ejpmr, 2021,8(11), 123-135

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

IMPACT OF PROBIOTICS, PREBIOTICS AND SYNBIOTICS IN MAINTAINING GASTROINTESTINAL MICROBIOTA: AN UPDATED REVIEW

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Article Received on 23/08/2021 **Article Revised on 13/09/2021** **Article Accepted on 03/10/2021**

ABSTRACT

The human gastrointestinal (GI) tract is colonised by a complex ecosystem of commensal microorganisms. Intestinal bacteria undergo a synbiotic co-evolution along with their host. Beneficial intestinal bacteria have various important functions such as production of various nutrients for their host, prevention of infections caused by intestinal pathogens, and modulation of normal immunological response. Modification of the intestinal microbiota is required in order to achieve, restore, and maintain favourable balance in the GI ecosystem. The activity of GI microorganisms is necessary for the improvement of health condition of the host. Probiotics have become a popular approach for managing digestive and immune health and are being recommended more frequently as effective therapeutic interventions by medical professionals. Probiotics are live microorganisms that promote health benefits upon consumption, but prebiotics are nondigestible food ingredients that selectively stimulate the growth of beneficial microorganisms in the GI tract. The introduction of probiotics, prebiotics, or synbiotics into human diet is favourable for the intestinal microbiota. They may be consumed in the form of raw vegetables and fruit, fermented pickles, or dairy products. Another source may be pharmaceutical formulas and functional food. This paper provides a review of available information and summarizes the current knowledge on the source, selection criteria, beneficial action and mechanism of action of probiotics, prebiotics, and synbiotics on human health.

KEYWORDS: Probiotic bacteria, prebiotics, synbiotics, human health, gut microbiota, clinical benefit.

1. INTRODUCTION

Nowadays, the increasing evidence not only suggest that the composition and metabolic effects of the gastrointestinal (GI) microflora are key importance for human health but also these are seems to exert important effects on systemic metabolism and immune functions. In the world of highly processed food, particular attention is drawn to the composition and safety of consumed products. The quality of food is very important because of the problem of food poisoning, obesity, allergy, cardiovascular diseases, and cancer-the plague of the 21st century (Hollingsworth, 1997). Considerable efforts have been made by dietary to influence the intestinal microbiota so that the health of the host is beneficially affected. Consumer's belief that certain foods can exhibit health benefits has resulted in the coining of the term functional foods. Functional food is described as nutrients that are separated from their established nutritional functions (Duggan et al., 2002). Functional food comprises of some bacterial strains and products of plant and animal origin containing physiologically active compounds which are beneficial for human health and reducing the risk of chronic diseases (Grajek et al., 2005).

Probiotics are defined as "live microbial food ingredients that are beneficial to health when administered in adequate amounts" (Hill et al., 2014); prebiotics are defined as "non-digestible food components that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, that have the potential to improve host health", and synbiotics are defined as "mixtures of probiotics and prebiotics that beneficially affect the host by improving the survival and implantation of live microbial dietary supplements in the GI tract" (Diplock et al., 1999). These definitions were issued by a consensus panel convened by the International Scientific Association of Probiotics and Prebiotics (ISAPP), which met to discuss the modern relevance of the 2001 Food and Agriculture Organization (FAO)/World Health Organization (WHO) definition of probiotics (FAO & WHO 2001). This review paper was highlighted on current knowledge of the source, selection criteria, beneficial action and mechanism of action of probiotics, prebiotics, and synbiotics on human health.

2. Probiotics

The word "probiotic" comes from the Greek word "pro bios" which means "for life"; completely opposite term of "antibiotics" which means "against life." The history of probiotics started with the consumption of fermented foods by Greek and Romans. It is hypothesized that Bulgarians are healthy and long-lived due to consumption of fermented milk products that consist of rod-shaped bacteria (*Lactobacillus* spp.) that affect the gut microflora and decrease the activity of microbial toxins (Gismondo et al., 1999).

The term "probiotic" was first used in 1965 by Lilly and Stillwell to describe the substances which stir up the growth of other microorganisms. Based on its mode of action and its beneficial effects on human health, the word "probiotic" was used in different interpretations. In 1974, Parker improved the definition of probiotic and defined "probiotic" as "substances and organisms which contribute to intestinal microbial balance." (Parker, 1974). In 1989, the definition of probiotic was re-defined by Fuller. Probiotic microorganisms do not act in the large intestine via affecting the intestinal flora. They also affect other organs, either by modulating immunological parameters, intestinal permeability, and bacterial translocation or by providing bioactive or otherwise regulatory metabolites (Fuller, 1989).

More than 400 bacterial species exist in the human intestinal tract. It is an enormously complex ecosystem that includes both anaerobic and facultative anaerobic microorganisms (Naidu et al., 1999). The composition of the gut microflora is constant but can be affected by some factors such as age, diet, environment, stress, and medication. The majority of probiotic microorganisms belong to the genera *Lactobacillus* and *Bifidobacterium*. Besides this, several other bacteria and some yeasts also have probiotic properties (Table 1).

Lactobacilli and *Bifidobacteria* are Gram positive lactic acid-producing bacteria that constitute a major part of the normal intestinal microflora in animals and humans. *Lactobacilli* are nonspore forming rod-shaped bacteria. They have complex nutritional requirements and are strictly fermentative, aerotolerant or anaerobic, and aciduric or acidophilic. *Lactobacilli* are found in a variety of habitats where rich, carbohydrate-containing substrates are available, such as on human and animal mucosal membranes, on plants or material of plant origin, on sewage, and on fermented milk products, fermenting or spoiling food (Vrese and Schrezenmeir, 2008).

Table 1: The probiotic microorganisms which are used to feed both man and animals (Anandharaj et al., 2014).

