (establishes in size over time without the need for periodic reintroduction of the bacteria by repeated oral doses or other means) a given area in the host that has not been affected by medical or experimental intervention, or by disease" (Schrezenmeir and de Vrese 2001). It should be noted that probiotics do not solely influence the GI tract, but they also influence other organs as well via by regulation of intestinal permeability, bacterial translocation, and immunomodulatory activities.

When considering probiotic usage, it must be taken into consideration that the GI tract contains a mixture of surfaces that are primarily colonized by differing types of microorganisms. For example, several indigenous, pathogenic, or beneficial microorganisms colonize the surface of the gut epithelium via adhesion mediated by special organelles, such as fimbriae (Beachey and Courtney 1987; Gibbons and Houte 1975), while the mucosal crypts are colonized by motile, spiral bacteria, such as *Borrelia, Treponema, Spirillum*, and *H. pylori* (Lee 1985).

The most commonly used probiotic food supplements include *Lactobacillus, Bifidobacterium, Enterococcus, Bacillus, Escherichia, Streptococcus,* and *Saccharomyces* (Jin et al. 2000; Alvarez-Olmos and Oberhelman 2001; Reid et al. 2003). The first probiotic, *Lactobacillus rhamnosus* GG (LGG), was first utilized in 1995, and has since shown beneficial health effect including improvement of intestinal immunity (Brestoff and Artis 2013). However, the concept of ameliorating microbial imbalance for longevity and health is almost a century old. In the early 1900s, Elie Metchnikoff, a Nobel laureate, also called the grandfather of modern probiotics, hypothesized about the consumption of fermented milk products in human health and longevity in his book *The Prolongation of Life*. Although his concept was not taken seriously until 80 years, now modern-day research has proven the importance of his hypothesis culminating in our increased understanding of mechanisms and the potential benefits of healthy gut flora (Anukam and Reid 2007).

3 Mechanism of Action

Probiotic microorganisms have several beneficial effects on the human body (Hemarajata and Versalovic 2013). Some are natural producers of vitamin B complex, can enhance the absorption of vitamins and minerals, and can trigger the generation of short-chain fatty acids, amino acids, and organic acids, resulting in enhancement of the host immune system (Sanders et al. 2007; Nova et al. 2007; Ouwehand et al. 1999; Mishra and Lambert 1996). They also have a direct and indirect influence on pathogenic bacteria, such as *Staphylococcus aureus* (Sikorska and Smoragiewicz 2013), *Clostridium perfringens* (Schoster et al. 2013), *Salmonella* Enteritidis (Carter et al. 2017), *Shigella* spp. (Hussain et al. 2017), *Escherichia coli* (Chingwaru and Vidmar 2017), and *Campylobacter jejuni* (Saint-Cyr et al. 2017). Probiotics can also suppress pathogens by stimulation, proliferation, and differentiation of the epithelial cell as well as fortification of the intestinal barrier (Thomas and Versalovic 2010). In addition to balancing the gut microflora, probiotics can be used to counter food poisoning, candidiasis (Kumar et al. 2013), dental caries (Näse et al. 2001) and as a treatment for food allergies (Thomas and Greer 2010; Markowiak and Śliżewska 2017), among many other applications. In terms of disease resistance, they operate by several mechanisms (Fig. 1), listed as follows:

1. **Generation and synthesis of vitamins, amino acids, and fatty acids.**
   - Probiotic microorganisms such as *Lactobacillus reuteri* (Gu et al. 2015), *L. plantarum* (Li and Gu 2016), *Bifidobacterium adolescentis* (Pompei et al. 2007), and *B. pseudocatenulatum* are known producers of vitamin B complex (B1, B2, B3, B5, B6, B7, B9, and B12) and can provide several essential amino acids and fatty acids to the host. Moreover, *Lactobacillus* can enhance the absorption of vitamins and mineral compounds.
2. **Competition with pathogens for adhesion to the epithelium and for nutrients and maintaining the balance of the host's intestinal microbiota** (Elli et al. 2000; Weinberg 1997).

