Antimicrobial Effect of Probiotics, Prebiotics and Synbiotics

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Today, the interest on probiotic, prebiotic and synbiotic is increasing and scientific investigations on this subject continue intensively due to consumer preference focused on foods which have beneficial health effects. Demand for new antimicrobial agents is increasing due to growing number of multi-drug resistant pathogens which have resistant to present antimicrobial drugs. Thus, probiotic, prebiotic and synbiotic have been attracting increasing attention due to their antimicrobial properties. In addition to their antimicrobial effect, they have also been found to improve immune system, prevent tooth decay, anticarcinogenic properties, effective against coronary heart diseases. *Lactobacillus*, *Bifidobacterium*, *Enterococcus* and *Streptococcus* strains are belong to the group of probiotic bacteria. Lactosucrose, inulin, fructooligosaccharide, galactooligosaccharide, soybean oligosaccharide have been reported as prebiotic. *Bifidobacterium*-fructooligosaccharide, L*actobacillus*-lactylol, *Bifidobacterium*-galaktooligosaccharide, *Bifidobacterium breve*-*Lactobavcillus lactis*-oligoalternan have been using as synbiotics. There has been a growing interest to their usage in food industry due to advantages such as extending shelf life and reduction of infection. In this part, antimicrobial properties of probiotic, prebiotic and synbiotic are discussed.

Keywords: probiotic, prebiotic, synbiotic, antimicrobial

1. Introduction

In recent years, consumer demand changed significantly in food production area. An increasing majority of consumers believe that food has effect on health directly. Today, foods are not consumed only to satisfy hunger and intake of essential nutrients for human, but also improve physically and mental health. From this point, functional foods play an important role. The interest in functional foods increasing day by day due to better understanding of the relationship between health and nutrition (1). As a result of this increasing interest, scientific researches focused on containing biologically active compounds which are beneficial to human health, as well as food's main role, being an energy source (2). Functional foods, including probiotic, prebiotic and synbiotic, defining as food or food components that have health or technologically beneficial properties beyond the nutritional value (3).

Functional foods exist in all food categories but there is no homogeneous distribution in terms of product diversity (1). Among functional foods, probiotics have positive effects on human health and gastrointestinal system microflora (2). Interest in non-dairy probiotic products is increasing day by day due to vegetarianism, cholesterol content of milk and lactose intolerant individuals (2).

It is known that gastrointestinal microflora play an important role on health and diseases of human and animal (4).

Today, the interest in probiotics which necessary and beneficial for a healthier life is increasing and researches on beneficial effect of probiotics on human health are maintaining intensely. The interest on probiotic, prebiotic and functional food is increasing day by day (5).

In this part, probiotics, prebiotics, synbiotics and their antimicrobial effects are discussed.

2. Probiotics

Nowadays, research studies on probiotic are increasing constantly due to consumer's demand on functional foods that safety, have beneficial health effects and high nutrition value (6). Probiotics are defined as live microorganisms that have beneficial health effect on consumer through creating and improving gastrointestinal microflora when administered in adequate amounts (7,8,9).

Many studies have been carried out on the probiotic microorganism effects on health and to protect from various diseases with different formulations (9,10). Probiotic bacteria, which isolated from human gastrointestinal microflora, usage is quite common in many products such as fermented dairy products (ayran, sour cream, yoghurt etc.), baby food due to their various nutritional and therapeutic properties (11).

Probiotic products are usually found in the market in the form of fermented milk or yoghurt. Due to the fermented dairy products have disadvantages such as these products can't be used by lactose intolerance individuals and having high cholesterol levels, and vegetarianism in developed countries, there is a growing demand on vegetarian probiotic products (8).

In order to have beneficial effect on health, probiotic microorganisms must be taken in sufficient quantities and be able to reach the area live at a certain number where they will be active (10,11). The number of viable probiotic microorganisms in the food presented for consumption is a matter that requires special attention, as the physiological activity of probiotic depends on dosage. In this respect, probiotic microorganism's survival rate in the food is important

during storage or ripening period (6). Providing the benefits expected from probiotic foods is largely based on preserving the viability of the probiotic bacteria they contain and these probiotic bacteria should be at least 10^7-10^9 cfu/g in the food products (12).