Lactobacillus species	*L. acidophilus*, *L. amylovorus*, *L. rhamnosus*, *L. gasseri*, *L. casei*, *L. reuteri*, *L. delbrueckii*, subsp. *Bulgaricus*, *L. crispatus*, *L. plantarum*, *L. salivarius*, *L. johnsonii*, *L. gallinarum*, *L. pentosus*, *L. fermentum*, *L. helveticus*, *L. oris*
Bifidobacterium species	*B. bifidum*, *B. animalis*, *B. breve*, *B. infantis*, *B. Longum*, *B. lactis*, *B. adolescentis*
Others	*Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus salivarius*, *Streptococcus thermophilus*, *Lactococcus lactis* subsp., *Propionibacterium freudenreichii*, *Pediococcus acidilactici*, *Saccharomyces boulardii*, *Leuconostoc mesenteroides*, *Weissella cibaria*, *Weissella confuse*, *Bacillus clausii*, *Escherichia coli* Nissle 1917.

Bifidobacteria comprise a major part of the normal intestinal microflora in humans throughout life. The number of *Bifidobacteria* in the colon of adults is 10^{10}-10^{11} cfu/gm, but this number decreases with age. Most of the Bifidobacterial species are strictly anaerobic, nonmotile, and nonsporulating rods with a varying morphological appearance (Vrese and Schrezenmeir, 2008; Anandharaj et al., 2014).

2.1 Selection criteria and requirements for probiotic strains

According to the suggestions of the WHO, FAO, and the European Food Safety Authority (EFSA), probiotic strains must meet safety, functionality criteria, and technological usefulness during their selection process as stated in Table 2 (Markowiak and Slizewska, 2017). The safety of a strain is defined by its origin, the absence of association with pathogenic cultures, and the antibiotic resistance profile. Functional aspects of a strain are defined by their survival in the GI tract and their immunomodulatory effect. Probiotic strains have to meet the requirements associated with the technology of their production, which means they have to be able to survive and maintain their properties throughout the storage and distribution processes (Lee, 2009).

Table 2: Selection criteria of probiotic strains (Markowiak and Slizewska, 2017).

Criteria	Required Properties
Safety	▪ Human or animal origin. ▪ Isolated from the GI tract of healthy individuals. ▪ History of safe use. ▪ Precise diagnostic identification (phenotype and genotype traits). ▪ Absence of data regarding an association with infective disease.

	▪ Absence of the ability to cleave bile acid salts. ▪ No adverse effects. ▪ Absence of genes responsible for antibiotic.
Functionality	▪ Competitiveness to microbiota inhabiting in intestinal ecosystem. ▪ Ability to survive and maintain the metabolic activity, and to grow in the target site. ▪ Resistance to bile salts and enzymes. ▪ Resistance to low pH in the stomach. ▪ Competitiveness to microbial species (including closely related species) inhabiting in intestinal ecosystem. ▪ Antagonistic activity towards pathogens Such as *Helicobacter pylori (H. pylori)*, *Salmonella* sp., *Listeria monocytogenes*, *Clostridium difficile*). ▪ Resistance to bacteriocins and acids produced by the endogenic intestinal microbiota. ▪ Adherence and ability to colonise some particular sites within the host organism, and appropriate survival in the GI system.
Technological usability	▪ Easy production of high biomass and high productivity of cultures. ▪ Viability and stability of the desired properties of probiotic bacteria during the fixing process (freezing, freeze-drying), preparation, and distribution of probiotic products. ▪ High storage survival rate in finished products (in aerobic and micro-aerophilic conditions). ▪ Guarantee of desired sensory properties of finished products (in the case of the food industry). ▪ Genetic stability. ▪ Resistance to bacteriophages.

2.2 Sources of probiotics

Yogurt, cultured buttermilk, and cheese are the most common sources of probiotics. Cultured buttermilk is prepared with bacteria that produce lactic acid which makes the product sour. Some cultured cheese uses bacteria to finish the maturation of the cheese. Kefir is another fermented dairy product which tends to have several probiotic bacteria whereas yogurt has only one or two bacteria. Japanese miso, tempeh, sauerkraut, beer, sour dough, bread, chocolate, kimchi, olives, and pickles are produced by bacterial fermentation. Yogurts and fermented milks are still dominating food vehicles for probiotics, because they provide a relatively low pH environment in which the probiotic bacteria survive (Roy and Kalicki, 2009). However, many studies show that probiotics strains are also found in nondairy fermented substrates such as cereal, legume, cabbage, maize, pearl millet, vegetable, sorghum, and so forth (Schrezenmeir and DeVrese, 2001).

2.3 Health benefits of Probiotics

The use of knowledge on microbiocenosis of the GI tract and the beneficial effect of probiotic bacteria is becoming important due to the widespread diseases and ageing societies. Major factor of harmful modification of human intestinal microbiota is the consumption of pre-processed food (fast food) which often containing excessive amounts of fat, and intake of insufficient amounts of vegetables. The system of intestinal microorganisms and its desirable modification with probiotic formulas and products may protect people against enteral problems, and influence the overall improvement of health. Probiotics may be helpful in the treatment of inflammatory enteral conditions, including ulcerative colitis, Crohn's disease, and non-specific ileitis. The aetiology of those diseases is not completely understood, but it is evident that they are associated with chronic and recurrent infections or inflammations of the intestine (Geier et al., 2007).

Certain research studies which are explored to improve the use of probiotics suggest that, probiotics play a beneficial role in several medical conditions, including diarrhea, gastroenteritis, irritable bowel syndrome, inflammatory bowel disease, cancer, depressed immune function, infant allergies, failure-to-thrive, hyperlipidemia, hepatic diseases, *H. pylori* infections, and others (Brown and Valiere, 2004). The overall health benefits of probiotic microorganisms are represented in Figure 1.