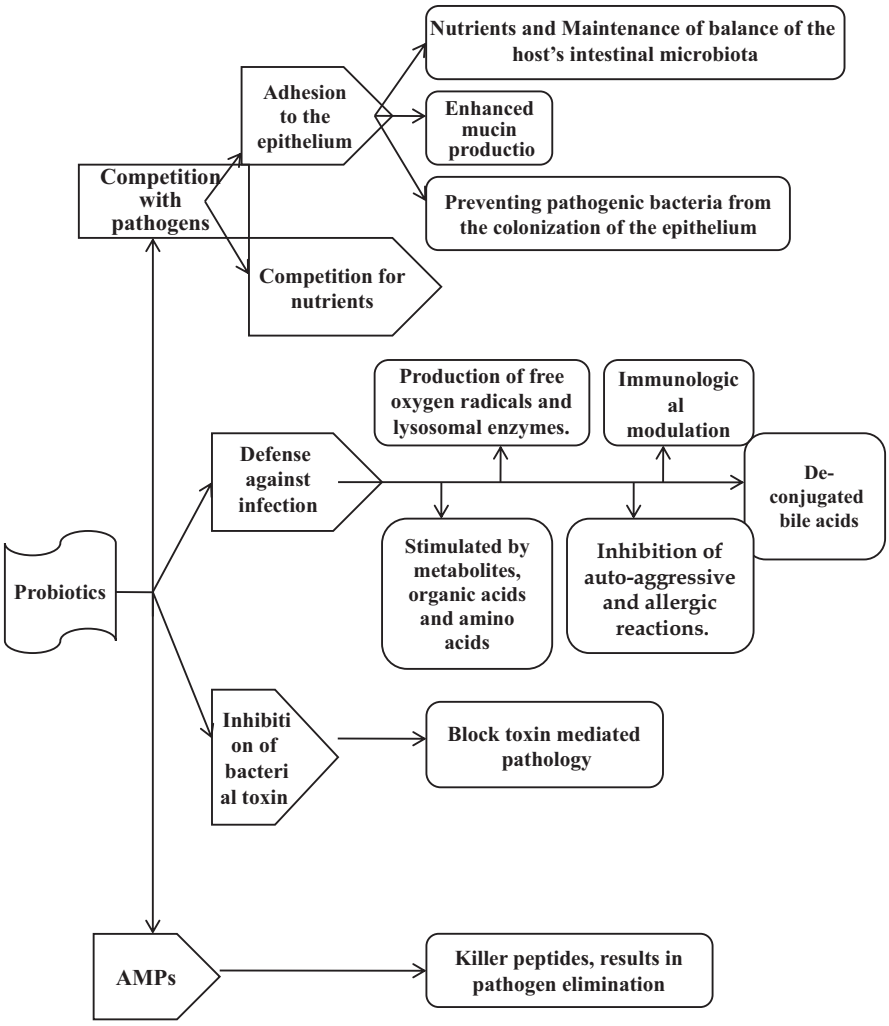

Fig. 1 Mechanisms of action of probiotics

- Lactic acid bacteria produce organic acids, predominantly lactate and acetate, creating an acidic environment that is inhibitory to pathogens.
- *Lactobacillus delbrueckii* inhibits the growth of other microbes by binding iron hydroxide to its cell surface, making it unavailable to other microbes The bacterium does not need iron in their natural environment, hence it becomes an advantage over other microorganisms.
- Lactobacilli coaggregate, leading to the formation of a protective physical barrier, preventing pathogenic bacteria from colonizing the epithelium.
- Probiotics often have better ability to adhere to epithelial cells.

3. **Direct defense against infection by antagonism through the production of antimicrobial substances** (Oelschlaeger 2010; Begley et al. 2006).
   - Probiotics synthesize proteins or peptides capable of inhibiting specific pathogenic strains. These antimicrobial compounds have potential applications as food preservatives or prophylactic agents against enteric infections.
   - Lactic acid bacteria produce many inhibitory peptides such as lantibiotics (class I), low-molecular-weight bacteriocins (class II) (LMWB), antibacterial peptides, high-molecular-weight (class III) bacteriocins, and antibiotics (acidophilin, lactacin).
   - Low-molecular-weight substances produced by probiotic microorganisms (e.g., hydroperoxide and short-chain fatty acids) can inhibit the replication of pathogens.
   - Deconjugated bile acids (derivatives of bile acids), like those produced by *Lactobacillus* and *Bifidobacterium* spp., result in stronger antibacterial bile salts as compared to those produced by their host.
4. **Enhancement of the host defense system against pathogens** (Guillot 2003; Brestoff and Artis 2013).
   - The mucosal epithelial cell barrier is the first line of defense against pathogen attack. The adhesion of probiotic microorganisms to epithelial cells may also trigger a signaling cascade, leading to immunological modulation.
   - Enhanced mucin production, as well as the reduction of gut permeability, prevents penetration of pathogenic organisms.
   - Probiotics can stimulate the activity of macrophages via production of free oxygen radicals and lysosomal enzymes.
   - The acquired immune system can be stimulated by metabolites or components of the cellular wall or DNA, which can trigger a signaling cascade, leading to immunological modulation.
   - Induction and maintenance of immunological tolerance to environmental antigens (nutritional and inhalatory), and induction and control of immunological reactions against pathogens of bacterial and viral origin.
   - Inhibition of auto-aggressive and allergic reactions.
   - Enhanced activity of macrophages and lymphocytes, and stimulation of γ-interferon production.
   - Generation of organic acids and amino acids resulting in regulation of host metabolism and immunological modulation.
   - Production of enzymes, such as esterase, lipase, and coenzymes A, Q, nicotinamide adenine dinucleotide (NAD), and nicotinamide adenine dinucleotide phosphate (NADP).
5. **Inhibition of bacterial toxin production** (Brandão et al. 1998)
   - Mucin production and reduction of gut permeability prevent the penetration of toxic substances.
   - Some lactobacilli use enzymatic mechanisms to modify toxin receptors and can block toxin-mediated pathology.

4 Probiotic Microorganisms and AMPs

Considering the recent alarming rise in antibiotic resistance among pathogens, there is an urgent need for the discovery of novel antimicrobials. A potential dual therapy to fight against infectious diseases is the use of probiotics and antimicrobial peptides (AMPs) as novel strategies in the control of multidrug-resistant (MDR) pathogens. This strategy provides additional advantages by combining the benefits of probiotics with the antimicrobial activity of AMPs (Candido et al. 2014). Therefore, many researchers are searching for novel AMPs (Silva et al. 2011), including a group of innate immune effectors which can sufficiently control MDR pathogens (Silva et al. 2011). Furthermore, various probiotic microorganisms have the ability to produce their own AMPs. A limitation of AMPs is that they cannot be taken orally, due to their quick degradation before reaching their targets (Candido et al. 2014). Therefore, probiotic microorganisms having capability to produce AMPs are good alternative sources of antimicrobial agents currently attracting keen interest as health supplements. Table 1 describes some examples of AMP, their bacterial sources, and their activities.

5 Probiotic Microorganisms

The majority of probiotic microorganisms belong to the genera *Bifidobacterium* and *Lactobacillus*, as they are normal gut inhabitants in humans and animals (Anukam and Reid 2007). However, some yeasts and other bacteria, such as *Bacilli*, also exhibit exceptional probiotic properties (Anukam and Reid 2007). Lactobacilli are Gram-positive lactic acid-producing bacteria found in an array of habitats that are rich with carbohydrate-containing substrates, such as animal and human mucosal membranes, spoiling food/plant materials, sewage, and fermented milk products.

Table 1 Examples of AMPs, their bacterial sources, and their activities

Bacterial source	AMP	Activity
Lactobacillus acidophilus *Lactobacillus amylovorus* *Lactobacillus brevis* *Lactobacillus bulgaricus* *Lactobacillus casei* *Lactobacillus curvatus*	Acidolin, acidophilin, lactacin B Lactobin A Lactobacillin, lactobrevin Bulgarin Lactocin 705 Curvacin A	- Control of enteropathogenic organisms and spore formers - Effects of organic acids and hydrogen peroxide - Antimicrobial activity - Control of *Listeria monocytogenes* and mainly foodborne pathogens - Control of *Listeria monocytogenes* and *Enterococcus faecalis*
Leuconostoc gelidum	Leucocin A	Bactericidal
Enterococcus faecium CTC492	Enterocin A	Anti-listerial activity
Pediococcus acidilactici	Pediocin AcH, pediocin F	Inhibit foodborne pathogens

Bifidobacteria are nonmotile, nonsporulating rods and are mostly composed of strict anaerobes. Regardless of the genera, in general, probiotic microorganisms are selected from lactic acid-producing bacterial strains or other microorganisms known to impart health benefits (Brestoff and Artis 2013). Some of the most commonly used probiotic microbes are listed here:

Bacteria

- ***Lactobacillus* spp.:** *L. amylovorus, L. acidophilus, L. casei, L. gasseri, L. helveticus, L. johnsonii, L. pentosus, L. plantarum, L. crispatus, L. reuteri, L. rhamnosus, Lactococcus lactis*

