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The role of probiotics in the modulation of intestinal microbiota in lactose intolerance

Abstract. *Lactose intolerance is one of the most common eating disorders. People affected by this disorder cannot digest large amounts of lactose due to the genetically low expression of the lactase enzyme. The human gut microbiota consists of the majority of diverse microbial communities that affect intestinal health, immunological balance and also metabolize lactose. One of the methods to combat this disorder is the use of probiotics. Probiotic microorganisms are contained in large quantities in live fermented milk products, which are used as functional food products all over the world because of their beneficial effects on human health. In addition, there are low lactose/lactose free fermented milk products on the world market, which, in addition to having a positive effect on the human body, contribute to the breakdown and reduction of the amount of lactose, thereby helping to tolerate lactose more easily. This review focuses on important developments that can neutralize the adverse effect of lactase on human health when consuming dairy products.*
Keywords: *gut microbiota, lactose, probiotics, lactase, fermented milk products.*

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Lactose intolerance is a common disease characterized by a violation of the body's ability to digest milk sugar - lactose. One of the most common approaches in the treatment and management of lactose intolerance is the use of probiotics - microorganisms that can have a beneficial effect on the intestinal microbiota. Probiotics can modulate the composition and activity of microorganisms in the intestinal microbiota, which can have a positive effect on the symptoms of lactose intolerance and alleviate its manifestations.

Probiotics are a variety of microorganisms, such as lactic acid bacteria (for example, *Lactobacillus* and *Bifidobacterium*), which can colonize the intestine and have a positive effect on its functioning. One of the main mechanisms of action of probiotics is their ability to break down lactose, which can reduce its concentration in the intestine and reduce the manifestations of lactose intolerance.

In addition, probiotics can interact with the intestinal microbiota, improving its composition and functionality. Uncontrolled reproduction of certain microorganisms in the intestine can contribute to the development of lactose intolerance, therefore, modulation of the microflora with probiotics can help restore the natural balance of microorganisms and reduce the symptoms of lactose intolerance.

Lactose intolerance refers primarily to a syndrome that manifests itself in various symptoms when consuming foods that contain lactose. The severity of symptoms can vary among individuals who have lactose intolerance. [1]. Lactose is a disaccharide that is present in many dairy products and consists of galactose bound to glucose by the β-1 → 4 glucoside link. β-galactosidase catalyzes the hydrolysis of lactose and bound to the membrane of the brush border of the small intestine, where is located the absorption of the split lactose into glucose and galactose [2]. Lactose intolerance refers primarily to a syndrome with various intestinal or extraintestinal symptoms when consuming lactose-containing foods, which is caused by the weak expression of lactase in the edge of the brush of the small intestine mucosa [1]. This disorder happens when lactose is not properly digested in the small intestine due to low levels or absence of lactase. Instead, lactose moves to the large intestine where it is fermented by intestinal microbiota, resulting in lactose intolerance symptoms.

Common indications of lactose intolerance consist of stomach discomfort, swelling, diarrhea, and on certain occasions, feeling nauseous and throwing up [3]. Occasionally, the peristaltic movement of the gastrointestinal tract might decline, resulting in constipation, perhaps because of the generation of methane. Research conducted on animals has displayed that the main migration complexes of the intestines decrease considerably when methane is introduced, which leads to the slowing down of intestinal transit.

Frequently, the fermentation of lactose that is not digested by the bacterial microflora produces abdominal pain and bloating. During this process, short-chain fatty acids (SCFA), hydrogen, methane, and carbon dioxide are generated, which cause an increase in intestinal pressure and transit time. When undigested lactose is present in the small and large intestine, it prompts the secretion of fluids and electrolytes, leading to the symptoms mentioned. acidification, and an elevated osmotic load in the large intestine, leading to shortened passage time and resulting in diarrhea and the excretion of stool [5].

There are three types of lactose intolerance; different factors cause lactase deficiency based on each type:

1. *Primary lactose intolerance or adult-type lactase insufficiency:* a common autosomal recessive disease resulting from changes in lactase gene expression regulated by development [6].

Lactase expression in the intestine in primary lactose intolerance it drops sharply, which makes it difficult to digest dairy products later in childhood or adolescence. About 70% of the world's adult population -. there is lactase instability or hypolactasia. Depending on the ethnic origin, the decrease in lactase expression changes. For example, in South America, Africa and Asia, lactase is not manifested in more than 50% of people. This disease is more common in the Mediterranean or southern Europe. In some Asian countries, up to 100% lactase is not tolerated.

Lactase stability is transmitted as a dominant Mendeleev sign. The genetic specificity of intestinal lactase expression stability may result from more than five independent single - nucleotide variants in the regulatory region (transcriptional enhancer) above the lactase gene. One of them is -13910*T (rs4988235), responsible for most cases of lactase stability in Caucasians, a -13907*G (rs41525747), -13915*G (rs41380347), -14009*G (rs869051967) and 14010*C (rs145946881) variables in the Middle East and Africa occurs with frequencies [7]. A number of specific variables can influence the development of symptoms in patients in case of lactase deficiency: the amount of lactose in the diet, the passage time through the intestine, lactase expression, the ability of the intestinal microbiota to spread and ferment, chemical and mechanical intestinal stimulation, and psychological factors.

2. *Secondary lactase insufficiency:* a transient condition that occurs as a result of damage to the intestine. Almost all pathological conditions that cause damage to the small intestine can lead to a decrease in lactase expression by detecting secondary and transient lactase insufficiency. Secondary lactose intolerance can be linked to certain medical conditions such as celiac disease, bacterial overgrowth, and Crohn's disease [8]. Radiation therapy or abdominal chemotherapy can cause lactase deficiency. Severe intestinal dysfunction with a subsequent decrease in lactase activity may be caused by an allergy to cow's milk (CMA). These patients may experience gastrointestinal symptoms due to cow's milk allergy and lactose intolerance. Therefore, the consumption of CMA can carry on reaction through different mechanisms.