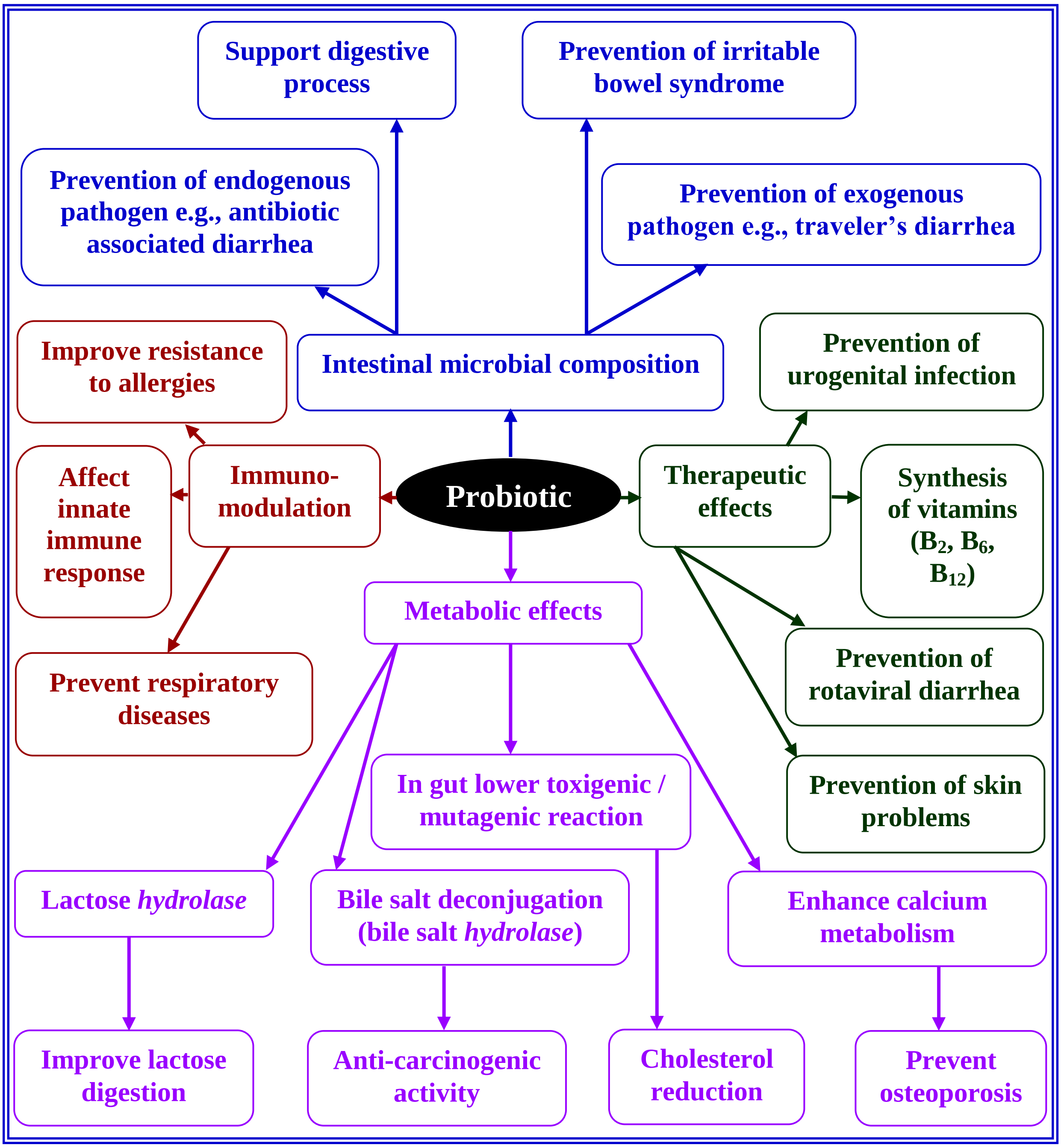

Figure 1: Health benefits of probiotics on human health (Anandharaj et al., 2014).

2.4 Mechanism of action of probiotics

In human organisms, probiotics have numerous advantageous functions such as the development of microbiota in organism to ensure proper balance between pathogens and the bacteria which are necessary for a normal function of the organism (Schachtsiek et al., 2004; Oelschlaeger, 2010).

The molecular and genetic studies established the following basic mechanisms of beneficial effect (Figure 2), which are: (i) competitive adherence to the mucosa and epithelium with proinflammatory microbes (Blander et al., 2107), (ii) regulation of the gut associated lymphoid immune system through intestinal cell pattern recognition receptors such as toll-like receptors and nucleotide-binding oligomerization domain-containing protein-like receptors or through the release of metabolites or immunomodulating peptides (Powell and MacDonald, 2017), (iii) bile-acid deconjugation by some lactobacilli strains, and thus reducing lipid absorption and calories intake (Rani et al., 2017), (iv) induction of lipolysis via production of trans-10, cis-12-conjugated linoleic acid (Lee et al., 2007), (v) increase the sympathetic nerve activity and suppress fat deposition via increased expression of angiopoietin-like 4, a circulating inhibitor of lipoprotein lipase (Tanida et al., 2008), (vi) induction of transcriptional activation of fatty acid β-oxidation-related genes in the liver and muscle (Kim et al., 2013), (vii) inhibition of the transcription of fatty acid *synthase* in the liver (Park et al., 2013), (viii) improve insulin sensitivity and glucose tolerance through short-chain fatty acids (SCFA) production and reduction of Lipopolysaccharide (LPS) translocation (Kang et al., 2013; Stenman et al., 2014), (ix) improvement of the gut barrier function, through SCFA production and immunomodulation of gut immune cells (Briskey et al., 2016), (x) modulation of gene expression profile in peripheral blood mononuclear cells (PBMCs) and intestinal immune cells of ROR-gt (down-regulated) and FOXP3 (up-regulated) transcription factors, dampening inflammation and promoting immunomodulation (Zarrati et al., 2013) and (xi) regulation of appetite (Parnell and Reimer, 2009).