***Bifidobacterium* spp.:** *B. adolescentis, B. breve, B. animalis, B. bifidum, B. infantis, B. longum,*

Other bacterial strains: *Enterococcus faecium, Streptococcus thermophilus, Bacillus clausii, Bacillus cereus, Escherichia coli, Propionibacterium freudenreichii*

Yeasts:

- *Saccharomyces cerevisiae, Saccharomyces boulardii*

6 Probiotic Selection Criteria

The microorganisms selected as candidate probiotics should be readily associated with gastrointestinal tract of healthy individuals, nonpathogenic and safe. They should have high cell viability and should be resistant to bile, hydrochloric acid, and pancreatic juices in order to survive the adverse acidic and alkaline conditions of the abdomen and duodenum. They should be highly competitive to gut microflora for effective colonization to be possible. Microorganisms having immunomodulatory or anticancerous ability are also preferred. Safety considerations are essential, and probiotics are subject to regulations of global food safety agencies, according to which they should be proven safe for human and animal health, or should be classified as GRAS (Generally Regarded As Safe), as determined by the Food and Drug Administration (FDA) in the United States (Anadón et al. 2006; Gaggìa et al. 2010). Additionally, probiotic microorganisms should be genetically stable, with no adverse genotypes, and have a low potential for antibiotic resistance development. They should also exhibit weak competition with regard to beneficial microbiota inhabiting the intestinal ecosystem, and their production should be simple and practical, producing highly viable and stable cell counts that are resistant to bacteriophages, and with a high storage survival rate in finished products. Finally, the finished product should have desirable sensory properties and palatability.

7 Commercially Available Probiotics

While any microorganism can have probiotic properties, most are bacterial, with lactic acid bacteria being the most common. Probiotics can be differentially categorized as natural health products (Canada), dietary supplements, drugs, live biotherapeutic agents, medical foods (USA), functional foods (Japan, China, Malaysia, and India), food supplements (Sweden, Denmark, and Finland), or biotherapeutic/pharmaceuticals (Belgium, Germany). According to the market analysis on the probiotic industry, the European market is the highest ranked, while Japan's is the second highest. Probiotics can be commercially available in various delivery forms, including powder, liquid, gel, paste, granules, capsules, injections, and sachets. Probiotic microorganisms may also be present in pharmaceutical products as food additives and may contain one or more selected microbial strains (Gilliland and Speck 1977). For example, VSL3 is a probiotic comprised of eight different strains of live, lyophilized lactic acid bacteria including *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*. Regardless of the formulation, commercial probiotic products should have an extended shelf life and should be able to deliver live active probiotic cells, even after prolonged storage, in inadequate quantity to the lower gastrointestinal tract. Some commercial probiotic products are enlisted in Table 2.

8 Status of Probiotics in India

Since the awareness about probiotics and their health benefits has grown tremendously among the Indian population, the demand for probiotic foods has greatly increased. Indian and multinational companies have multiplied rapidly since they first entered the Indian food industry in 2007, with milk and fermented milk products comprising 62% of the market share. In fact, the Indian probiotic market, valued at just $2 million USD in 2010, increased to nearly $310 million by 2011, and the value is estimated to increase to as high as $522.8 million by 2018.

Major pharmaceutical companies have become active in the probiotic market, and are attempting to formulate newer, more effective, drugs and more desirable products, such as probiotic-based nutritional supplements. In India, Amul, Nestle, and Mother Dairy are contributing significantly to the production and distribution of probiotic dairy products, and acceptance among the urban population is helping to grow the industry [Raja and Arunachalam 2011]. Several probiotics-based pharmaceutical products are already available on the market, some of the most prevalent of which are listed in Table 3.

Table 2 Commercially available probiotics

Strains	Probiotic product	Company	Country
Lactobacillus rhamnosus GG	Leporanta	Valio Dairy, Helsinki (www.valio.com)	Finland
Lactobacillus casei Shirota, *Bifidobacterium breve*	Yakult	Yakult, Tokyo (www.yakult.co.in)	Japan
Lactobacillus johnsonii Lal		Nestle, Lausanne (www.nestleinstitutehealthsciences.com)	Switzerland
Lactobacillus acidophilus NCFM		Rhodia, Madison	USA
Lactobacillus casei CRL-43i Gilliland (La-Mo)		Chr. Hansen, Wisconsin (www.chr-hansen.com)	USA
Lactobacillus reuteri SD 2112	Protectis	BioGaia, North Carolina (www.biogaia.com/research/lactobacillus-reuteri-strains/)	USA
Lactobacillus plantarum 299V	ProbiDigestis	Probi, Lund (https://probi.com)	Sweden
Lactobacillus casei DN 014001	Actimel	Danone, Paris (www.actimel.com)	France
Streptococcus thermophilus 1131		Meiji Milk Products, Tokyo (www.meiji.com/global/)	Japan
Bifidobacterium longum SBT-2928		Snow Brand Milk Products, Tokyo (www.meg-snow.com/english)	Japan
Saccharomyces boulardii CNCM I-745	Enterol	Biocodex, Seattle (http://ua.biocodex.com/en/Product/577/)	USA
Bifidobacterium longum BB536		Morinaga Milk Industry (www.probiotaamericas.com/morinaga-milk/)	Japan

9 Prebiotics

The term "prebiotic" was first coined by Gibson and Roberfroid (1995) and has generally been applied to carbohydrates which are metabolized by gut microorganisms, providing nutrition to intestinal epithelial cells (IECs), eventually improving overall gut health. In 2004, the definition was updated, and "prebiotics" were defined as "selectively fermented components allowing specific changes in the composition and/or activity of microorganisms in the gastro-intestinal tract, beneficial for the host's health and well-being" (Gibson et al., 2004). Finally, in 2007, the FAO/WHO described prebiotics as a "nonviable food component that confers a health benefit on the host's health by selectively stimulating the growth and activity of some genera of microorganisms in the colon, generally Lactobacilli and Bifidobacteria" (De Vrese and Schrezenmeir 2008). Prebiotics are generally nonabsorbable polysaccharides having positive effects on host health, increasing diversity

