Review Article

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Obstacles and Challenges in the Use of Probiotics

S. Sadeghi (MSc)[1], F. Jaberi Ansari (MSc)[2], H. Jalili (PhD)[3*]

1.Department of Life Science Engineering, Faculty of New Sciences and Technologies, University of Tehran, Tehran, I.R.Iran
2.Department of Medical Nanotechnology, Faculty of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, I.R.Iran
3.Department of Life Science Engineering, Faculty of New Sciences and Technologies, University of Tehran, Tehran, I.R.Iran

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ABSTRACT

BACKGROUND AND OBJECTIVE Probiotics are living microorganisms whose adequate intake has shown healthful effects in the host body and have been suggested to have beneficial effects in the prevention and treatment of many diseases. This study was conducted to investigate the obstacles and challenges of probiotic products in the production process and their effects on human health.

METHODS: For data collection in this Narrative review article, articles containing one of the words “probiotic”, “lactobacillus”, “bifidobacterium”, “biogenic amine” and “antibiotic resistance” from 1990 to 2017 were searched and studied in Thomson Reuters, Pubmed, Scopus, Science Direct and Islamic World Science Citation Center (ISC) databases.

RESULTS: Research has shown that systematic infections and chronic diseases, over-stimulation of the immune system, transfer of antibiotic resistance genes, production of biogenic amines and D-lactic acid, lack of survival and sustainability of microorganisms and ultimately the change in the taste and flavor of probiotic products are the obstacles and challenges facing the production of probiotics. The use of bifidobacterium in terms of transfer antibiotic resistance genes is safer for the production of probiotic products rather than other microorganisms.

CONCLUSION: Based on the results of this study, probiotics are only safe in healthy people, although they are very useful for human health, but their use in children, pregnant women and people with a weakened immune system causes infection.

KEYWORDS: *Probiotics, Lactobacillus, Bifidobacterium, Biogenic Amine, Antibiotic resistance*..

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***Corresponding Author: H. Jalili (PhD)**
Address: Faculty of New Sciences and Technologies, University of Tehran, Kargar Shomali St., Tehran, I.R.Iran
Tel: +98 21 86093268
E-mail: hjalili@ut.ac.ir

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Introduction

Probiotics are defined as living organisms that are resistant to bile, stomach and pancreatic secretions, are attached to epithelial cells and are colonized in the human intestine (1-4). The main mechanism action of probiotic bacteria is to prevent the pathogenic bacterial colonization (5-7). Many researchers believe that probiotics should stay alive in the intestines and apply their beneficial effects by sticking to the epithelium of the intestine (1, 8). Most probiotics belong to bifidobacterium and lactobacillus species (1). Probiotics can be used as dietary supplements or therapeutic agents (9). Today, bacteria producing lactic acid have become an important industrial microorganism in the production of fermented foods such as yogurt, cheese and butter (10). Probiotic bacteria are attached to enterocytes and thus prevent binding to intestinal pathogens to the intestinal mucosa through the production of inhibitors such as bacteriocin, lactic acid, and toxic oxidative metabolites (11). Binding to the intestinal mucosa are essential for probiotics, while on the other hand this binding increases the ability of the bacteria in terms of movement and pathogenesis (12). There are also concerns about the possible transmission of antimicrobial resistance from probiotic strains to pathogenic bacteria in intestinal microflora. On the other hand production of toxic metabolites, such as biogenic amines and D-lactic acid, are the main risks of the use of probiotics (13, 14). Therefore, given the potential benefits of using probiotics, the use of these microorganisms does not always have advantages and there are concerns about their use in clinical and industrial applications. Few experiments have been conducted on the quality control of probiotic products and the potential risks associated with their use. Although the use of probiotic foods has many health benefits, but like many foods, there are some limitations that have been underestimated. It is necessary that their application limitations be carefully reviewed and consumers should be informed about these types of products. This review article was conducted to evaluate the use of probiotics for people at risk

Methods

For data collection in this Narrative review article, articles containing one of the words “probiotic”, “lactobacillus”, “bifidobacterium”, “biogenic amine” and “antibiotic resistance” from 1990 to 2017 were searched and reviewed at Thomson Reuters, Pubmed, Scopus, Science Direct and Islamic World Science Citation Center (ISC) databases. Of 158 articles found in different databases, 52 articles that addressed the barriers and problems of probiotic products in the production process and health effects on humans were selected, and other articles that were not related to the subject were excluded from the study.

