Probiotics and their increasing importance in human health and infection control

Abdolmajid Ghasemian[a], Majid Eslami[b], Morvarid Shafiei[c], Sohrab Najafipour[a] and Ali Rajabi[d]

Probiotics include a group of microorganisms with numerous effects acting as normal flora and masking binding sites of pathogens and inhibition of their colonization. Most common probiotic species include *Bifidobacterium* spp., *Lactobacilli* and *Saccharomyces boulardii*. Some other beneficial properties of probiotics include cancer prevention, reduction of blood cholesterol and its absorption from the intestine (by bile digestion), stimulation and strengthen of the immune system, treatment and prevention of acute diarrhea, reducing inflammation in the intestines, and food allergies or eczema in children, improving the symptoms of irritable bowel syndrome and colitis, and remedy of vaginal yeast infections, and also antibiotics associated diarrhea, oral lesions, dental caries, and vaginal swelling. Furthermore, probiotics contribute to prevent viral infections, athlete's foot and fungal infections, and improvement of digestion and enhancing nutrition absorbance, inhibition of biofilm formation and increase in vitamins biosynthesis; especially those in groups B and K. Probiotics use in defined amounts has desirable outcomes. Side effects of probiotics are rare which occur among immunocompromised patients and pediatrics, thus care should be taken to avoid their side effects. Use of germ-free animals and study of symbiotic interactions among probiotics is possibly helpful for future perspectives.

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Historical aspects of probiotic

The history of the use of live microorganisms in food, in particular the bacteria producing lactic acid, is very long to maintain and improve human health. A Roman historian, 76 BC, recommended the use of milk fermentation products to treat gastroenteritis. Since the advent of the microbial age, some researchers have attributed these beneficial effects to the intestinal microbial balance [1]. The hypothesis of probiotics was formed in the early 1900s, when Elie Metchnikoff won the Nobel Prize, arguing that the consumption of yogurt containing lactobacillus led to a decrease in the number of toxin-producing bacteria in the intestine and, as a result, increases the host's lifespan [2]. The first clinical studies on probiotics in the 1930s focused on the effectiveness of constipation. Since then, the number of these studies has steadily increased, and many of these studies have been conducted in Europe and Asia [3].

It was proposed that the proper microbial balance of the intestine can prevent the disease, and the imbalance of the intestinal flora causes various diseases such as diarrhea, inflammation of the intestine and stomach, constipation, and bowel Irritable syndrome (IBS), Crohn's disease, colon inflammation, food allergy, and some cancers [4].

Equilibrium of flora through competition compels the pathogenic bacteria from the intestines and stimulates the immune system, and enhances levels of vital nutrients such as short chain fatty acids, vitamins, arginine, cysteine, and glutamine amino acids, growth factors and various antioxidants products. Studies have revealed that probiotic consumption increases some types of

[a]Department of Microbiology, Fasa University of Medical Sciences, Fasa, [b]Department of Bacteriology and Virology, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, [c]Department of Microbiology, Pasteur Institute of Iran, Tehran, and [d]Shahrekord University of Medical Sciences, Shahrekord, Iran.

Correspondence to Ali Rajabi, Researcher of Shahrekord University of Medical Sciences, Shahrekord, Iran.

Tel: +98 03833330061; e-mail: alir.rajabi@gmail.com

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microflora in the intestine, but the total bacterial count in the intestine does not increase [5].

Perhaps justifying the use of microbes or bacteria is a little surprising, as germs are often known to be pathogenic and harmful, although this is not known, and many more organisms are found, such as probiotics in human life to be useful. In the 1980s, active supermarkets were introduced in Japan. These foods were called FOSHU Foods for specified health use [6].

Definition of probiotics

From the point of view of words, the root is the Greek Probiotic word, but in fact the word consists of the Latin prefix 'Peru' and the ancient Greek word 'BIOS', a literal combination meaning 'for life'. This term was first used by Lily and Steller in 1965 to distribute secretory materials by a microorganism that stimulates the growth of another microorganism, and thus contrasts with the term antibiotics [6].

