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A REVIEW ON: PROBIOTIC PREBIOTICS AND SYMBIOTICS – AS FOOD, DRUG AND DIETARY SUPPLEMENT

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ABSTRACT

Probiotics are living microorganisms which when taken in adequate amount provides benefit to the host. While this beneficial effect was originally thought to stem from improvements in the intestinal microbial balance. Identification of clinical characteristics of effective probiotic strains, their mechanisms of action and testing of probiotic-based treatment may provide the true beneficial effect of probiotics in various disorders. Probiotics have been investigated as a potential dietary supplement that can positively contribute to an individual's health. This health benefits are not limited to the intestinal tract, but also include amelioration of systemic metabolic disorders, such as Type – II Diabetes Mellitus and Cardiovascular diseases. Prebiotics are dietary substances that consist of non-starch polysaccharides and oligosaccharides. These are poorly hydrolyzed by digestive enzymes and preferably favour for the growth of probiotics such organism are *Lactobacillus* and *Bifidobacter* that are helpful in gut health maintenance, treat cancer, cardiovascular diseases and protect from colitis condition, improve immunity system. Hence prebiotics are widely used in food industry and pharmaceutical formulations. Synbiotic contain both probiotic bacteria and prebiotic sugars. The microbial additions (probiotics) may be used in conjugation with specific substrates (prebiotic) for growth. Synbiotics. are used not only for the improved survival of beneficial microorganisms added to food or feed, but also for the stimulation of the proliferation of specific native bacterial strains present in the gastrointestinal tract. The present review summarizes and discusses the effects of probiotic, prebiotic or synbiotic administration on growth performance, stress tolerance, intestinal microbiota, immune response and as well as food and drug.

KEYWORDS: Food and Drug, Prebiotic, Probiotics, Synbiotic.

INTRODUCTION

Increasing awareness on healthy foods has led to increasing interests on natural food products and nutraceuticals such as Probiotics. Probiotics have been defined as 'living microorganisms which when administered in adequate amount confer a health benefits on the host' (FAO/WHO 2001). Probiotic microorganisms have shown much health beneficial effects via *in vivo* trials, accompanied by much promising new potentials as developed by *in vitro* experiments.[1] In general, probiotics have been demonstrated to improve intestinal microbial balance, provide protection against gut pathogens and modulate immune system. Trend for probiotics products was first observed to gain momentum in Japan in late 1980 and soon spreaded into areas such as Asia Pacific, European Union and United States.[2] In present, given the greater understanding of the linkage between diet, nutrition and health, market for functional foods especially the probiotics are rapidly expanding. The public has also been increasingly accepting alternative therapies which include probiotics, in replacing synthetic drugs.[3]

What is Probiotic

A probiotic is a live micro-organism which, when given in adequate quantity, has a beneficial effect on the host. Probiotics can be formulated into many different types of products, including foods, drugs, and dietary supplements. The Greek word probiotic means **"for life",** was introduced by Parker. Definition put by FDA and WHO jointly is "Live microorganisms which when administered in adequate amounts confer a health benefit to the host.[4-6]

History of probiotics development

The knowledge of the beneficial effects of lactic acid fermentation on human health dates back to ancient times. The Bible mentions sour milk several times. Ancient Romans and Greeks knew various Nutrients recipes for fermented milk. A specific type of sour milk, called "leben raib", prepared from buffalo, cow, or goat milk, was consumed in ancient Egypt. In India, fermented milk drinks were known already 800–300 years B.C., and in Turkey in the 8th century.[7]

A milk drink called "ajran" was consumed in Central Russia in the 12th century, and "tarho" was consumed in Hungary in the 14th century.[8]

Table 1: Example of probiotic micro organisms.