Lactic acid bacteria and *Bifidobacterium* spp. are the most researched and used bacteria as probiotics. Their usage in food industry is common and they could be found in human gastrointestinal microbiota (1). In addition, these bacteria are included in the GRAS (Generally Recognized as Safe) list. *Lactococcus, Enterococcus, Propionibacterium*, and *Sacchromyces* species and filamentous fungi (such as *Aspergillus oryzae*) are used as probiotics due to their health effects (13).

Generally, probiotic microorganisms are divided into two groups as bacteria and fungi (14). Microorganisms used as probiotic are shown in Table 1.

Table 1. Microorganisms used as probiotics (14,15)

***Lactobacillus* spp.**	*Lactobacillus acidophilus*, *L. casei*, *L. brevis*, *L. bulgaricus*, *L. cellebiosus*, *L. delbrueckii*, *L. johnsonii*, *L. lactis*, *L. reuteri*, *L. rhamnosus, L. plantarum*, *L. fermentum*, *L. helveticus, L. curvatus, L. salivarius*, *L. gasseri*
***Bifidobacterium* spp.**	*Bifidobacterium adolescentis*, *B. bifidum*, *B. breve*, *B. longum*, *B. infantis, B. thermophilum*
***Bacillus* spp.**	*B. subtilis, B. pumilus, B. lentus, B. licheniformis, B. coagulans, B. cereus*
***Pediococcus* spp.**	*P. cerevisiae, P. acidilactici, P. pentosaceus*
***Streptococcus* spp.**	*S. cremoris, S. thermophilus, S. intermedius, S. lactis, S. diacetilactis*
***Bacteriodes* spp.**	*B. capillus, B. suis, B. ruminicola, B. amylophilus*
***Propionibacterium* spp.**	*P. shermanii, P. freudenreichii*
***Leuconostoc* spp.**	*L. mesenteroides*
Mould	*Aspergillus niger*, *Aspergillus oryzae*
Yeast	*Saccharomyces cerevisiae*, *Saccharomyces boulardii*, *Candida torulopsis*

Although the idea of using probiotics for human health has been contemplated for almost 100 years, interest has recently shifted to the prevention and treatment of a number of diseases, such as sensitive bowel syndrome, eczema, allergies, *Helicobacter pylori* infection, as well as beneficial effect of digestive and immune system with probiotics (16). It is reported that probiotics in the complex structure of foodstuffs, play an important role in human health as having beneficial effect (8).

Studies show that regular consumption of products containing probiotic bacteria strengthens the human immune system, has an anti-allergic effect, reduces cancer risk, lowers cholesterol, eliminates digestive difficulties and prevents gastrointestinal system infections (12). It has been indicated that the consumption of probiotics would be appropriate to improve bacterial impairments in the large intestine (17).

Probiotic bacteria found naturally in intestinal microbiota are microorganisms that have human health protective effects against diseases. Probiotic bacteria are known to produce hydrogen peroxide, bacteriocin and organic acids such as lactic and acetic acid. Probiotics are known to have many mechanisms to inhibit pathogenic microorganisms. The main ones of these mechanisms are to reduce the pH of the food by producing lactic acid, to produce compounds with antimicrobial properties such as microcin, hydrogen peroxide and free radicals, to compete for food sources by attaching to receptors, formation of protective mucin (main substance of mucus composed of epithelial or connective tissue origin, mixture of glycoprotein and mucoprotein) and stimulate the production of secretory IgA (11). In addition to their antimicrobial effects, they have also been found to strengthen immune system, prevent tooth decay, exhibit anticarcinogenic properties and effective against coronary heart disease (18). Probiotics are known to have indirect or direct effects on the intestinal physiology and stimulate the immunity system. In this context, it is known that the host has potential to reduce the disease risk by improving the mood and health of the upper respiratory tract and urogenital system including the oral and digestive system of the host. The stimulatory effect of probiotics on non-specific defense barriers in the intestines is explained by normalization of increased intestinal permeability and alteration of intestinal microflora. It is also stated that this effect may be related to increased response to intestinal immunoglobulin A (IgA) and alleviation of intestinal inflammatory response. It has been suggested that probiotics show these effects by increasing phagocytic activity, cytokine release, natural killer cell activity, immunoglobulin activity (IgA, IgG, IgM), T and B cell function. It has been emphasized that this activity of probiotics is also important for individuals with allergic sensitivities. It has been determined that probiotic bacteria show different phagocytic activity in healthy and allergic

individuals. While it stimulates the immune system in healthy individuals, it alleviates the inflammatory response in allergic individuals. This shows that probiotics can be used in disorders of the intestinal mucosa barriers such as gastroenteritis, food allergies and inflammatory bowel diseases (14).