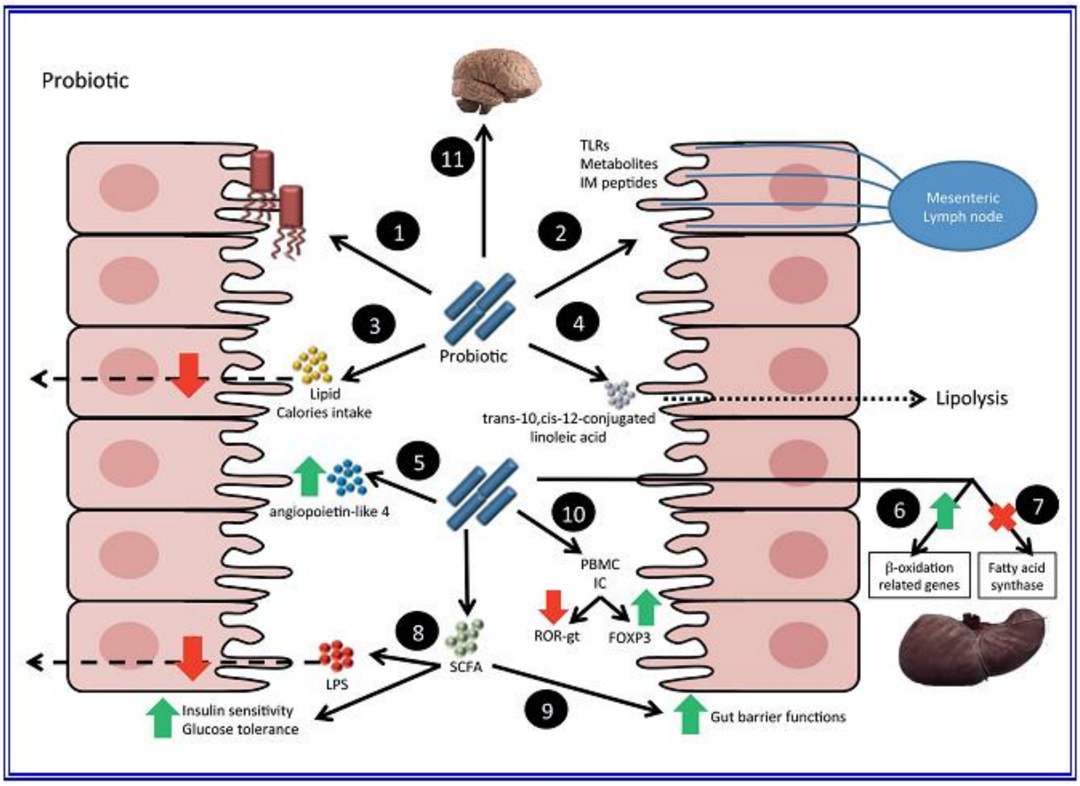

Figure 2: The biological mechanism of action by which probiotics exerts their health effects (Ferrarese et al., 2018).

3. Prebiotics

In 1995, Gibson and Roberfroid used term prebiotic (Gibson and Roberfroid, 1995). Prebiotics are "indigestible fermented food substrates that selectively stimulate the growth, composition, and activity of microflora in the GI tract and improve hosts' health and well-being" (Roberfroid, 2000). About fifty years ago, lactulose was used as a prebiotic to increase the number of *Lactobacillus* strains in infants' intestines (Macgillivray et al., 1959). Fructooligosaccharides, inulin, oligofructose, lactulose, and galactooligosaccharides have been identified as prebiotics due to the resistance to gastric acidity, hydrolysed by mammalian enzymes and fermented by GI microflora to stimulate the growth and activity of beneficial microorganisms. Oligosaccharides (isomaltooligosaccharides, lactosucrose, xylooligosaccharides, and glucooligosaccharides), sugar alcohols, and polysaccharides (starch, resistant starch, and modified starch) have gut resistant properties and selective fermentability by intestinal microorganisms and are known as prebiotics (Ooi and Liong, 2010).

Prebiotics stimulate the growth of different gut bacteria. Prebiotics have enormous potential for modifying the gut microbiot at the level of individual strains and species. The gut environment, especially pH, plays a key role in determining the outcome of interspecies competition. Due to efficacy and of safety, the development of prebiotics intended to benefit human health has to take account of the highly individual species profiles that may result (Chung et al., 2016).

3.1 Selection criteria and requirements of prebiotics

There are five basic criteria for the classification of prebiotics (Figure 3) (Wang, 2009). The first criterion is that the prebiotics are not digested (or just partially digested) in the upper segments of the alimentary tract; result of they reach the colon and are selectively fermented by potentially beneficial bacteria (a requirement of the second criterion) (Maccfarlane et al., 2008). This fermentation may lead to alteration of different SCFAs, increase stool mass, a moderate reduction of colonic pH, reduction of nitrous end products and faecal enzymes, and an improvement of the immunological system which is beneficial for the host (a requirement of the third criterion) (Crittenden et al., 2009). The fourth criterion is the selective stimulation of growth and/or activity of the intestinal bacteria associated with health protection and wellbeing (Gibson et al., 2004). The fifth criterion is that a prebiotic must be able to withstand food processing conditions and remain unchanged, non-degraded, or chemically unaltered and available for bacterial metabolism in the intestine (Wang, 2009).

Several commercially available prebiotics showed no significant changes of their prebiotic activity in various processing conditions (Huebner et al., 2008). It was reported that the activity/ability of gut bacteria may be altered by using starch *in vitro* (Ze et al., 2012). The structure of prebiotics should be appropriately documented, and components used as pharmaceutical formulas, food, or feed additives should be relatively easy to obtain at an industrial scale (Angelakis, 2017).