Type Lactobacillus	Type Bifidobacterium	Other Lactic Acid Bacteria	Other Microorganisms
L.amylovorus (b),*	B.adolescentis (a)	Enterococcus faecium (a)	Bacillus clausii (a),*
L. casei (a),(b),*	B. animalis (a),*	Lactococcus lactis (b),*	Escherichia coli Nissle (a)
L. gasseri (a),*	B. bifidum (a)	Streptococcus Thermophilus (a),*	Saccharomyces cerevisiae (boulardi) (a),*
L. helveticus (a),*	B. breve (b)		
L. johnsonii (b),*	B. infantis (a)		
L. pentosus (b),*	B. longum (a),*		
L. plantarum (b),*			
L. reuteri (a),*			
L. rhamnosus (a), (b),*			

a) **Mostly as pharmaceutical products**

b) **(b) mostly as food additives**

QPS (Qualified Presumption of Safety) microorganisms

Selection criteria of probiotic strains

According to the suggestions of the WHO, FAO (Food and Agriculture Organization of the United Nations), and EFSA (the European Food Safety Authority), in their selection process, probiotic strains must meet both **safety** and **functionality criteria**, as well as those related to their **technological usefulness**.

Safety

- Human or animal origin.
- Isolated from the gastrointestinal tract of healthy individuals.
- History of safe use.
- Precise diagnostic identification.
- Absence of the ability to cleave bile acid salts.

Functionality

- Competitiveness with respect to the microbiota
- 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.
- Antagonistic activity towards pathogens (e.g., H. pylori, Salmonella.
- Resistance to bacteriocins and acids produced by the endogenic intestinal microbiota.

- Adherence and ability to colonise some particular sites within the host organism.
- Survival rate in the gastrointestinal system.

Technological usability

- Easy production of high biomass amounts 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.
- Guarantee of desired sensory properties of finished products (in the case of the food industry).
- Genetic stability.
- Resistance to bacterio phages.

Mechanism of probiotics

The beneficial effect of probiotic, involving four mechanisms:

1. Antagonism through the production of antimicrobial substances.
2. Competition with pathogens for adhesion to the epithelium and for nutrients.
3. Immunomodulation of the host.
4. Inhibition of bacterial toxin production.

The first two mechanisms are directly associated with their effect on other microorganisms. Those mechanisms are important in prophylaxis and treatment of infections, and in the maintenance of balance of the host's intestinal microbiota. The ability of probiotic strains to co-aggregate, as one of their mechanisms of action, may lead to the formation of a protective barrier preventing pathogenic bacteria from the colonisation of the epithelium.[9] Probiotic bacteria may be able to adhere to epithelial cells, thus blocking pathogens. That mechanism exerts an important effect on the host's health condition. Moreover, the adhesion of probiotic microorganisms to epithelial cells may trigger a signalling cascade, leading to immunological modulation. Alternatively, the release of some soluble components may cause a direct or indirect (through epithelial cells) activation of immunological cells. This effect plays an important role in the prevention and treatment of contagious diseases, as well as in chronic inflammation of the alimentary tract of a part thereof. There are also suggestions of a possible role of probiotics in the elimination of cancer cells.[10] The immune modulatory effect of the intestinal microbiota, including probiotic bacteria, is based on three, seemingly contradictory phenomena:[11]

1. Induction and maintenance of the state of immunological tolerance to environmental antigens
   (Nutritional and inhalator);
2. Induction and control of immunological reactions against pathogens of bacterial and viral Origin;
3. Inhibition of auto-aggressive and allergic reactions.

Probiotic-induced immunological stimulation is also manifested by the increased production of immune globulins, enhanced activity of macrophages and lymphocytes, and stimulation of –interferon production. Probiotics may influence the congenital and acquired immunological system through metabolites, components of the cellular wall, and DNA, recognized by specialized cells of the host (e.g., those equipped with receptors).[12] The principal host cells that are important in the context of the immune response are intestinal epithelial cells and intestinal immune cells. Components of the cellular wall of lactic acid bacteria stimulate the activity of macrophages. Those, in turn, are able to destroy microbes rapidly by the increased production of free oxygen radicals and lysosomal enzymes. Probiotic bacteria are also able to stimulate the production of cytokines by immune competent cells of the gastrointestinal tract. Those compounds stimulate the response of the reticulo endothelial system.[13]

Probiotics for human use

Probiotics may be helpful in the treatment of:

- Gastrointestinal diseases (e.g., irritable bowel syndrome, gastrointestinal disorders, elimination of Helicobacter, inflammatory bowel disease, diarrhea).
- Allergic diseases (e.g., atopic dermatitis).
- Treatment for Diseases such as obesity.
- Insulin resistance syndrome.
- Treatment for Type - II diabetes.
- Treatment for Non-alcoholic fatty liver disease.
- Increasing the body’s immunity immune modulation).
- Treatment for cancer & side effects associated with cancer.