Results

Nutritional and clinical concerns

Systematic Infections and Chronic Diseases: Some case reports indicate infections caused by probiotic bacteria in patients taking probiotics. The most frequent reports are about 32 cases of fungal infections due to the presence of saccharomyces cerevisiae and saccharomyces boulardii in patients taking probiotics. About 8 cases of bacteremia have been reported in association with the use of lactobacillus species (15). In other cases, the consequences of infection are lethal, but this lethality is associated with a pre-existing disease and does not directly result from probiotic infection (1,16,17). Over the past 10 years, many articles have been published on the assessment of the immunity of lactobacilli, based on experimental use to determine the pathogenicity of these microorganisms. There are 13 species of streptococcus in fermented food (18), which are considered opportunistic pathogens and are involved in human infections such as meningitis, heart valve infection, bacteremia, and especially urinary tract infection (19). Enterococci are resistant to many antibiotics. Factors involved in infection with enterococcus faecalis include factors that have cell adhesion properties, production of cytolysin (haemolysin), the presence of surface protein Esp, extracellular superoxide dismutase, or Zinc dependent metalloproteinase (gelatinase), having compounds similar to protein M and leucine decomposition capability. These characteristics have raised doubts about the use of enterococci as probiotics. Another undesirable characteristic of enterococci is the presence of transferable genes that encodes antibiotic resistance genes such as vancomycin (19,20). Bifidobacteria are involved in the formation of polyps in humans, which are considered as one of the factors contributing to cancer (21). The most important concern for probiotics is the risk of poisoning (1, 22). Cancer, diabetes and organ transplantation (especially the liver) have been shown to increase the chance of infection with lactobacillus (23). Various reports are available on lactobacillus poisoning and probiotic bacteria (Table 1) (1). Rautio et al. reported a liver infection in a 47-year-

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old woman with diabetes mellitus due to the use of probiotic bacteria lactobacillus rhamnosus GG (24). In a study by Gasser et al. during the years 1938 to 1993, 56 cases of heart valve infection were reported, which were caused by the presence of lactic acid bacteria (25). Table 2 shows lactobacilli and bifidobacteria that are commonly present in the intestine, as well as species associated with human infections (19). Based on the characteristics of the cases reported so far, a list of low risk and high risk factors for probiotic infections have been presented (Table 3) (1).

Overstimulation of immune system: Experiments on mice showed that intestinal microflora is important for stimulating the immune system. The presence of intestinal microflora is necessary for various immune functions such as antibody production, creation and durability of oral tolerance to food antigens, and the formation of germinal centers within oral follicles. The opposite effects of intestinal microflora manipulation have been suggested, especially in the case of neonates, in which the long-term changes in the microflora can alter the immune response. The second group who is at increased risk of immune stimulation due to the use of probiotics is pregnant women. During pregnancy, the response of T cells to Th2 is necessary to maintain the survival of the fetus. Because Th1 cytokines cause abortion (1). Lactobacillus probiotic species suppresses cytokine Th2 responses in vitro and in some human studies, increase the production of cytokine Th1 interferon gamma (1, 26). These effects may cause abortion. However, there is currently no evidence of this, and such a threat remains theoretical.