Table 3 Commercially available probiotics in India

Product	Company	Microorganisms	Formulation	Used for treatment of
Eubioz	Lupin (www.lupinpharmaceuticals.com)	*Lactobacillus acidophilus* *Lactobacillus rhamnosus* *Bifidobacterium bifidum* *Bifidobacterium longum* *Streptococcus thermophilus* *Saccharomyces boulardii*	Oral (tablet)	Constipation, acute diarrhea Immunity, bacterial infection, antibiotic-associated diarrhea, AIDS, bacterial infections, traveler's diarrhea, high cholesterol levels, depression
Econova	Glenmark (www.glenmarkpharma.com)	*Lactobacillus reuteri* *Lactobacillus rhamnosus*	Oral (capsule)	Antidiarrheal
Bifilac	Tablets, Tamil Nadu, India (www.tabletsindia.com)	*Lactobacillus sporogenes* *Streptococcus faecalis* *Clostridium butyricum* *Bacillus mesentericus*	Oral (tablet)	Diarrhea as well as the associated bloating, flatulence, and constipation

Product	Company	Microorganisms	Formulation	Used for treatment of
Actigut	Alembic (www.alembicpharmaceuticals.com)	*Lactobacillus acidophilus* *Lactobacillus rhamnosus* *Bifidobacterium longum* *Bifidobacterium bifidum* *Saccharomyces boulardii* *Streptococcus thermophilus*	Oral (capsule)	Diarrhea, traveler's diarrhea, rotavirus diarrhea in children, diarrhea associated with using antibiotics
Becelac	Dr. Reddy Lab (www.drreddys.com)	*Lactobacillus acidophilus*	Oral (capsule)	Vitamin B12 deficiency, wound healing, diarrhea, Alzheimer disease, high cholesterol, anemia, treatment of megaloblastic anemias due to a deficiency of folic acid
Vi Bact	Unique Biotech Ltd (www.uniquebiotech.com)	*Streptococcus faecalis* *Clostridium butyricum* *Bacillus mesentericus* *Lactobacillus sporogenes*	Oral (sachet)	Irritable bowel syndrome, antibiotic treatments, diarrhea, long-lasting inflammation in the digestive tract, vaginosis, ulcers in the digestive tract, sugar intolerance, irritable bowel disease
Lactisyn	Franco-Indian (www.francoindian.com)	*Lactobacillus acidophilus* *Lactobacillus lactis* *Streptococcus thermophilus* *Streptococcus lactis*	Injection	Bacterial infections, gastrointestinal disorders, diarrhea, rotavirus diarrhea in children, traveler's diarrhea, diarrhea associated with using antibiotics, immunity

(continued)

Table 3 (continued)

Product	Company	Microorganisms	Formulation	Used for treatment of
Binifit	Rexcel (www.sunpharma.com)	*Clostridium butyricum* *Streptococcus faecalis* *Bacillus mesentericus* *Lactobacillus sporogenes*	Oral (capsule)	Immunity, gastrointestinal disorders, bacterial infections
Ecoflora	Tablets India Ltd Allianz Biosciences (P) Ltd (www.abpl.co.in)	*Lactobacillus rhamnosus* *Lactobacillus reuteri*	Oral (capsule)	Vaginosis, antibiotic treatments, sugar intolerance, diarrhea, irritable bowel syndrome, irritable bowel disease, skin diseases in infants and children who are allergic to cow's milk
Sporlac	Sanzyme Ltd (www.sanzyme.com)	*Lactobacillus sporogenes*	Oral (capsules and sachet)	Diarrhea, irritable bowel syndrome, long-lasting inflammation in the digestive tract, antibiotic treatments, vaginosis, ulcers in the digestive tract
Vizyl	Unichem (unichemlabs.com)	*Bacillus mesentericus* *Clostridium butyricum* *Lactobacillus sporogenes* *Streptococcus faecalis*	Oral (capsules)	Bacterial infections, diarrhea in young children, irritable bowel syndrome, immunity, vaginosis
Darolac	Aristo Pharmaceuticals Pvt Ltd (aristopharma.org)	Lactic acid bacteria	Oral (sachet)	Bowel problems, acute diarrhea, indigestion, dyspepsia, antibiotic-associated diarrhea, inflammatory bowel disease, urinary tract infections, eczema, AIDS

in human gut microbiome, and stimulating immunomodulatory activity. They also promote mineral absorption and can act as a fertilizer for healthy gut microflora. Since the human body is not capable of digesting these plant fibers, they are directly used to boost the expansion of various desirable microorganisms within the gut. Prebiotics can be readily fermentable dietary fibers, oligosaccharides such as fructooligosaccharides (FOS), inulin, galactooligosaccharides (GOS), mannan-oligosaccharides (MOS), xylooligosaccharides (XOS), and human milk oligosaccharides. They also include conjugated linoleic acid (CLA), polyunsaturated fatty acids (PUFA), and some phytochemicals. Fruit, vegetables, cereals, and various edible plants are other sources of carbohydrates, making them potential prebiotics (Markowiak and Śliżewska 2017). Some other synthetic prebiotics include lactulose, cyclodextrins, and lactosaccharose. Fructans, like inulin and oligofructose, are believed to be the most used and most effective, in regard to several species of probiotics (Jakubczyk and Kosikowska 2000).

10 Health Benefits of Prebiotics

Prebiotics have a huge potential for modifying the gut microbiota. This potential is directly influenced by the nature of the individual strain and species, and by the gut atmosphere, especially in terms of pH, as it plays a key role in deciding the end result of interspecific competition and colonization of the gut lining (Chung et al. 2016). Prebiotics also have many health advantages, such as decreasing the prevalence and duration of diarrhea, relief from inflammation and different symptoms related to intestinal bowel disorder, and protection against colon cancer (Peña 2007). Additionally, prebiotics are also involved in enhancing the bioavailability and uptake of minerals, lowering of some risk factors of cardiovascular disease, and promoting repletion and weight loss, thereby preventing obesity (Pokusaeva et al. 2011).

11 Types of Prebiotics

Prebiotics can be grouped into various types based on their chemical nature, as follows:

1. **Polysaccharides**
   (a) **Starch and polyfructans** are good sources of prebiotics and are currently available in the market. Starch is insoluble polyglucan linked by α-(1→4) and α-(1→6) bonds, and synthesized in chloroplasts, while soluble polyfructan is stored in vacuoles (Heldt 2005). Both polysaccharides are hydrolyzed enzymatically into prebiotic oligosaccharides.
   (b) **Pectin** is a complex, galacturonic acid-rich polysaccharide and is one of the most important components of plant cell walls (Ridley et al. 2001). It is made up of covalently linked homogalacturonan (HGA), rhamnogalacturo-

nan-I (RG-I), and rhamnogalacturonan-II (RG-II) (Ridley et al. 2001), which can be used to synthesize pectic oligosaccharides by enzymatic hydrolysis or physical methods. For example, oligosaccharides of 3–4 kDa can be produced in membrane reactors by enzymatic hydrolysis of citrus and apple pectins (Olano-Martin et al. 2001), while low atomic weight arabinose-based oligosaccharides can be produced by nitric acid hydrolysis of citrus peels (Fishman et al. 1999).