In the face of widespread diseases and ageing societies, the use of knowledge on microbiocenos is of the gastrointestinal tract and on the beneficial effect of probiotic bacteria is becoming increasingly important. The consumption of pre-processed food (fast food), often containing excessive amounts off at and insufficient amounts of vegetables, is another factor

of harmful modification of human intestinal microbiota. There is currently no doubt about the fact that 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. Clinical studies have demonstrated that probiotics lead to the remission of ulcerative colitis, but no positive effect on Crohn's disease has been observed. Numerous studies assessed the use of probiotics in the treatment of lactose intolerance, irritable bowel syndrome, and the prevention of colorectal cancer and peptic ulcers. Considering their role in the inhibition of some bacterial enzymes, probiotics may reduce the risk of colorectal carcinoma in animals. However, the same effect in humans has not been confirmed in clinical trials. On the other hand, a positive effect on the urogenital system (prevention and treatment of Urinary Tract Infections (UTIs) and bacterial vaginitis) constitutes an excellent example of the benefits associated with the use of probiotics.[14] There were attempts to apply probiotics to pregnant women and neonates in order to prevent allergic diseases such as atopic dermatitis. However, the scope of action is controversial in this kind of case. There is evidence that the consumption of probiotics-containing dairy products results in the reduction of blood cholesterol, which may be helpful in the prevention of obesity, diabetes, cardiovascular diseases, and cerebral stroke.[15] The reduction of cholesterol level achieved due to probiotics is less pronounced compared to the effect of pharmaceutical agents, but leads to a significant minimization of side effects. Other studies confirmed the effect of the probiotic formula VSL #3 and of the Oxalobacter formigenes bacterial strain on the elimination of oxalates with urine, which may potentially reduce the risk of urolithiasis.[16] Studies on animals demonstrated that orally administered Lactobacillus acidophilus induces expression of *m*-opioid and cannabinoid receptors in intestinal cells and mediate analgesic functions in the intestine, and that the observed effect is comparable to the effect of morphine.[17] However, the effect has not been demonstrated in humans. There are many reports on the application of probiotics in the treatment of diarrhoea. The application of Saccharomyces boulardii yeast to patients with acute, watery diarrhoea resulted in the cure and reduced frequency of that type of complaints in two subsequent months.[18] The efficacy of probiotic strains in the therapy of nosocomial, non-nosocomial, and viral diarrhoeas has also been documented. It turns out that probiotics may increase the amount of IgA antibodies, which leads to the arrest of a viral

infection.[19] Antibiotic-associated diarrhoea (AAD) is a common complication of most antibiotics and Clostridium difficile disease (CDD), which also is incited by antibiotics, and is a leading cause of nosocomial outbreaks of diarrhoea and colitis. The use of probiotics for these two related diseases remains controversial. A variety of different types of probiotics show promise as effective therapies for these two diseases. Using meta-analyses, three types of probiotics (*Saccharomyces boulardii, Lactobacillus rhamnosus* GG, and probiotic mixtures) significantly reduced the development of antibiotic-associated diarrhoea. Only *S. boulardii* was effective for CDD.[20] Studies performed in a foster home in Helsinki (Finland) demonstrated that the regular use of *Lactobacillus rhamnosus* GG in the form of a probiotic resulted in a reduced number of respiratory tract infections.[21] Other studies demonstrated that the application of a diet depleted of fermented foods caused a reduction of congenital immunological response, as well as a significant reduction of stool Lactobacillus count and of the stool amount of short-chain fatty acids. Moreover, the reduction of phagocytic activity of leukocytes was observed after two weeks of the diet, which could have a negative impact on the organism's ability to protect against infections.[22] The effect of a fermented product containing Lactobacillus gasseri CECT5714 and Lactobacillus coryniform is CECT5711 strains on blood and stool parameters was studied in a randomised, double-blind trial on 30 healthy volunteers. No negative effects were observed in the group of subjects receiving the probiotic strains. Some positive effects were observed, including: the production of short-chain fatty acids, humidity, frequency and volume of stools, and subjective improvement of intestinal function. Studies by Alvaro et al. (2007) demonstrated a significant reduction of *Entero bacteriaceae* count and increased galactosidase activity in the alimentary tract of yoghurt consumers, compared to those who did not eat yoghurt.[23]