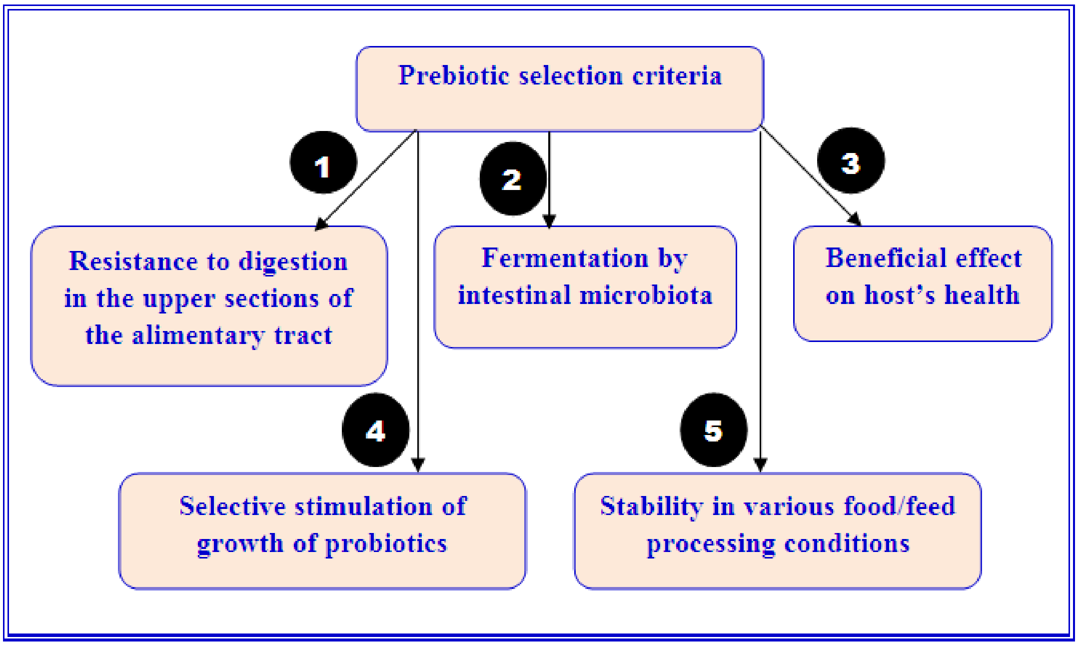

Figure 3: Requirements for potential prebiotics (Wang, 2009).

3.2 Sources of prebiotics

The main sources of carbohydrates containing prebiotics are fruits, vegetables, cereals, and other edible plants. Traditional dietary sources of prebiotics include tomatoes, bananas, asparagus, berries, garlic, onions, chicory, green vegetables, legumes, raw oats, linseed, unrefined barley, unrefined wheat, wheat soybeans, yacon and inulin sources (such as Jerusalem artichoke, jicama, and chicory root). Lactulose, galactooligosaccharides, fructooligosaccharides, maltooligosaccharides, cyclodextrins, and lactosaccharose are some artificially produced prebiotics. Lactulose consists of a significant amount oligosaccharides (about 40%). Fructans, such as inulin and oligofructose, are believed to be the most used and effective probiotics (Huebner et al., 2008).

Some oligosaccharides are found in breast milk and are believed to play an important role in the development of a healthy immune system in infants. The breast feeding infants have *Lactobacilli* and *Bifidobacteria* dominated flora, considered as original prebiotics and an important primer for the immune system which boost up the baby's defence against pathogens (Newburg, 2005; De Morais and Jacob, 2006). Some peptides, proteins, nondigestible oligosaccharides and certain lipids have received the most attention as prebiotics (Ziemer and Gibson, 1998).

3.3 Health benefits of prebiotics

Prebiotics exhibits various health benefits. Studies reveal that intake of inulin and oligofructose in the form of vegetables exhibits beneficial effect on colorectal carcinoma. Another advantages of prebiotics is the reduction of the blood low-density lipoprotein (LDL) level, stimulation of the immunological system, increased absorption of calcium, maintenance of correct intestinal pH value, low caloric value, and alleviation of symptoms of peptic ulcers and vaginal mycosis. Other effects of inulin and oligofructose on human health are the prevention of carcinogenesis, as well as the support of lactose intolerance or dental caries treatment. Rat studies demonstrated that administration of inulin for five weeks caused a significant reduction of blood triacylglycerol levels. Human studies demonstrated that the daily use of 12 g of inulin for one month led to the reduction of blood very low-density lipoprotein (VLDL) levels (Huebner et al., 2008).

This effect is associated with the hepatic metabolism and the inhibition of acetyl-CoA carboxylase and of glukose-6-phosphate dehydrogenase. It is also supposed that oligofructose accelerates lipid catabolism. In 2001, Asahara et al. demonstrated a protective effect of galactooligosaccharides (GOS) in the prevention of *Salmonella typhimurium* infections in a murine model (Asahara et al., 2001). Fructooligosaccharides (FOS) showd a positive effect on protection against *Salmonella typhimurium* and *Listeria monocytogenes* infections (Buddington et al., 2002).

Prebiotic-enriched diet leads to significant reduction of carcinogenesis indexes. Butyric acid and propionic acid may possess anti-inflammatory properties in relation to to colorectal carcinoma cells. The administration of inulin and oligofructose to rats caused the inhibition of azoxymethane-induced colorectal carcinoma at the growth stage (Verghese et al., 2002). The supplementation of inulin and oligofructose at the dose of 5%-15% had also an effect on reduced occurrence of breast cancer in rats and of metastases to lungs (Taper, 2002). The beneficial effects of prebiotics are schematically represented in Figure 4.