2. **Oligosaccharides**
   (a) **Isomaltooligosaccharides (IMOs)** are found in fermented foods, such as miso and soy sauce, sake, and honey and can be made from starch via a two-stage enzymatic process. In the first stage, starch is converted to maltooligosaccharides by treating with α-amylase and β-amylase. Thereafter, transglycosylation of α-(1-4) linkages into α-(1-6) linkages is performed by α-glucosidase (Yoo et al. 2012). Basically, IMOs have only α-(1-6) linkages with a DP (degree of polymerization) range of 2–6. Panose, a glucose trisaccharide, has both α-(1-4) and α-(1-6) linkages. It was observed that these IMOs can be utilized by many probiotic bacteria, such as bifidobacteria and *Bacteroides fragilis*, promoting their growth (Sarao and Arora 2017).
   (b) **Gentiooligosaccharides** include α-(1-6) linked glucoses having DP range of 2–6. They are made from the hydrolysis of starch by enzymatic transglucosylation (Wichienchot et al. 2009). GOS are not digested in the stomach and small intestine therefore reaching the colon intact (Yoo et al. 2012).
   (c) **Fructooligosaccharides (FOSs)** are inulin and the structurally related FOSs are nondigestible oligosaccharides (NDO) which are commonly consumed in the human diet. Since they are not digested in the upper human gastrointestinal tract, they reach the colon intact, where they can be metabolized as dietary fibers by the resident microbiota. Inulin is widely distributed in nature as plant storage carbohydrates, being present in more than 36,000 plant species (Sarao, and Arora 2017). Good sources of inulin include garlic, onion, asparagus, chicory, artichoke, and wheat. Chemically, inulin is considered as oligosaccharide and polysaccharide having the structure GFn (where G = glucose, F = fructose, and n = the number of fructose residues linked to one another). The fructose residues are arranged in a linear form by β-(2,1) bonds, however, a single glucose molecule is linked to the end of the polysaccharide by an α-(1, 2) bond. The DP length of chicory fructans ranges from 2 to 60, with an average DP of 10 (Flickinger et al. 2003). In fact, the highest number of linked fructose residues, in general (~60), has been reported in chicory. Other types of fructans that are structurally similar to inulin have both GFn and FFn molecules, where the number of fructose residues can range from 2 to more than 70 units. These FOS, having a lower molecular weight as compared to inulin, have a positive effect on intestinal *Bifidobacteria* and are categorized as important prebiotics. Inulin extracted from chicory roots can be hydrolyzed by the enzyme inulinase under controlled conditions to produce short-chain FOSs as Glu-α1-2(β-D-Fru 1-2)n, where n = 2–9. Additionally, the

other FOS product, called "neosugar" or "meioligo," is a combination of oligosaccharides of varying lengths, including 1-ketose (Glu-Fru2) and 1F-β-fructosylnystose (Glu-Fru4). These oligosaccharides are enzymatically synthesized from sucrose by the transfructosylation of β-fructosidase.

Moreover, the β configuration of anomeric carbon in fructose is thought to make FOS resistant to digestion (Desai et al. 2004). In vitro, they selectively stimulate the growth of *Bifidobacterium* (Sarao and Arora 2017). Other bacteria, such as *Klebsiella pneumoniae, Bifidobacteria*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis, Enterococcus faecium*, *Bacteroides vulgatus, Bacteroides thetaiotaomicron, Bacteroides ovatus, Bacteroides fragilis, Lactobacillus acidophilus,* and *Clostridium*, can utilize inulin and other FOSs.

(d) **Galactooligosaccharides (GOS)** are one of the most common and well-studied types of prebiotic oligosaccharide. Lactose is transformed in GOS via β-galactosidase-mediated transgalactosylation reactions (Fai and Pastore 2015; Vera et al. 2016), namely, β-galactosidase-mediated hydrolysis of lactose followed by polymerization of β-linked sugars (Yoo et al. 2012). First, covalent bonding of the lactose molecule through its galactosyl moiety occurs with the enzyme, enabling a catalysis reaction. Thereafter, the reaction can be diverted into various paths based on the selectivity degree between the lactose concentration and enzyme, affecting the type of the galactosyl acceptor. For example, if water molecule is the acceptor, hydrolysis takes place, and as a result, a galactose-free molecule is formed. However, if the acceptor is a sugar molecule (lactose, GOS, glucose, or galactose), it acts as both the donor and the acceptor of the galactosyl moiety. The resulting oligosaccharides produce mixtures of GOS having a DP of up to 10 (Muñiz-Marquez et al. 2015). These GOSs are similar in structure and prebiotic characteristics to the oligosaccharides found in human milk (Sharon and Ofek 2000).

(e) **Xylooligosaccharides (XOSs)** are oligomers having xylose residues linked by β(1 → 4) xylosidic bonds with normal DP ranges from 2 to 6 (and up to 20) (Samanta et al. 2015). They are NDOs obtained by the hydrolysis of xylans and categorized by the number of monomers among them (xylobiose, xylotriose, xylotetraose, xylopentaose, xylohexose) (Kumar and Satyanarayana, 2011) and can be formed by chemical, enzymatic, and autohydrolysis processes (Xue et al. 2016). XOSs are considered to be ideal prebiotics, as they are soluble fibers stable over a wide range of temperatures (up to 100 °C) and pH conditions (2.5–8.0). The best sources of XOSs are various food products, such as fruits, vegetables, honey, milk, sugarcane bagasse, bamboo, corncobs, barley straw, wheat bran, and cotton stalk (Carvalho et al. 2013; Alice et al. 2012; Singh et al. 2015). In comparison to FOSs, XOSs are more stable during several food-processing techniques, such as pasteurization and autoclave sterilization at low pH characteristics (Courtin et al. 2009; Wang et al. 2009).

Health benefits of XOS are due to its selective growth of gut microbiota; increasing number of probiotic microorganisms, such as *Bifidobacteria* and

lactobacilli; immunomodulation; regulation of insulin secretion; reduction of blood cholesterol levels; enhanced mineral absorption; antioxidant activity; and anticancerous and anti-inflammatory effects (Mäkeläinen et al. 2009; Chapla et al. 2012; Samanta et al. 2015; Bian et al. 2013; Kallel et al. 2015a, b; Kyoji et al. 2006).