Transfer of resistance genes: Antibiotic resistance in bacteria can be intrinsic or acquired. Intrinsic resistance is a natural characteristic and can be considered as a characteristic of the species. This kind of resistance is in most cases non-transferable and is present in almost all members of a taxonomic group. Acquired resistance is on the opposite side of intrinsic resistance. Acquired resistance occurs in the following cases: 1. The accumulation of DNA mutations that lead to resistance to antibiotics. 2. The acquisition of resistance genes from antibiotic resistant bacteria. External DNA can be acquired through conjugation, transmission through the virus, or transformation. Antibiotic resistance due to acquisition of external DNA can be transmitted through plasmid or transposon to other bacterial species (27). Lactobacilli naturally show resistance to a wide range of antibiotics (28). In most cases, antibiotic resistance is not transferable. Lactobacillus strains with antimicrobial resistance usually do not cause concern. Several strains of lactobacilli, such as lactobacillus rhamnosus and lactobacillus casei, are intrinsically resistant to vancomycin (28–30). Many lactobacillus strains that are intrinsically resistant to vancomycin are considered safe to be used as probiotics (31). Resistance to antibiotics due to plasmids rarely occurs among lactobacilli (32, 33), because antibiotic resistance genes can be transferred between phylogenetically distant bacteria (34). Most bifidobacteria are intrinsically resistant to nalidixic acid, neomycin, polymyxin B, kanamycin, gentamicin, streptomycin and metronidazole (33). In early studies, vancomycin had an inhibitory effect on bifidobacteria (35), while recent studies have shown that resistance to vancomycin is a general characteristic of all bifidobacteria (33).

Production of Toxic Metabolites

Production of biogenic amines: Biogenic amines (BA) are organic bases with low molecular weight with heterocyclic, aromatic or aliphatic structures that are formed by decarboxylation of amino acids or amination and transamination of aldehydes and ketones. Since several lactic acid bacteria produce BA, starter cultures of lactic acid bacteria should be free of decarboxylase enzymes to prevent the production of high levels of BA in fermented food (13, 36). Other BAs, such as putrescine, also have toxic effects (37, 38), and tryptamine and phenylethylamine are considered undesirable amines due to their inappropriate effects (39). In addition, secondary amines can interact with nitrites in foods to produce carcinogenic nitrosamines (36). Processed meat products are one of the foods that can contain biogenic amines due to the use of low-quality raw materials, microbial contamination and inappropriate conditions during the process.

D-Lactic Acid Production: Depending on the host and the strain used, harmful metabolic activities such as induction of acidosis through the production of D-lactic acid or bile salts may occur. Such processes occur due to the activity of internal or external flora in the stomach, especially the clone (14).

Human metabolism produces L-lactic acid isomer. A common feature in patients with D-lactic acidosis is excessive exposure of carbohydrate to bacteria that producing D-lactic acid. For these patients, re-colonization with unproductive D-lactate bacteria is necessary. In general, the use of D-lactate-producing bacteria should be done more cautiously, especially for patients at risk for metabolic acidosis, such as patients

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who have undergone intestinal surgery, and those with "irritable bowel syndrome" as well as infants (40).

Limitations of the use of probiotics in the industry: In order to use probiotic bacteria, these strains must maintain their reproducibility during the production or processing. Adding probiotic bacteria should not result in loss of product quality (41). Below are two main constraints on the use of probiotics in the industry.

Lack of viability and stability: The main challenge associated with the use of probiotic cultures in the production of functional foods is maintaining their viability during the process. Probiotic microorganisms should be technologically suitable for use in food products, so that these microorganisms can maintain their viability and stability in food products (in industrial scale) and during the consumption (42). According to a review article published by Evivie et al. in 2017, many probiotic bacteria were destroyed during storage, exposure to low pH, and acidic conditions in the stomach (43). In addition, in 2013, it was shown that the viability and survival of specific probiotic bacteria was exclusive to strains, and therefore, microencapsulation methods such as solvent evaporation technique were successfully used to protect bacterial cells from environmental damage (44). Freeze – drying methods maintain the long-term viability and stability of probiotic microorganisms (16, 45).