2.1. Antimicrobial Effects of Probiotics

Probiotic bacteria have been shown to be effective in the gastrointestinal system by causing enteropathogenic microorganisms to compete for retention zones in the intestinal epithelial surface in order to prevent colonization of the gastrointestinal tract of the host and to inhibit harmful bacteria from living in the environment by decreasing intestinal pH through the production of organic acids such as lactic acid and acetic acid, production of many antimicrobial agents such as hydrogen peroxide (H_2O_2), carbon dioxide (CO_2), diacetyl, acetaldehyde, reuterin, bacteriocin and bacteriocin-like substances have been shown to control the growth of pathogenic bacteria and to stabilize the microflora (5).

Some *Lactobacillus* are used in the production of yoghurt, cheese, sauerkraut, pickles, sour dough, wine and other fermented products. In these products, sugars are metabolized to lactic acid, resulting in an environment unsuitable for microorganisms that cause deterioration, and the protection of food is ensured (17).

Mixed probiotic formulations, containing various probiotic bacteria, have been shown to be effective against pathogens such as *Esherichia coli*, *Campylobacter jejuni* and *Shigella* species which cause travel diarrhea. The most commonly used probiotic microorganisms against these pathogens are *Lactobacillus acidophilus*, *Lactobacillus rhamnosus* GG, *Saccharomyces boulardii*, *Bifidobacterium bifidum* and *Bacillus coagulans*. *Lactobacillus* and other probiotics have been used with antibiotics to provide promising results in the treatment of bacterial vaginosis (17).

Donskey et al. (2001) investigated the effect of *Bacillus coagulans* on vancomycin-resistant enterococci in the mouse digestive tract. *B. coagulans* were given orally at a concentration of 10^7 cfu/g for 4 days. As a result, it has been found that one in every three mouse, *B. coagulans* consumption causes a decrease in the vancomycin-resistant enterococcal colon (19).

Abdollahi et al. (2008) investigated the effect of probiotics to compare the efficacy of ulcerative colitis relapse prevention with mesalazine used in standard therapy. According to the results, probiotics also reduce the incidence of disease recurrence and that this effect is comparable to mesalazine (20).

In a study maintained by Mountzouris et al. (2007), the effect of feed containing a new probiotic multibacterial mix on poultry was investigated. The probiotic culture mix contains 2 *Lactobacillus* strains, 1 *Bifidobacterium* strain, 1 *Enterococcus* strain and 1 *Pediococcus* strain. Four trials were conducted in this study, which lasted for 6 weeks on 400 chicks that 1-day-old. Probiotics have been added to their feed and water. The effect of the application on the performance of the animals and on the microbial flora of the feces was determined. According to the results, the addition of probiotics to food and water has the same effects on their development as the use of antibiotics. The positive effect of consumption of probiotics added to water and feed is almost the same as consumption of avilamycin. In addition, the effect of probiotics on fecal microflora was found to be important as a result of probiotic consumption (4).

Ha et al. (2008) researched the anticancer activity and bacterial enzyme inhibition of *Bifidobacterium adolescentis* SPM0212. *B. adolescentis* SPM0212 inhibited the formation of three colon cancer cell lines and inhibited the harmful fecal enzymes such as α-glucuronidase, α-glucosidase, tryptophanase and urease (21).

Helicobacter pylori is a Gram negative pathogen leading to gastritis, ulcer and stomach cancer. Laboratory studies have shown that some *Lactobacillus* species are antagonistic to *H. pylori*. However, therapeutic use of probiotics is not recommended due to the probiotic species to be used in this respect are not fully detected and the inability to determine the appropriate amount and time (22).

Lactic acid bacteria have been used safely in food for many years because they are beneficial to human health and fermentable. For this reason they have a great deal of importance in the food industry. In addition, these bacteria have an important role in the biocontrol of food. Most pathogenic bacteria are susceptible to certain substances produced as final products by lactic acid bacteria. Among the antagonistic mechanisms of lactic acid bacteria, lactic acid, hydrogen peroxide and bacteriocin are the most frequently accentuated substances in recent years (22). Low molecular weight metabolites such as lactic and acetic acid, other aroma components and seconder metabolites have a wide inhibition effect on *Salmonella*, *E. coli*, *Clostridium* and *Helicobacter*. *L. rhamnosus* GG produces low molecular weight antimicrobials (23).