(f) **Mannan-oligosaccharides (MOSs)** belonging to hemicellulose groups are present in plant cell walls, and as storage carbohydrates in plant seeds (Mikkelson et al. 2013). Their nomenclature is based on the main sugar constituent. For example, mannan contains only mannopyranosyl units linked by β-1,4 bonds, and glucomannan consists of mannopyranosyl and glucopyranosyl units linked by β-1,4 bonds, and they may also have α-1,6 galactopyranosy l residues as side groups, known as galactomannans and galactoglucomannans, respectively (Mikkelson et al. 2013). The main constituent of hemicellulose is glucomannan/galactoglucomannan and galactomannan, mainly found in seeds (Moreira 2008). MOSs are less explored, but valuable, prebiotic compounds, as they stimulate the growth of probiotic microorganisms while inhibiting pathogenic microorganisms (Patel and Goyal 2012). Additionally, MOSs can be used in food, feed, and pharmaceutical fields, as these compounds exhibit a positive effect on immune-pharmacological, therapeutic, and biomedical properties (Ferreira et al. 2012; Yamabhai et al. 2016; Srivastava and Kapoor 2017).

3. Long-Chain Beta-Glucans

Cereal beta-glucans pass undigested through the GI tract, ultimately acting as substrates for probiotic microflora (Gibson et al. 2004), and thus can also be used as prebiotics (Bigliardi and Galati 2013). Pleuran, beta-glucans isolated from the fruiting body of mushroom, *Pleurotus*, are also used as food supplements and are known for their prebiotic and immunosuppressive properties (Patel and Goyal 2012). Some commercially available beta-glucan products are Ceapro from oats (Tomasik and Tomasik, 2003), Glucan Elite, a mixture of grain, yeast, and mushroom β1,3-D-Glucan (by Pro Formulations Md), Beta-1,3/1,6-D-Glucan (Now Foods), Glucagel from barley (Lam and Cheung 2013), and Betamune from Yeast (Vetvicka et al. 2008).

4. Short-Chain Fatty Acids (SCFAs)

SCFAs are produced as end-products of the metabolism of prebiotics. These volatile fatty acids have fewer than six carbons arranged in straight and branched-chain conformation, such as acetic acid, carboxylic acid, and butyric acid. They are made within the large intestine as fermentation products of unabsorbed and undigested food elements by gut microbiota. SCFAs also stimulate the synthesis of hepatic triacylglycerols. The major sources of SCFA are carbohydrates, but, amino acids, such as isoleucine, leucine, and valine, can also be transformed into isobutyrate, isovalerate, and 2-methylbutyrate, which are known as branched-chain SCFAs (BSCFAs) (Vitali et al. 2010).

12 Some Examples of Novel Prebiotics

(a) **Acacia gum (AG)** (Fibregum™) is an example of a natural prebiotic, having high gut tolerance. Due to its low viscosity and its resistance to processing, it can be used to formulate a wide range of food products with nutritional and health benefits. It is not metabolized in the upper GI tract, as it is resistant to various digestive enzymes, such as galactanases or arabinases. In the colon, AG represents an extra carbon source, providing fuel for microbial fermentation, resulting in SCFAs stimulating the growth of probiotics (Meance 2004) (Fig. 2).

(b) **Human milk oligosaccharides (HMO)** are considered to be "the first prebiotics in humans" (Coppa et al. 2004). An array of human milk oligosaccharides have been discovered recently for pediatric uses, such as lacto-N-neotetraose (LNnT) and lacto-N-biose I. Both tetrasaccharides are highly specific, natural prebiotics for *Bifidobacteria*. Lacto-N-biose I and Lacto-N-neotetraose have been artificially synthesized using N-acetylglucosamine (GlcNAc) by adding sucrose and lactose, respectively.

(c) ***L. barbarum* polysaccharides (LBP)**, isolated from *Lycium barbarum* (goji berries), contain arabinose, rhamnose, xylose, mannose, galactose, and glucose residues and have been reported to promote the proliferation of lactic acid bacteria strains, especially *Bifidobacterium longum subsp. infantis* Bi-26 and *Lactobacillus acidophilus* NCFM. It promotes the bacterial biosynthetic and metabolic processes, gene expression, transcription, and transmembrane transport. Furthermore, LBP improves cell vitality during freeze-drying and tolerance of the gastrointestinal environment. LBP can be used as a potential prebiotic for *Bifidobacterium* and *Lactobacillus* (Sohail et al. 2010)

(d) **Mushroom polysaccharides**: The polysaccharides obtained from mushrooms, e.g., *Lentinula edodes* stipe, *Pleurotus eryngii* base, and *Flammulina velutipes* base, can enhance the survival rate of *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium longum subsp. longum* in simulated gastric and bile juice conditions to achieve beneficial effects in the host. These results show that mushroom wastes, which are cheaper than most other sources, could be an important, new, alternative source of prebiotics (Singdevsachan et al. 2016).

13 Mechanism of Action of Prebiotics

Although prebiotics are naturally present in various food products, they may also be used as additives to improve the nutritional and health value of foods. Given that prebiotics are unmetabolized by digestive enzymes, they reach the colon unaltered, where they can be used as a substrate for probiotics, and can stimulate their growth, often leading to a dramatic increase in the numbers of beneficial bacteria (Schiffrin et al. 2007; Vulevic et al. 2008). Table 4 presents the mechanism of action of prebiotics on different diseases. Prebiotics modulate the intestinal microbiota and its metabolic activity by altering lipid metabolism, mineral absorption, immune system activity, and bowel function (Van Loo et al. 2005). There are many proposed models