In the first aquaculture, Yasuda and Taga in 1980 predicted that bacteria would be found to be useful not only as food but also as a biological regulator of other diseases and food cycling activators. Fuller, in 1989, called probiotics as living microbes that are used as food additives and are beneficial to host animals by improving their intestinal microbial interactions. This definition emphasized the vitality of probiotic microorganisms as a major factor in their preparation. But in this definition, the role of the environment is neglected. In 1999, Gatsup introduced another definition of probiotics in aquaculture, so that probiotics are known as protozoal cells that host gastroenterology and survive to improve health. These definitions focus on the probiotic consumption and its ability to improve the host's health due to the presence of the gastrointestinal tract and thus being of the most comprehensive definitions of probiotics in relation to aquaculture [7].

From delivering, the infant obtains some bacterial genera such as *Bacteroides*, *Bifidobacterium*, *Lactobacillus*, and *Escherichia coli*. *Bifidobacterium*, *Lactobacillus* spp. are the most common species. *Lactobacilli* are the most commonly used bacteria in fermented dairy products. These species are capable of converting carbohydrates (such as lactose) into lactic acid, and thus make the taste of sour in fermented dairy for example, yogurt. Lactic acid also prevents corrosion of dairy products. Common probiotics include various species of *Bifidobacterium*, *lactobacillus*, and some yeast species [8]. Their count should be 1×10^9 CFU per diet. However, maintaining the balance between healthy (85%) and harmful bacteria (15%) is necessary depending on age, genetics and diet. Any imbalance called dysbiosis leads to ailments such as ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), celiac disease, colon cancers, diarrhea, traveller's diarrhea, constipation, *Helicobacter pylori* infection, pouchitis and even possibility of diabetes, mental health, depression, autism, inflammation and obesity, pediatric atopic dermatitis, acne, allergic reactions, necrotizing enterocolitis and neonatal sepsis, low birth weight (LBW) and very LBW infants, blood pressure (BP), nonalcoholic fatty liver disease and cirrhosis, rheumatoid arthritis and kidney stones [9]. However, probiotics have very few disadvantages such as diarrhea (if high numbers are taken short-time), sepsis in cancer patients. Some conditions such as stress, high sugar and processed foods, low fibrous food consumption, diet with low fermented foods, specific medications and antibiotics consumption will cause the imbalance of probiotics. In addition, kefir, yoghurt (especially from goat), Sauerkraut, raw dairy and other fermented and fibrous foods are proper diets [10].

Probiotic microorganisms

Until today, several factors have been used to treat human bacteria and fungi. The bacteria that have been studied so far and their role as a proper probiotic agent include *Lactobacilli* species (*L. acidophillus*), *Bulgaricus* (*L. bulgaricus, L. heleveticus*, *L. casei*, *L. paracasei*, *L. plantarum* and *L. sake*), *B. longum*, *Enterococcus facium* and *Enterococcus faecalis, Lactococcus lactis, Streptococcus thermophilus, Clostridium butiricum, Saccharomyces boulardii, Saccharomyces cerevisiae* and some other agents. According to studies from probiotic bacteria, *Lactobacillus* and *Bifidobacterium* species have the highest efficacy and among yeasts, the most effects has been revealed for *S. bullaria* [11,12].

Probiotic inherent properties

Some inherent properties of probiotics include lack of toxicity and pathogenicity, the ability to survive against the inherent defense mechanisms of the body in the upper gastrointestinal tract, including survival against gastric acid and bile salts, colonization in the intestinal mucosa, induction of health improvement in the host. However, these organisms should be in vivo and in high amounts, remain alive and stable during use and storage, and be able to survive in the intestinal ecosystem. It should also be metabolically active in the intestine, and should not produce biochemical changes such as proteolysis, carbohydrate metabolism, or organic acids in the food [13].

Functions of probiotics

Various mechanisms have been proposed for the function and activity of probiotics with potential of preventing the various diseases in the host body:

(1) Prophylactic material production:

Probiotics can prevent the development of some infectious diseases by producing substances that can inhibit microorganisms such as lactic acid, bacteriosin, hydrogen peroxide, and so on [14].