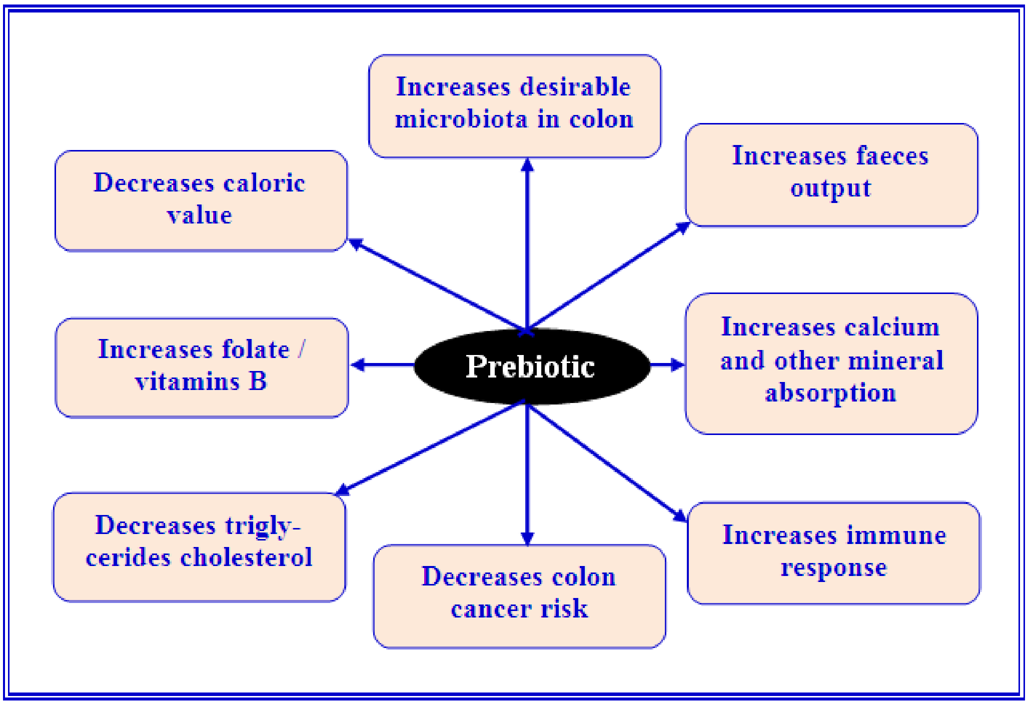

Figure 4: Health benefits of prebiotics on human health (Anandharaj et al., 2014).

3.4 Mechanism of action of prebiotics

Prebiotics affect intestinal bacteria by increasing the numbers of beneficial anaerobic bacteria and decreasing the population of potentially pathogenic microorganisms. Mechanisms of action include receptor competition, effects on mucin secretion, immunomodulation of gut associated lymphoid tissue, increased immunosuppressiveness and decreased proinflammatory mediators (Srinivasan, 2003). After interacting with commensal or potential pathogenic microbes, it generate metabolic end products such as SCFA, and communicate with host cells through chemical signaling, which impacts on mucosal immune mechanisms, and as well as affect the intestinal ecosystem (Figure 5). These mechanisms can lead to antagonism of potential pathogens, improve intestinal environment, bolstering the intestinal barrier, down-regulates the inflammation, and up-regulation the immune response to antigenic challenges. These phenomena are thought to mediate most beneficial effects such as reduction in the incidence and severity of diarrhea (Brown and Valiere, 2004). The molecular and genetic studies established four basic mechanisms of beneficial effect, which are: (i) antagonism through the production of antimicrobial substances (Vandenbergh, 1993); (ii) competition with pathogens for adhesion to the epithelium and for nutrients (Guillot, 2003); (iii) immunomodulation of the host (Isolauri et al., 2001); (iv) inhibition of bacterial toxin production (Brandao et al., 1998).

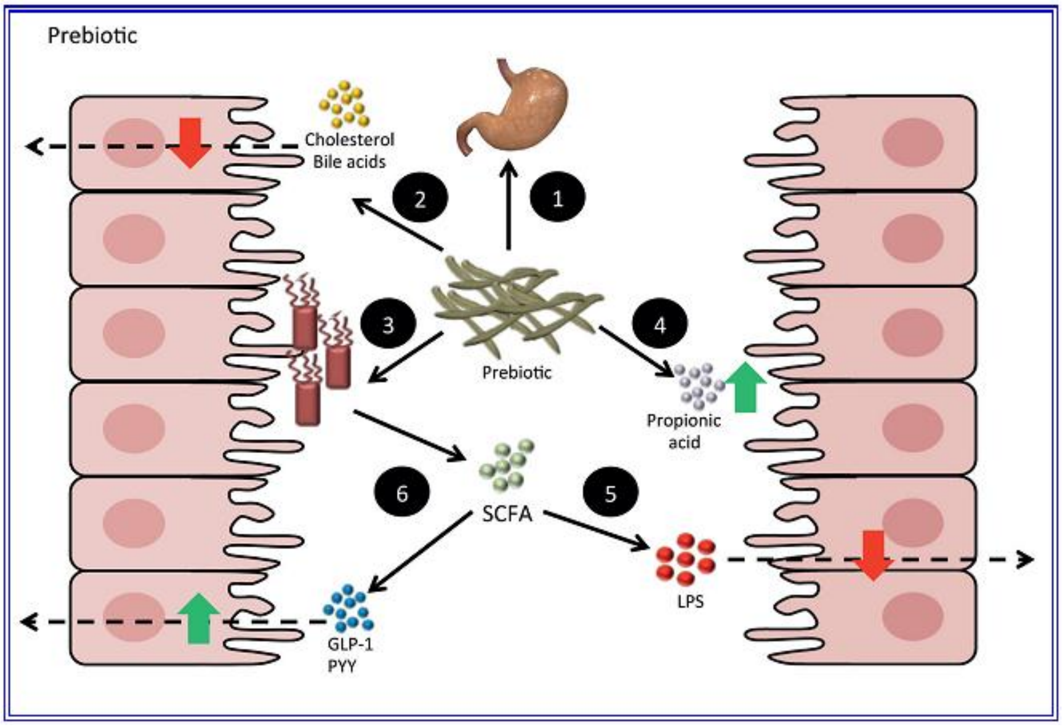

Figure 5: The biological mechanism of action by which prebiotics exerts their health effects (Ferrarese et al., 2018).