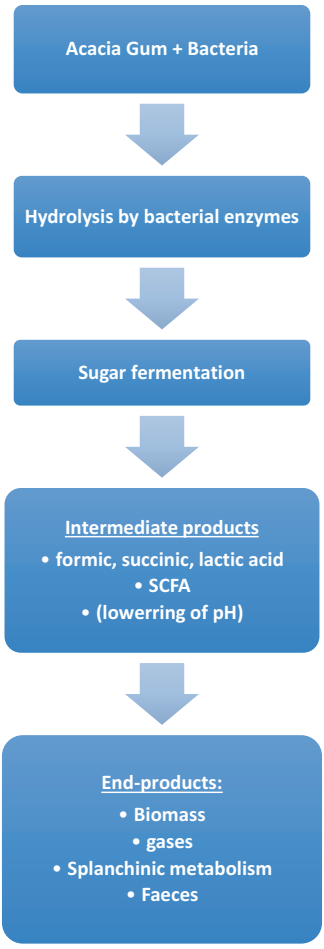

Fig. 2 Fermentation of acacia gum in the colon resulting in beneficial effects on host health through both the improvement of the composition of the large intestine microflora and SCFA formation. Yacon (*Smallanthus sonchifolius*) contains beta-1, 2-oligofructans as the main saccharides, and its roots are consumed in various South American countries. Traditionally, yacon roots and infusions from dried leaves were consumed by people suffering from diabetes or from various digestive disorders in countries such as Brazil. The percentage of FOS in yacon is 70–80% of its dry weight. Thus, yacon could be a potential prebiotic and has been found to exert an effect on the intestinal ecosystem. Yacon root flour has an immunomodulatory effect, and this effect may be indirect, being that the prebiotic stimulates the growth of *Bifidobacteria* and *Lactobacilli*. (Gibson and Roberfroid 1995)

to describe the beneficial effect of prebiotics on immunomodulation, which are as follows (Schley and Field 2002):

(a) By increased production of SCFAs, such as propionic acid, prebiotics are able to regulate the action of hepatic lipogenic enzymes.

Table 4 Prebiotics and their mechanism of action on different diseases

Prebiotic used	Disease name	Mechanism of action	References
Inulin	Crohn's disease	Enhancement of immune response	Hijová et al. (2013)
	Colitis	Effect on innate immunity	Macfarlane et al. (2008)
	Constipation	Modification of microbiota and increase in *Bifidobacteria*	Hopping et al. (2009)
FOS (fructooligosaccharide)	Crohn's disease	Increase in *Bifidobacteria*	Scholtens et al. (2006)
	Colitis	Decrease in colon pH	Benjamin et al. (2011)
	Constipation	Secretion of anti-inflammatory substances	Cummings et al. (2001a, b)
	Traveler's diarrhea	Local induction of Reactive oxygen species (ROS)	Arslanoglu et al. (2008)
GOS (galactooligosaccharide)	Crohn's disease	Improvement of growth performance and immune responses	Saavedra and Tschernia, (2002)
	Colitis	Diminishment of intestinal bacterial growth	Macfarlane et al. (2008)
Soluble fiber (guar gum, pectin)	Crohn's disease	Enhancement of short-chain fatty acid production, and mainly acetate	Peng et al. (2013)
	Colitis	Effect on epithelial permeability	Chen et al. (2013)
	Celiac disease	Normalization of intestinal microbiota	Slavin (2013)
	Metabolic syndrome	Anti-inflammatory effect	Cao et al. (2011)

(b) The produced SCFAs, such as butyric acid, can modulate histone acetylation, resulting in increased transcription.
(c) An increase in mucin production.
(d) FOS and several other prebiotics cause an increase in the number of lymphocytes and/or leukocytes in gut-associated lymphoid tissues (GALTs).
(e) The phagocytic function of intra-inflammatory macrophages has also been reported to increase the secretion of IgA by GALTs.

14 Prebiotic Selection Criteria

Any food element possessing the following properties can be considered as a prebiotic:

(i) It should be resistant to the action of extreme pH and hydrolyzing enzymes within the intestine, and should not be absorbed in the upper GI tract, instead targeting the distal colon.

(ii) It should be simply fermentable and selectively stimulate the growth and activity of beneficial intestinal microflora (Kuo 2013).

Some other desired properties of prebiotics are:

- The fermentation of prebiotic compounds results in the enhanced production or modification of various SCFAs, the reduction of pH, and an overall improvement of the immune system (Lee and Salminen 2009).
- Have low dosage requirements and low calorific value.
- Have multifarious properties with no undesired side effects.
- Should be easily added into food and possess various types of glycosidic bonds and sugar residues.
- Should have varying molecular weight and viscosity.

15 Synbiotics

The term "synbiotic" was first introduced by Gibson and Roberfroid in 1995 to describe a combination of synergistically acting probiotics and prebiotics, such as a product containing oligofructose and probiotic *Bifidobacteria*. Prebiotics are used to selectively stimulate and enhance the survival, as well as the colonization, of probiotic microorganisms in the intestine. Although more studies are required to elucidate the mechanisms of action, the health benefits of synbiotics are found to be associated with the individual combination of prebiotic and probiotic (De Vrese et al. 2008). As there can be a large number of possible combinations, the scope of application of synbiotics is very wide (Scavuzzi et al. 2014). Some commonly used examples of synbiotics are listed in Table 5.

16 Mechanism of Action

Prebiotics are used as substrates for the growth of probiotic microorganisms, and these microorganisms can flourish in the intestine (Sekhon and Jairath 2010). Synbiotics create viable dietary supplements for microorganisms and also build a suitable environment, resulting in a positive impact on the host's health. Two modes of action of synbiotics have been devised (Manigandan et al. 2012), including improving the viability of probiotic microorganisms, and providing positive health effects. They do not let the pathogen to colonize as prebiotics help probiotic microbes in colonizing the gut and give the pathogens tough competition for growth factors, nutrients and for adhesion sites (Biofilm formation) and coaggregation. The combination of pre- and probiotics strengthens host health by increased nutrient absorption. They influence the activity of certain enzymes so as to modify toxin receptors and block toxin-mediated pathology. They may be directly affecting the growth of pathogens due to their antimicrobial activity as production of AMPs as well as inhibitory compounds as hydrogen peroxide, bacteriocin, lactic acid, and

Table 5 Examples of synbiotics

Synbiotic		References
Probiotics	**Prebiotics**	
Lactobacillus casei strain *Shirota*	Oligomate 55™	Figueroa-González et al. (2010)
Bifidobacterium longum	Oligofructose	Sarao and Arora (2017)
Bifidobacterium lactis Lafti™B94	Resistant starch	Crittenden et al. (2001)
Bifidobacterium breve strain *Yakult*	Galactooligosaccharide	Kano et al. (2013)
Lactobacillus acidophilus ATCC 4962	Mannitol, fructooligosaccharide, and inulin	Liong and Shah (2005)
Lactobacillus sakei JCM	Fructooligosaccharide and trehalose	Yanagida et al. (2005)
Lactobacillus plantarum and *L. acidophilus*	Xylo- and fructooligosaccharide	Olveira and González-Molero (2016), and Sáez-Lara et al. (2016)
Lactobacillus	Inulin	Crittenden et al. (2006), Olveira and González-Molero (2016), and Sáez-Lara et al. (2016)
Lactobacillus, Streptococcus, and Bifidobacterium	FOS	Crittenden et al. (2006), Olveira and González-Molero (2016), and Sáez-Lara et al. (2016)
Lactobacillus and *Bifidobacterium*	Lactulose	Crittenden et al. (2006), Olveira and González-Molero (2016), and Sáez-Lara et al. (2016)
Lactobacillus and *Bifidobacterium*	Lactosucrose	Crittenden et al. (2006), Olveira and González-Molero (2016), and Sáez-Lara et al. (2016)
Lactobacillus sporogenes	Arabinogalactan	Dixit et al. (2016)
Lactobacillus casei or *rhamnosus*	Tagatose	Dixit et al. (2016)
Bifidobacterium and *Streptococcus* *Enterococcus* and *Lactococcus* *Staphylococcus* and *Peptostreptococcus* *Lactobacillus, Saccharomyces* *Propionibacterium*	High amylose carbohydrate Amylose-resistant starch product Fructooligosaccharide Potato Protein	Dixit et al. (2016)