Probiotics are able to inhibit or eliminate pathogenic microorganisms by several mechanisms or pathways. These are;

- Decrease the pH of the lumen by producing lactic acid,
- Producing antimicrobial microcin, hydrogen peroxide and free radicals,
- Clinging to receptors and competing for food sources,
- Stimulate the formation of protective mucin,
- Stimulate the production of secretory IgA (24).

The antagonistic activity of *L. rhamnosus* GG against enteropathogenic bacteria was observed in mice and against *Salmonella typhimurium* in vivo. *Lactobacillus acidophilus* strain LB was reduced viability of *Staphylococcus aureus, Listeria monocytogenes, S. typhimurium, Shigella flexneri, Escherichia coli, Klebsiella pneumoniae, Bacillus cereus, Pseudomonas aeruginosa* and *Enterobacter* spp. in vitro. It has been reported that antibacterial non-bacteriocin

components produced by *L. acidophilus* (johnsonii) strain LA1, inhibit various Gram negative and Gram positive pathogens such as *S. aureus, L. monocytogenes, S. typhimurium, S. flexneri, K. pneumoniae, P. aeruginosa* and *Enterobacter cloacae* (23).

In a study, the effect of probiotic bacteria (*Bifidobacterium, Streptococcus* and *Lactobacillus* strains) and *Saccharomyces cerevisiae* strains on enniatin (an organic chemical compound produced by *Fusarium*) was investigated. It was found that bacteria degraded the enniatum (25).

In a study made by Arslan et al. (2013), twenty *Bacillus* spp. isolates of thirteen different breadstuff were investigated. According to the results, *Lactobacillus rhamnosus* inhibited rope producing strains of *Bacillus* spp. on agar diffusion, broth medium and dough. Thus, it has been stated that probiotic biopreservative agents beneficial for human health can be used instead of chemical preservatives harmful to human health (26).

It has been suggested that *Bacillus subtilis* spores are probiotics that suitable for animal consumption and may be used in humans in the treatment of *H. pylori* and diarrhea (17).

Shanahan et al. (2001) found that fecal coliform and enterococci levels decreased in mice fed with *L. salivarius* spp. *salivarius* UCC118 (27).

3. Prebiotics

Prebiotics are nutrients that reach directly into the large intestine without digestion in the small intestine and increase the beneficial effects of probiotics on health (1,5). Lately, there has been much interest in prebiotic usage as a functional food to regulate the composition of the gastrointestinal microbiota in order to show beneficial effect to the health of host (28). Prebiotics are functional food ingredients that enhance the quality of many foods. Prebiotics are used as food supplement in fermented dairy products, bread, jams, beverages and candies (3).

Enrichment of the human diet with prebiotics has positive effects on the gastrointestinal system microflora. In order to be recognized as a prebiotic, a food ingredient must carry the following qualities;

- It must be resistant to digestion (should not be absorbed in the stomach and small intestine),
- It should be hydrolyzed by colon microflora bacteria,
- It should be selective for the beneficial microorganisms in the colon and encourage their proliferation,
- It should has positive effects on host health (3,24).

Lactosucrose, inulin, fructooligosaccharide, galactooligosaccharide, soy oligosaccharide and isomaltooligosaccharide are products that used as prebiotically. In colorectal cancer studies, oligofructose, lactulose, resistant starch and wheat bran ± inulin are usually as used prebiotically (5). Inulin and oligofructose, which are derived from resistant starches, are the most studied and well-known prebiotics. Oligosaccharides play an important role in obesity control by increasing the feeling of satiety and reducing the feeling of hunger (1).

Prebiotics can help protecting against intestinal diseases and according to clinical experimental studies, prebiotics may show positive effects on the gastrointestinal system. The prebiotics reaching the colon without any change in their structure are being hydrolyzed by bacteria in the colon (3).

Prebiotics can influence the development and survival of probiotic cultures through improving the development and metabolites of probiotic and starter cultures (1).

Inulin is a component of many edible plants such as chicory, onion and garlic. Inulin is a fructose and glucose-based, slightly digestible mixture. These oligosaccharides reach the colon and selectively stimulate the development of bifidobacteria (29).