The biological mechanisms of prebiotics are exhibited by the following ways: (1) delayed gastric emptying, thereby affecting nutrient kinetics and satiety (Frost et al., 2003), (2) enhancement of intestinal viscosity, that impairing the uptake of dietary cholesterol and reduces bile acids reabsorption (Frost et al., 2003), (3) increment of bacterial fermentation in the colon and promotion of beneficial bacterial replication and metabolic production of SCFA and thus increasing the molar ratio of propionate to acetate, which affect gut barrier integrity and cholesterol metabolism (Wong et al., 2006), (4) inhibition or down-regulation of liver lipogenic pathways through propionic acid production (Yoshida et al., 2006), (5) production of SCFA that reduced the translocation of Gram-negative bacteria derived LPS systemic metaflammation both in human and animal models (Dehghan et al., 2014), and (6) SCFA production affects the secretion of gastrointestinal hormones such as regulation of incretin hormone GLP-1 and other gastrointestinal peptides (the PYY satiety hormone for example) (Meier et al., 2006; Delzenne et al., 2005; Ferrarese et al., 2018).

4. Synbiotics

Use of probiotics and prebiotics in combination is known as "synbiotics" which enhances the survival and activity of the organism, e.g., FOS is conjunction of *Bifidobacterium* strain or lactitol with *Lactobacillus* strains (Gibson and Roberfroid, 1995). The combination of prebiotic and probiotic has synergistic effects. Synbiotics also act to improve the survival, implantation, and growth of newly added probiotic strains. Synbiotics are also used for the stimulation of the proliferation of specific native bacterial strains present in the GI tract (Gourbeyre et al., 2011). The effect of synbiotics on metabolic health remains unclear but it may be stated that the health effect of synbiotics is probably associated with the individual combination of a probiotic and prebiotic (DeVrese and Schrezenmeir, 2008). Considering a huge number of possible combinations, the application of synbiotics for the modulation of intestinal microbiota in humans seems promising (Scavuzzi et al., 2014).

4.1 Selection criteria of synbiotics

Selection of appropriate probiotic and prebiotic which individually exert positive effect on the host's health is the first aspect to be taken into account when composing a synbiotic formula. The determination of specific properties to be possessed by a prebiotic to have a favourable effect on the probiotic seems to be the most appropriate approach. A prebiotic should selectively stimulate the growth of microorganisms, having a beneficial effect on health, with simultaneous absent (or limited) stimulation of other microorganisms (Markowiak and Slizewska, 2017).

4.2 Sources of synbiotics

Previously it was stated that probiotic microorganisms and prebiotic substances are most commonly used in human nutrition. A combination of *Bifidobacterium* or *Lactobacillus* genus bacteria with fructooligosaccharides in synbiotic products seems to be the most popular. Table 3 represents the most commonly used combinations of probiotics and prebiotics.

Table 3: Examples of prebiotics and synbiotics used in human nutrition (Olveira and Gonzalez-Molero, 2016; Saez-Lara et al., 2016).	
Human Nutrition	
Prebiotics	**Synbiotics**
FOS	
GOS	
Inulin	*Lactobacillus* genus bacteria + inulin
XOS	*Lactobacillus, Streptococcus* and *Bifidobacterium* genus bacteria + FOS
Lactitol	*Lactobacillus, Bifidobacterium, Enterococcus* genus bacteria + FOS
Lactosucrose	*Lactobacillus* and *Bifidobacterium* genus bacteria + oligofructose
Lactulose	*Lactobacillus* and *Bifidobacterium* genus bacteria + inulin
Soy oligosaccharides	
TOS	

4.3 Health benefits of synbiotics

Synbiotics have the following beneficial effects on humans: (i) increment of *Lactobacillus* and *Bifidobacterium* genus count and maintenance of intestinal microbiota balance, (ii) improvement of hepatic function in liver cirrhosis patients, (iii) improvement of immunomodulative abilities, and (iv) prevention of bacterial translocation and reduces the incidence of nosocomial infections in patients' post-surgical procedures and similar interventions (Figure 6) (Zhang et al., 2010).

LPSs, ethanol and SFCAs, the translocation of bacterial metabolism products penetrate into liver which stimulate the synthesis and storage of hepatic triacylglycerols that may intensify the hepatic detoxication mechanisms and result of steatosis of the organ. Synbiotic containing five probiotics (*Lactobacillus plantarum*, *Lactobacillus delbrueckii* spp. *bulgaricus*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Bifidobacterium bifidum*) and inulin as a prebiotic showed a significant reduction of intrahepatic triacylglycerol in adult subjects with non-alcoholic steatohepatisis (Wong et al., 2013).