ammonia by probiotics. Furthermore, synbiotics can support the immune system of the host by stimulating IgA and cytokines (TNF-α, IFN-γ, and IL-10), having an adjuvant effect, stimulating phagocytes, decreasing MMP production, immunomodulation via increased production of mucin, and producing SCFAs (propionic acid and butyric acid). The various mechanisms of synbiotic action, based on the

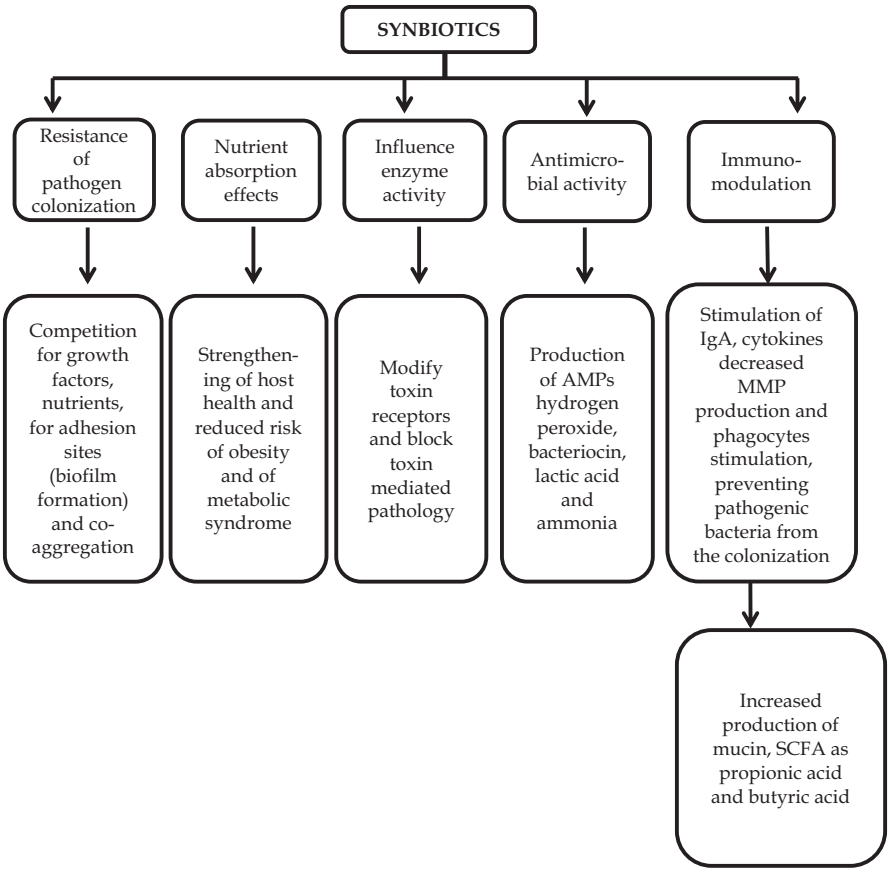

Fig. 3 Mechanism of action of synbiotics

modification of intestinal microbiota with probiotic microorganisms and appropriately selected prebiotics as their substrates, are presented in Fig. 3.

17 Beneficial Effects on Human Health

Probiotic microorganisms are stimulated by the presence of prebiotics, thereby regulating metabolic activity in the intestine. The ideal synbiotics include those with antibacterial, anti-oncogenic, and anti-allergic effects. They are helpful for the treatment of inflammatory diseases, such as inflammatory bowel disease and other syndromes, and are generally recommended along with antibiotic therapy in order to maintain the microbial balance of the intestinal tract. Synbiotics reduce the concentrations of toxic metabolites and oncogenic substances, and inhibit potential pathogens present in the GI tract (De Vrese et al. 2008). The use of synbiotics also causes significant increases in the level of SCFAs, carbon disulfides, ketones, and methyl

acetates, thus providing health benefits to the host (Markowiak and Śliżewska 2017). They also regulate the immune system, can prevent osteoporosis, and can reduce blood fat and sugar levels. Synbiotics have various other positive effects on humans including enhanced *Lactobacillus* and *Bifidobacterium* counts and the maintenance of a balanced intestinal microbiome and inhibition of bacterial translocation and reduced incidence of nosocomial infections in postsurgical procedures and similar interventions (Zhang et al. 2010). Synbiotics have also been recently shown to aid in the treatment of neurological disorders linked with abnormal liver function cirrhotic patients (Pandey et al. 2015) and can aid in the treatment of skin ailments, such as atopy. In addition to these works, countless other applications of synbiotics are currently ongoing, such as in the treatment of chronic kidney disease.

18 Synbiotic Selection Criteria

During composition of a synbiotic formula, the first feature to be taken into account is the selection of a suitable probiotic and prebiotic that each has a positive impact on the host's health when used individually. A selected prebiotic should selectively stimulate the growth of subject microorganisms, while other microorganisms remain unaffected. In addition to this, probiotics should be able to metabolize the prebiotic compounds in the environment of the GI tract and synbiotics should be in a position to inhibit the growth of pathogenic microorganisms.

19 Conclusion

As the problem of antibiotic resistance among pathogens is increasing, there is an urgent need for the discovery of novel alternative strategies. The direct and indirect beneficial effects of probiotic microorganisms can help in the fight against infectious diseases. Additionally, they can be used along with specific prebiotics as a dual therapy for the management of multidrug-resistant (MDR) pathogens. As their combined action can possibly balance the dysbiosis and these synbiotics can be further developed to directly inhibit the growth and colonization of pathogens as well as regulate the immune system, for combating antibiotic resistance in pathogens.

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