Change in the taste, flavor and aroma of products containing probiotics: Probiotic cultures usually do not change the taste, flavor and aroma of the products. The main concern is related to probiotic cheeses containing bifidobacteria, because these bacteria produce large quantities of acetic acid and lactic acid through the shunt pathway of fructose 6-phosphate. In low amounts, acetic acid has a positive effect on the aroma of probiotic cheeses. But its high concentration is undesirable and causes loss of taste and aroma of cheese. Table 4 shows the major problems associated with the production of probiotic cheeses and its solutions(41).

Table 1. Bacterial infections associated with probiotic intake in humans (1).

Study	Age	Risk factors	Probiotic	Method of identification	Form of sepsis
Rautio et al (24)	74 y	Diabetes mellitus	LGG	API 50 CH, PFGE of DNA restriction fragments	Liver abscess
Mackay et al (46)	67y	Mitral regurgitation, dental extraction	*Lactobacillus rhamnosus*,3 10^9 CFU/d	API 50 CH, pyrolysis mass spectrometry	Endocarditis
Kunz et al (47)	3mo	Prematurity,short gut syndrome-	LGG	No confirmatory typing	Bacteremia
	10wk	Prematurity, inflamed intestine, short gut syndrome	LGG	PFGE of DNA restriction fragments	Bacteremia
De Groote et al (48)	11mo	Prematurity, gastrostomy, short-gut syndrome, CVC, parenteral nutrition, rotavirus diarrhea	LGG, 1/4 capsule/d	rRNA sequencing	Bacteremia
Land et al (49)	4 mo	Cardiac surgery, antibiotic diarrhea	LGG, 10^{10} CFU/d	Repetitive element sequence-based PCR DNA fingerprinting	Endocarditis
	6 y	Cerebral palsy, jejunostomy feeding, CVC, antibiotic associated diarrhea	LGG, 10^{10} CFU/d	Repetitive element sequence-based PCR DNA fingerprinting	Bacteremia
Richard et al (50)	47 y	Not stated	*Bacillus subtilis*, 8 10^9 spores/d	Antibiotic susceptibility	Bacteremia
	25y	Not stated	*Bacillus subtilis*, 8 10^9 spores/d	Antibiotic susceptibility	Bacteremia
	63 y	Neoplastic disease	*Bacillus subtilis*, 8 10^9 spores/d	Antibiotic susceptibility	Bacteremia
	79 y	Not stated	*Bacillus subtilis*, 8 10^9 spores/d	Antibiotic susceptibility	Bacteremia
Oggioni,etal(17,51)	73 y	Chronic lymphocytic leukemia	*B. subtilis*, 10^9 spores/d	16S rRNA sequencing	Bacteremia

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Table 2. Lactobacilli and bifidobacteria that are commonly found in the human intestine. The underlined species are found in clinical infections and the species in bold are observed in fermented foods (20).

Lactobacillus acidophilus	*Bifidobacterium adolescentis*
L. brevis	*B. angulatum*
L. buchneri	*B. bifidum*
L. crispatus	*B. breve*
L. delbrueckii	*B. catenulatum*
L. fermentum	*B. dentium*
L. gasseri	*B. infantis*
L. johnsonii	*B. longum*
L. paracasei	*B. pseudocatenulatum*
L. plantarum	
L. reuteri	***Enterococcus faecalis***
L. rhamnosus	***E. faecium***
L. ruminis	
L. salivarius	

Table 3. Risk factors proposed for probiotic infection (1).

Major risk factors
1) Immune compromise, including a debilitated state or malignancy
2) Premature infants
Minor risk factors
1) CVC
2) Impaired intestinal epithelial barrier, eg, diarrheal illness, intestinal inflammation
3) Administration of probiotic by jejunostomy
4) Concomitant administration of broad spectrum antibiotics to which probiotic is resistant
5) Probiotics with properties of high mucosal adhesion or known pathogenicity
6) Cardiac valvular disease (*Lactobacillus* probiotics only)

Table 4. Technological barriers to the production of probiotic cheeses in the industry and its solutions (42).