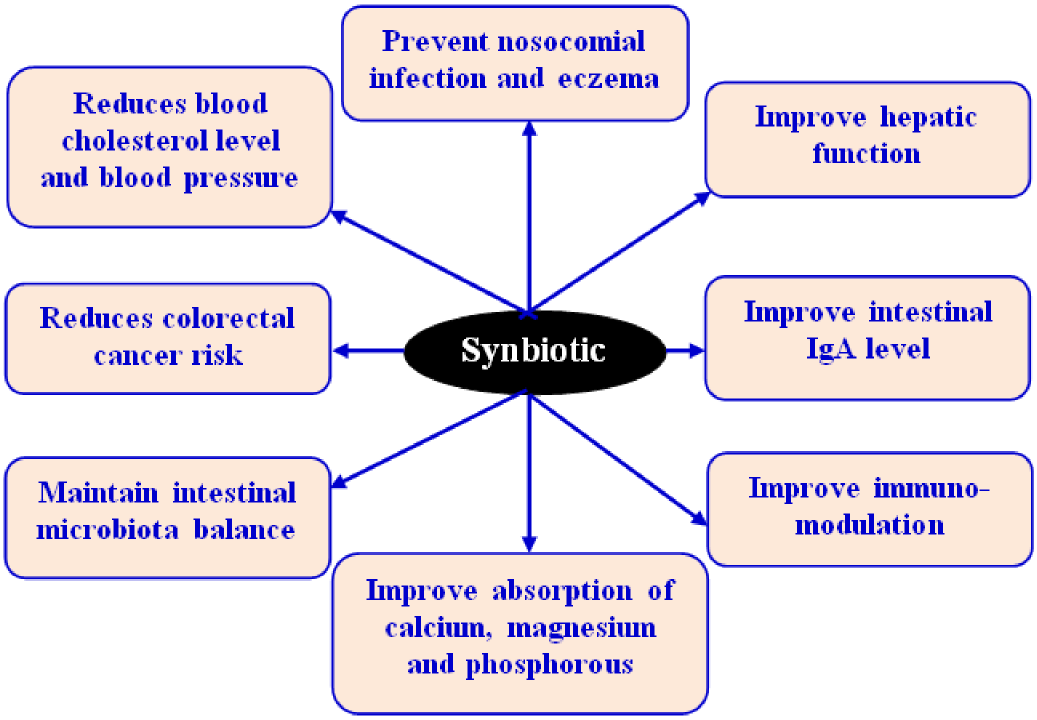

Figure 6: Health benefits of synbiotics on human health (Zhang et al., 2010).

LPSs induces pro-inflammatory cytokines like tumour necrosis factor alpha (TNF-α) which plays a significant role in insulin resistance and inflammatory cell uptake in non-alcoholic fatty liver disease is ameliorated by a synbiotic product containing a blend of probiotics (*Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, *Lactobacillus bulgaricus*) and fructooligosccharides (Eslamparast et al., 2014).

Synbiotic product containing *Lactobacillus rhamnosus* and *Bifidobacterium lactis*, inulin and oligofructose as prebiotics to the diet increases the intestinal IgA level. Synbiotics lead to reduced blood cholesterol levels and lower blood pressure. Synbiotics are used in the treatment of hepatic conditions and improve the absorption of calcium, magnesium, and phosphorus (Perez-Conesa et al., 2006). Synbiotics may reduce the incidence of eczema in infants (Dang et al., 2013). Fructooligosaccharides combined with *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* Bb12 reduces the risk of colorectal carcinoma (Loo et al., 2005).

4.4 Mechanism of action of synbiotics

Probiotic is essentially active in small and large intestine where as prebiotic is active in large intestine, but their combination may have a synergistic effect. Prebiotics are mostly used as a selective medium for the growth of a probiotic strain, fermentation and intestinal passage (Hamasalim, 2016). The use of prebiotics and probiotic microorganisms' acquire higher tolerance to the environmental conditions including oxygenation, pH, and temperature in the intestine of a particular organism. However, the mechanism of action that provides higher tolerance is not sufficiently explained. Combination of these components leads to the creation of viable microbiological dietary supplements, and ensuring an appropriate environment allows a positive impact on the host's health (Sekhon and Jairath, 2010).

Two modes of synbiotic action are known (Manigandan et al., 2012): (1) action through the improved viability of probiotic microorganisms; and (2) action through the provision of specific health effects. The stimulation of probiotics with prebiotics results in the modulation of the metabolic activity in the intestine with the maintenance of the intestinal bio-structure, development of beneficial microbiota, and inhibition of potential pathogens present in the GI tract (DeVrese and Schrezenmeir, 2008). Synbiotics reduces concentrations of undesirable metabolites, as well as the inactivation of nitrosamines and cancerogenic substances. Their use leads to a significant increase of levels of SCFAs, ketones, carbon disulphides, and methyl acetates, which potentially results in a positive effect on the host's health (Manigandan et al., 2012).

5. Conclusion and future prospects

Probiotics, prebiotics, and synbiotics have been found to be clinically effective for a large number of disorders. Probiotic microorganisms have high therapeutic potential against obesity, insulin resistance syndrome, type 2 diabetes, non-alcohol hepatic steatosis, irritable bowel syndrome, enteritis, bacterial infections, various GI disorders, diarrhoeas, and cancer to some extent. Prebiotics may be used as an alternative to probiotics, or as an additional support for them. It turns out that the development of bio-therapeutic formulas containing both appropriate microbial strains and synergistic prebiotics may lead to the enhancement of the probiotic effect in the small intestine and the colon. Those "enhanced" probiotic products may be even more effective, and their protective and stimulatory effect superior to their components administered separately.

However, some issues like dosage and viability of probiotic strains, industrial standardization, and safety aspects are needed to be studied well. However, extensive research is required to screen the potent probiotic strains and their evaluation for the effective management in the body. The combination of probiotics and prebiotics significantly reduces the serum cholesterol level and that can be used as an alternative remedy for hypercholesterolemic problems without any side effects to the consumers. Future studies is required to explore the explain the mechanisms of actions of those components, which may confer a beneficial effect on human health.

ACKNOWLEDGEMENT

Author express gratefulness to Ramananda College, Bishnupur, Bankura for providing the facilities to execute this review work. Author of this review paper is highly obliged to the Principal of this college for constant help and encouragement.

Declaration of interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

Abbreviations

EFSA : European Food Safety Authority
FAO : Food and Agriculture Organization
FOS : Fructooligosaccharides
GI : Gastrointestinal
GOS : Galactooligosaccharides
H. pylori : *Helicobacter pylori*
ISAPP : International Scientific Association of Probiotics and Prebiotics
LDL : Low-density lipoprotein
LPS : Lipopolysaccharide
PBMCs : Peripheral blood mononuclear cells
SCFA : Short-chain fatty acids
TNF-α : Tumour necrosis factor alpha
TOS : Transgalactooligosaccharides
VLDL : Very low-density lipoprotein
WHO : World Health Organization
XOS : Xylooligosaccharides

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