What is Prebiotics

Prebiotics are defined as non-digestible food ingredients that selectively stimulate the growth and/or the metabolism of health-promoting bacteria in the intestinal tract, thus improving an organism's intestinal balance (Gibson and Roberfroid, 1995). The health-promoting bacteria most commonly augmented by prebiotics include those of the genus *Lactobacillus* and *Bifidobacter,* which tend to limit the presence of harmful bacteria. Examples of prebiotics include mannanoligo saccharides, lactose, galacto-gluco-mannans, oligofructose, and inulin. Many of these prebiotics are carbohydrates, primarily short-chain oligosaccharides consisting of three to ten carbohydrate units, which are derived from various plants or cell wall components of yeast. A commercial product that possesses prebiotic properties is the yeast-based

product GroBiotic®-A, which is a mixture of partially autolyzed brewer's yeast, dairy ingredient components, and dried fermentation products. The various prebiotic compounds are generally not altered by diet processing and require limited regulatory approval, making their use much simpler than using drugs or chemical therapeutic agents.[24]

Example of prebiotics

- Fructo oligo saccharides (FOS).
- Malto oligo saccharide (MOS).
- Xylo oligo saccharides (XOS).
- Arabino xylo oligo sachrides (AXOS).
- Galacto oligo saccharides (GOS).
- Polyols (xylitol, sorbitol, mannitol).
- Disaccharides (lactulose, lactilol).
- Oligosaccharides (raffinose, soybean).

Prebiotics for human use

- Indirectly produce short chain fatty acids (SCFAs) that trun to trophic (nourishing) effect on the intestinal epithelium.
- Indirectly produce immune stimulants, by the promotion of bifidobacteria that excrete an end product inhibitory to pathogenic bacteria.
- Promote a host-mediated attack against tumor sites and promote certain strains of lactobacilli.
- Enhancing phagocyte activity in the blood.
- Arabino galactans are non-starch polysaccharides used as a dietary fibers and which exist in many edible sources including carrots, larch, radishes, black beans, maize, red wine, tomatoes and coconuts.

The presence of prebiotics in the diet may lead to numerous health benefits. Studies on colorectal carcinoma demonstrated that the disease occurs less commonly in people who often eat vegetables and fruit. This effect is attributed mostly to inulin and oligofructose. Among the advantages of those prebiotics, one may also mention the reduction of the blood LDL (low-density lipoprotein) level, stimulation of the immunological system, increased absorbability 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 VLDL (very low-density lipoprotein) levels (the reduction of triacylglycerols by 27% and of cholesterol by 5%).