(2) Blocking the binding sites of pathogens:
Probiotics prevent and inhibit colonization and persistence of pathogenic microorganisms.
(3) Competition for nutrition:
Probiotics use existing foods before being used by pathogen microorganisms.
(4) Stimulation of the immune system:
Probiotics can induce both proprietary and nonspecific immunity against intestinal diseases. For example, *L. casei* increases the immune response in viral diarrhea [15].

The probiotics advantages

Probiotics confer numerous advantages as followings:

(1) Alleviation of the lactose intolerance symptoms, because LAB causes lactose to be converted to lactic acid (*Bifidobacterium* spp., *Lactobacilli*, *S. boulardii* and *Streptococcus thermophiles* among which *Bifidobacterium animalis* was predominant) [16].
(2) Prevention of colon, small intestine, liver and breast cancer (*Bifidobacterium* spp., *Lactobacilli*, *S. boulardii*) [17].
(3) Reduction of blood cholesterol and its absorption from the intestine (by digestion of bile in the intestine) and reduction of BP (*B. animalis, Lactobacilli, S. boulardii*) [18,19].
(4) Improvement and strengthen of the immune system and infections prevention (*Bifidobacterium* spp., *Lactobacilli*, *S. boulardii,* ...) [20].
(5) Prevention and healing of acute diarrhea (*Bifidobacterium* spp., *Lactobacilli,* ...).
(6) Reducing intestinal inflammation (*Bifidobacterium* spp., *Lactobacilli*, ...).
(7) Reducing pediatrics food allergies or eczema.
(8) Improve the absorption of minerals and vitamins.
(9) Improve the symptoms of IBS and colitis (large intestinal mucous membranes) (*Bifidobacterium* spp., *Lactobacilli*, *S. boulardii*) [9].
(10) Prevention of the growth and replication of harmful bacteria.
(11) Treatment and prevention of vaginal yeast infections, diarrhea associated with antibiotics, oral pest, dental caries, vaginal swelling, athlete's foot, fungal infections, and oral candidiasis.
(12) Improvement of digestion and absorb nutrition.
(13) Contributing synthesis of groups B and K vitamins [21–23].

Applied aspects of probiotics

Most of the recent probiotic strains are of human origin. Probiotic strains should be able to survive and grow under the physiological conditions of the ecological unit. The ability to bind and colonize is also necessary to have a close connection with the potential effects of exposure to prolonged contact with the lymph tissue associated with the intestine.

The production of antimicrobial agents including bacteriocins, similar bacteriocins, lactic acid, and hydrogen peroxide by probiotics is one of the preventive factors against the growth of pathogens [24,25].

The survival of the strain and the preservation convenience and desired growth during the production and storage of the probiotic is also one of the factors necessary for the probiotic to be an advantageous strain. The survival of the strain depends on factors such as the final pH of the product, the presence of other microorganisms, the storage temperature, the presence or absence of microbial inhibitors in the substrate. High growth and the production of odors and flavors desired by the strains are also important in the production of functional or general probiotic foods [25,26].

Probiotics selection criteria

Probiotics are generally human sources and are considered as nonpathogenic bacteria. The selection of probiotic species is based on history of their use for a long time without any harmful side effects. Other relevant criteria for the use of suitable bacterial species include:

(1) Resistance and survival in the technological process.
(2) Live and active in the digestive system, which means resistance to gastric acid and bile acids.
(3) Ability to attach and colonize to the epithelial cells of the intestine.
(4) The ability to inhibit pathogens by producing antibacterial compounds, eliminating their competitive ability or reducing intracellular pH.

Ability to stabilize intestinal bacterial flora

From a practical point of view, probiotic products should have a suitable life span, consume a large number of live cells, and are nonpathogenic and nontoxic. Probiotics member which are mostly studied in various fields include those Lactic acid bacteria and *Bifidobacterium* spp. These two bacterial genera do not induce the inflammation, an important reasons for their selection as probiotics. Those most common species have been depicted in table1. The selection of probiotic species is mainly based on history of their use for a long time without any harmful side effects.