3.1. Antimicrobial Effects of Prebiotics

While prebiotics are selectively used by the beneficial microflora (such as *Lactobacillus*, *Bifidobacterium*) in the colon, it has been reported that the potential pathogenic microorganisms such as toxin producing *Clostridium*, proteolytic *Bacteriodes* and toxigenic *E. coli* are inhibited (24).

Prebiotics inhibit pathogenic bacteria proliferation and make laxative effects. In animal experiments, diarrhea, serum triglyceride levels, postprandial glucose and insulin levels are reduced. Oligosaccharides act as cell surface receptors, linking pathogenic microorganisms to themselves and allowing throw out with stool (28).

The antimicrobial effect of prebiotics occurs only when it can be used by certain species that have beneficial effects on human health. These species also produce antimicrobial compounds that regulate the immune system and inhibit pathogens. In addition, soluble oligosaccharides prevent colonization of pathogens by reducing their colonization properties (30).

4. Synbiotics

Foods containing probiotic and prebiotic are described as synbiotics due to the synergistic relationship between them (1). Probiotic bacteria survive longer and colonize better in the colon with synbiotic application. The aim in synbiotic

product is to obtain a useful agent for both the small intestine and the large intestine. According to the in vitro studies maintained, showed that a synbiotic application alone is more advantageous than either prebiotic or probiotic. In a related study, a synbiotic mixture containing *B. breve, L. lactis* and prebiotic component was reported to be more effective than only lactic acid bacteria, and has an inhibitory effect on the development of colon cancer cells (5).

In practice, the most common combination application of synbiotics is *Bifidobacterium* and oligosaccharides (3).

4.1. Antimicrobial Effects of Synbiotics

In a study made by Loo et al. (2007), the ability to reduce colon cancer of synbiotics (oligofructose-enriched inulin + *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12) in humans has been investigated. As a result, synbiotic usage has led to considerable changes in fecal microflora. *Bifidobacterium* and *Lactobacillus* numbers are increased and *Clostridium perfringens* number is decreased. The usage of synbiotics significantly reduced colorectal proliferation, reduced the amount of fecal water which cause necrosis in colon cells, improved epithelial barrier properties in polypectomy patients. According to the data obtained from genotoxicity tests of colonic biopsy samples, a decrease in the amount of genotoxin exposure towards the end of usage was observed. Synbiotic consumption prevented interleukin 2 production and increased interferon γ production in cancer patients. As a result, it has been reported that synbiotic consumption changes in significant amounts on the bacterial ecosystem in colon (31).

In a study made by Rowland et al. (1998), the activity of bacterial enzymes (b-glucuronidase and b-glucosidase), which are believed to play a role in colon cancer, and the concentration of ammonia produced by bacteria which assumed to cause tumor formation, were evaluated using *Bifidobacterium longum* and inulin. Co-consumption of *Bifidobacterium* and inulin resulted more reduction in the amount of azoxymethane and ACF (aberrant crypt foci) (29).

It has been reported that bacteriocins such as nisin and lacticin have more inhibition effect on *Salmonella kentucky* and *Listeria innocua* when combined with organic acids such as sodium sulphate and sodium lactate. In addition, there was a decrease in the total bacteria number (32).

The best known synbiotics are *Bifidobacterium* + Fructooligosaccharide, *Lactobacillus* + lactylol and *Bifidobacterium* + galactooligosaccharide combinations (32).

5. Discussion

As a result of the prevention of chronic diseases and protection of the optimum health condition during the life of people, diet has become the focus of attention. Due to increasing demand for healthy food, new designs and new products continue to develop internationally in the food industry. Probiotic strains are produced successfully and applied to foods that are preferred by consumers in large quantities, at the same time they can protect their vitality and function. In addition to its technological properties, there are various strains that change accordingly their impact on human health (23).

Probiotics, prebiotics and synbiotics are mostly used to strengthen the gastrointestinal beneficial microflora. Also it has been reported to have a therapeutic or protective effect against many diseases. Interest on the subject is increasing day by day and the usage of these products is also becoming more popular (32).

The utilization of probiotics in the food industry is expanding from dairy products to fruit juices, energy bars and chocolate products. In these new products, maintaining viability of probiotics is rather difficult compared to dairy products (33).

Studies on the development of foods containing probiotics such as *Lactobacillus* and *Bifidobacterium* have been intensively carried out. The usage of synbiotics should be encouraged in future research which will provide more bacteria reach to colon alive. Studies on the use of probiotics in combination with enzymes or antibiotics should be research (34).

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