This effect is associated with the effect of the probiotic on hepatic metabolism and the inhibition of acetyl-CoA carboxylase and of glukose-6-phosphate dehydrogenase. It is also supposed that oligofructose accelerates lipid catabolism.[25] A sahara et al. (2001) demonstrated a protective effect of galactooligosaccharides (GOS) in the prevention of Salmonella Typhimurium infections in a murine model. Buddington et al. (2002) confirmed a positive effect of fructooligosaccharides (FOS) on protection against Salmonella Typhimurium and Listeria monocytogenes infections. Moreover, prebiotics are helpful in combating pathogenic microorganisms, such as Salmonella Enteritidis and Escherichia coli, and reduce odour compounds. There are many reports regarding the positive effect of prebiotics on the carcinogenesis process. Results of rat studies proved that a prebiotic-enriched diet leads to significantly reduced indexes of arcinogenesis. Scientific research demonstrated that butyric acid may be a chemopreventive factor in carcinogenesis, or an agent protecting against the development of colorectal carcinoma through the promotion of cell differentiation.[26] Besides butyric acid, propionic acid also may possess anti-inflammatory properties in relation to colorectal carcinoma cells. *In vitro* studies on human L97 and HT29 cell lines (representing early and late stages of colorectal carcinoma) demonstrated that inulin fractions in plasma supernatant caused a significant inhibition of growth and induction of apoptosis in human colorectal carcinoma. According to scientific reports, the administration of inulin and oligofructose to rats caused the inhibition of azoxy methane-induced colorectal carcinoma at the growth stage. 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.[27]

Prebiotic Selection Criteria

According to Wang (2009), there are five basic criteria for the classification of food components such as prebiotics. The first criterion assumes that prebiotics are not digested (or just partially digested) in the upper segments of the alimentary tract. As a consequence, they reach the colon, where they are selectively fermented by potentially beneficial bacteria (a

requirement of the second criterion). The fermentation may lead to the increased production or a change in the relative abundance of different short-chain fatty acids (SCFAs), increased 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 (the requirement of the third criterion). Selective stimulation of growth and/or activity of the intestinal bacteria potentially associated with health protection and wellbeing is considered another criterion.[28] The last criterion of the classification assumes that a prebiotic must be able to withstand food processing conditions and remained unchanged, non-degraded, or chemically unaltered and available for bacterial metabolism in the intestine. Huebner et al. (2008) tested several commercially available prebiotics using various processing conditions. Meanwhile, Ze et al. (2012) showed that it was possible to alter the ability of gut bacteria by utilising starch *in vitro*. 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.[29]

Table 2: Benefits of Probiotics and prebiotics.

Probiotics	**Prebiotics**
Modify intestinal micro biota.	Increase production of SCFAs.
Stimulate immune system.	Increase biomass and stool bulking.
Reduce inflammatory reaction.	Increase B-Vitamin synthesis.
Prevent pathogen colonization.	Improve mineral absorption.
Enhance animal performance.	Prevent cancer.
Decrease carcass contamination.	Lower serum cholesterol.
Decrease ammonia and urea excretion.	

What is Synbiotic

Synbiotic contain both probiotic bacteria and prebiotic sugars. The microbial additions (probiotics) may be used in conjugation with specific substrates (prebiotic) for growth. The advanced research in the functional food market is combine probiotics with prebiotics, enhance the effect of probiotics. The product consisting probiotics with prebiotics is called as Synbiotics. Synbiotics are used not only for the improved survival of beneficial microorganisms added to food or feed, but also for the stimulation of the proliferation of specific native bacterial strains present in the gastrointestinal tract. It should be mentioned that the health effect of synbiotics is probably associated with the individual combination of a probiotic and prebiotic. Considering a huge number of possible combinations, the application of synbiotics for the modulation of intestinal microbiota in humans seems promising.[30]

Synbiotic Selection Criteria

The first aspect to be taken into account when composing a synbiotic formula should be a selection of an appropriate probiotic and prebiotic, exerting a positive effect on the host's health when used separately. The determination of specific properties to be possessed by a prebiotic to have a favorable 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.[31]

CONCLUSION

Finally it is conclude that there is a popularity increasing use of pre-and/or probiotics products due their wide application, consumers frequently demand that the health properties of probiotics strains evident on the labels and comply with the regulation. One is that sufficient numbers of probiotic cells survive throughout the shelf life of the product. Hence there are the alternate drug products for various diseases. Synbiotic contain both probiotic bacteria and prebiotic sugars. The microbial additions (probiotics) may be used in conjugation with specific substrates (prebiotic) for growth.

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