Probiotics, in particular, bacteria with different mechanisms, have beneficial effects in their hosts, such as balancing intestinal flora and preventing the binding of

pathogenic bacteria to the intestinal mucosal wall, suppressing inflammation and reducing the occurrence of cancer noted that all of them are based on the factor regulating the immune system [27].

Extensive research on probiotics and health effects have been implemented in humans and more in laboratory animals, including rats and even aquatic animals, including the effects of probiotics and especially *Lactobacillus* spp. on the improvement of growth indices and improvement of the immune system and resistance to diseases [21].

Studies have shown that the antithetic effect of probiotics on enzymes from the large intestine of humans and animals, inhibition of the toxicity of carcinogens in the in vitro conditions as well as laboratory conditions by them, the suppression of cancer-inducing damage and tumors under conditions Laboratory results.

Probiotic function also help in preventing the development of some infectious diseases such as vaginal infection that causes early abortion, reducing the absorption of allergens through the intestines and even reducing eczema among infants [28].

Mechanisms of probiotic effects

There are many proposed mechanisms to justify the ability of probiotics to protect host against gastrointestinal disorders. The sum of all the processes by which bacteria control the colonization of other bacterial species in the body is called colonization resistance. Different species of *Bifidobacterium* are known to be resistant to the colonization of pathogenic bacteria in the large intestine [29].

A probiotic bacterium may inhibit different pathogens with different mechanisms. The definition of the mechanism of the effect of probiotics on host protection against gastrointestinal diseases is as followings:

Competition for colonization

Competitive ability for bacterial binding sites on the intestinal epithelial surfaces is another mechanism of probiotic efficiency. Given this issue, some probiotic species have been selected for attachment to epithelial cells. Probiotics, possibly, also increase the intestinal potential of *E. coli* by increasing the intestinal mucin, which has a pathogenic potential to the intestine [30].

Competition for nutrition

Competition for nutrition has been proposed as one of the mechanisms of the effect of probiotics. Probiotics are likely to use those nutrients absorbed by pathogens. Laboratory studies have revealed that intestinal microorganisms are more efficient than *Clostridium difficile* to absorb monocalcium, glucose, *N*-acetyl-glucosamine and sialic acid in the colon [31].

Production of inhibitory compounds

Probiotics produce different materials that have an inhibitory effect on both Gram-positive and Gram-negative bacteria. These inhibitory compounds include organic acids such as acetate, propionate and butyrate, H_2O_2 and bacteriocins compounds. These materials not only reduce the number of the pathogens, but also may affect the bacteria metabolism or the toxins production by them. The production of bacteriocins or protein compounds by acid-producing bacteria, with specific inhibitor activity against bacterial species, has been most commonly studied [32].

Receptor masking and toxin digestion

It has been uncovered that *S. boulardii* and *Bacillus clausii* protect the animals and human against the intestinal infections caused by *C. difficile* via the enzymatic elimination or cover of toxin receptors in the intestinal mucosa [32,33].

The immune system stimulation

Probiotics affect the immune system at several levels, including increased levels of cytokines and immunoglobulins, increased mononuclease cell proliferation, macrophage activation, increased activity of natural killer cells, self-immune modulation and immune stimulation against pathogenic bacteria and protozoa. It has been uncovered that all bacterial cells increase the proliferation of immune cells and produce pro-inflammatory cytokines such as TNF-α and IL-6 [34]. Conversely, probiotics interfere with the suppression of lymphocyte proliferation and the production of cytokines by T cells. Most importantly, probiotics use these positive effects on the immune system without producing a harmful inflammatory response. The immune response may be increased when several probiotics are used together and act as synergistic. This effect is generally observed when combined with *Lactobacilli* and *Bifidobacterium* spp. Probiotics balance phagocytosis in healthy and allergic people in a different way. In healthy people, there is an immunosuppressive effect, whereas in allergic people, a decrease in inflammatory responses was observed [35,36].

Inhibition of biofilm formation

The inhibitory effects of probiotics; especially *Bifidobacterium* spp. and *Lactobacillus* spp. in biofilm formation by food and urinary tract pathogens, *Streptococcus mutans*, *Candida albicans*, have been revealed [37–40]. Most of

biofilm inhibitory effects are conferred via those mechanisms performed by probiotics for inhibition of attachments and colonization of pathogenic agents.