Stage	Problem	Possible solutions
Addition of probiotic inoculum	✓ Interactions of the probiotic and starter may cause negative impact ✓ Loss of viable probiotic cells in the whey during draining.	✓ Preliminary tests to choose the most suitable probiotic and starter combination; ✓ Use of strains from the same supplier; ✓ Check different moments of addition of the probiotic inoculum (observing the impact on the final cost of the product and probiotic survival).
Salting	✓ Probiotic bacteria are sensitive to high salt concentrations	✓ Microencapsulation; ✓ Suitable strain selection (information from the strain supplier).
Packaging	✓ Probiotic bacteria are sensitive to oxygen.	✓ Choose suitable packaging system: film plastic with low permeability to oxygen, vacuum packaging or active packaging; ✓ Cell incubation under sub-lethal conditions to develop salt resistance ✓ Suitable strain selection (information with the strain supplier).
Ripening	✓ Survival of probiotic bacteria through the cheese ripening period.	✓ Microencapsulation; ✓ Optimize ripening conditions through preliminary tests.
Storage conditions	✓ Inadequate storage conditions affect the probiotic survival.	✓ Strict control of storage temperature.

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Discussion

According to the mentioned cases, the use of probiotics is only safe in healthy people and should be used with caution in children, the elderly, pregnant women and patients due to the risk of infection. Many studies on probiotic infection suggest that people with pre-existing bowel disease, such as small intestine diarrhea, are susceptible to infection. This can be a general index for the use of probiotics. The presence of vascular catheters is another cause of probiotic infection (52). Infections in premature children appear to be high in these reports, because they have a weakened immune system. High sensitivity of premature children and their weakened immune system has been confirmed by animal studies (53). People with a weakened immune system are at risk of lactobacilli infections, but no reports of infection after using bifidobacteria are available and animal studies have demonstrated the low pathogenicity of this group of probiotics. Therefore, bifidobacteria are better than other probiotics for immunity (53). The essential role of intestinal microflora in regulating the immune system shows that manipulating it to modify the microflora can have great effects in modulating the immune system. Probiotic bacteria produce biogenic amines. The presence of large amounts of biogenic amines in foods will lead to poisoning. Another harmful substance produced by probiotic species is D-lactic acid. If D-lactate is produced excessively, it produces metabolic acidosis (38). On the other hand, the stability of probiotics is essential to ensure efficacy and to induce its beneficial effects on product formation. Therefore, probiotic cultures should be able to maintain their properties after the process. The stability of probiotics is influenced by various factors such as species type, water activity, and temperature, concentration of hydrogen ion (pH), osmotic pressure and oxygen (54). Sedighi et al. have shown that the addition of chlorella vulgaris and spirulina platensis, due to having nutrients, increases the viability of probiotic microorganisms during the production and storage of fermented dairy products (55). Probiotic bacteria used in food products, such as lactobacillus strains and bifidobacteria, have microaerophilic or anaerobic metabolism. As a result, oxygen is a threat to their survival.

Generally, bifidobacteria are more susceptible to oxygen than lactobacillus acidophilus because they are highly anaerobic. Other characteristics including the acidity of the environment, the ability to grow in a medium containing milk, the fermentation time, the oxygen level in products, the permeation of oxygen through packaging, the sensitivity to antimicrobials materials produced by bacteria and the risk of contamination during the preparation of the inoculum are also effective in the growth and survival of probiotic microorganisms (41, 56). It can be concluded from the obtained results that bifidobacterium strains are more safer in terms of transfer antibiotic resistance genes rather than other microorganisms, and by optimizing other parameters mentioned in this study, can expect low pathogenicity and production of undesirable substances. It is suggested that caution be exercised when using probiotics in the presence of a high risk agent or several low risk agents.

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