Antiviral effects

Several probiotic bacterial species have been shown to inhibit the attachment and replication of viral agents such as *Leuconostoc mesenteroides* YML003 against low-pathogenic avian influenza (H9N2) virus in chickens, lactic acid bacteria against viral agents (by immune cell stimulation, inhibition of receptor attachment, antiviral inhibitory metabolites and direct interactions), *Enterococcus faecium* inhibitory effect on the propagation of swine influenza A virus and inhibitory effects of *B. longum* and *L. acidophilus* against intestinal infection by rotavirus [41–44].

Therapeutic effects of probiotics

Various clinical studies on humans have revealed that the use of lactic acid producing bacteria at 10–110 ng/dose can reduce the incidence, duration, and severity of some diseases of the digestive system. Probiotics have been shown to maintain intestinal uniformity and complications of a number of digestive diseases such as antibiotic-dependent diarrhea, IBD, childhood diarrhea, travel diarrhea, lactose intolerance, *H. pylori* infection, IBS and *C. difficile*-induced intestinal illness. In addition, various laboratory and clinical studies have shown that probiotics have promisingly beneficial effects in the prevention or treatment of genitourinary, high-fat, allergic, and cancerous infections [15,45].

Probiotics shady or disadvantageous effects

Despite huge advantages, probiotics confer very few undesired effects such as diarrhea when consumed in high numbers and sepsis in cancer patients. It seems that they have not side effects on healthy normal individuals. Moreover, excessive immune stimulation in susceptible individuals, deleterious metabolic activities, gene transfer and gastrointestinal side effects have been stated in case reports and clinical trials [46]. In immunocompromised patients, invasive disease have been demonstrated by *L. mesenteroides*, *Pediacoccus pentosaceus*, *Lactobacillus plantarum*, *Lactobacillus paracasei* subspecies *paracasei* F19, LGG, *Lactobacillus johnsonii* LA 1, VSL #3, *S. boulardii* (HIV) and *L. plantarum* 299V (liver transplant) strains [47,48]. In addition, one mechanical choking episode was reported by LGG, LC705, Bb99, and *Propionibacterium freudenreichiis* pp *shermanii, Bb12* and *Lactobacillus reuteri* strains [49,50]. Thus it seems that side effects related to the probiotics is generally uncommon or rare, mostly depending upon the healthy status of patients. Among immunocompromised patients and children populations they should be consumed cautiously.

Conclusion

Probiotics have the ability to prevent and improve infections and some other impairs in the host body via several mechanisms such as production of prophylactic material and some inhibitory substances such as bacteriocins, lactic acid, hydrogen peroxide, and so on. Masking binding sites of pathogens and inhibition of their colonization, competition for nutrition, and stimulation of the immune system in intestinal diseases such as *Lactobacillus casei* effect in viral diarrhea are other mechanisms. Some other beneficial properties of probiotics include colon, small intestine, liver and breast cancer prevention, reduction of blood cholesterol and its absorption from the intestine (by digestion of bile in the intestine), regulation of BP, stimulation and strengthen of the immune system, treatment and prevention of acute diarrhea, reducing inflammation in the intestines, and food allergies or eczema in children, improving the absorption of minerals and vitamins, and also the symptoms of IBS and colitis (large intestinal mucous membranes), and remedy of vaginal yeast infections, and also antibiotics associated diarrhea, oral lesions, dental caries, vaginal swelling. Furthermore, probiotics cause prevention of viral infections, athlete's foot and fungal infections, oral candidiasis, improvement of digestion and enhancing nutrition absorbance, inhibition of biofilm formation and increase in vitamins biosynthesis; especially those in groups B and K. During recent years, beneficial effects of probiotics have increasingly reported and it has been revealed to confer antiviral and antibiofilm formation properties via various mechanisms. Side effects of probiotics are rare which occur among immunocompromised patients and pediatrics where care should be taken when consuming them.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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