3. *Congenital lactase insufficiency:* a very rare autosomal recessive disease characterized by a lack or decrease in enzymatic activity from birth.

This condition should be distinguished from developing lactose intolerance, which can be observed in premature babies. In such children, lactase levels may decrease, since enterocytes expressing lactase in the small intestine develop in the third trimester.

Congenital lactase insufficiency typically manifests in infants within the first few days of consuming breast milk or lactose-containing formula, and is characterized by symptoms such as watery diarrhea, flatulence, and malnutrition. A typical feature of congenital lactase insufficiency is the absence or very low level of lactase expression due to mutations in the chlorizinghydrolase (LPH) gene located in 2q21.3 [6, 9].

Risk factors for lactose intolerance:

Age	Premature babies and children with an immature digestive system usually show symptoms of lactose intolerance since the production of lactase enzymes occurs in late pregnancy. Studies show that approximately 40% of children who experience colic actually suffer from temporary lactose intolerance. As people get older and modify their dietary habits, their bodies naturally generate fewer lactase enzymes. This causes the prevalence of lactose intolerance to rise with age. Around 60% of grown-ups are believed to experience lactose intolerance to some degree.
Ethnicity	Individuals of East Asian ancestry are the most likely to experience lactose intolerance during adulthood. Additionally, lactose intolerance is highly prevalent in those with West African, Arab, Jewish, Greek, and Italian heritage.
Intestinal damage	Damage to the small intestine as a result of gastroenteritis, persistent diarrhea, excessive bacterial growth in the small intestine, giardiasis, chemotherapy, or other damage to the mucous membrane of the small intestine can lead to temporary lactose intolerance.
Intestinal disorders	Celiac disease, Crohn's disease, inflammatory bowel diseases and other intestinal disorders cause damage to the villi in the intestine, at the site of lactase production.

Probiotics: definition, indications for use, effect on the intestinal microbiome

The human gut microbiota consists of complex and diverse microbial communities that are related to human gut health and can undergo changes due to various factors such as dietary habits, lifestyle choices, exposure to harmful substances, and use of antibiotics. Such changes can have an impact on health and disease and may also affect the immune system. [10, 11]. Research indicates that it has been demonstrated that the intestinal microbiota consists of about 100 trillion microbial cells, which in turn provide a wide range of metabolic functions, the development of the host intestine and protection from pathogenic bacteria [12]. The intestinal microbiota also has a significant function in preserving the immune equilibrium in the gastrointestinal tract by means of direct engagement with immune cells. The decomposition of complex carbohydrates from plant sources is crucial and accomplished by the intestinal microbiota. The host is unable to digest these carbohydrates due to the absence of enzymes needed to decompose the structural polysaccharides found in plant matter [13]. Microorganisms in the large intestine are strictly anaerobic bacteria [14]. Another function of the human intestinal microbiota is the decomposition and production of organic acids and short-chain fatty (SCFA) organic acids: propionate, acetate, and butyrate, which control the makeup of the microbiome. Many research studies have indicated that the inability to maintain the balance of intestinal microbiota leads to negative changes in the metabolism of the host, which are associated with chronic diseases like inflammatory bowel disease, cancer, cardiovascular diseases, and metabolic syndrome [13, 15]. It has been recognized that microbiota imbalance Additionally contributes to the onset of asthma [16].

Recent research has demonstrated that the modulation of the arrangement of microorganisms in the gut microbiota, the regulation of intestinal microbial metabolites, as well as the improvement of intestinal barrier function, with the help of probiotics, have a positive impact on the human body [17, 18].

Ilya Mechnikov initially proposed the use of beneficial living microorganisms to improve health by displacing harmful intestinal microorganisms and increasing life expectancy through the consumption of fermented milk containing lactobacilli [19]. However, the term "probiotic" did not have a clear definition until Lilly and Stillwell defined it as growth-stimulating factors produced by microorganisms in 1965 [20]. Later, Parker defined probiotics as organisms and substances that contribute to the microbial balance of the intestine, meanwhile, Fuller suggested that probiotics are living microorganisms that positively affect the body, improving its internal microbial balance, in line with Mechnikov's concept [21]. All these definitions focused on the impact on the intestinal microbiota, but scientific studies have shown that probiotics can also affect the immune system. As a result, two novel definitions have been put forth, characterizing probiotics as a live microbial culture, or fermented dairy item that has advantageous impacts on health and nutrition and have greater health benefits than the daily dose of probiotics when ingested in certain quantities [22].

The most studied types of probiotic microorganisms include *Lactobacillus, Bifidobacterium, Saccharomyces,* and others (Table 1, Figure 1) [23].

Table 1

Probiotic microorganisms

Bifidobacteria	Lactobacillus	Bacillus	Other microorganisms
Bifidobacterium bifidum	*Lactobacillus acidophilus*	*Bacillus subtilis*	*Escherichia coli*
Bifidobacterium longum	*Lactobacillus bulgaricus*	*Bacillus licheniformis*	*Candida albicans*
Bifidobacterium lactis	*Lactobacillus plantarum*	*Bacillus cereus*	*Enterococcus faecium*
Bifidobacterium infantis	*Lactobacillus fermentum*		*Saccharomyces boulardii*
Bifidobacterium breve	*Lactobacillus casei*		
Bifidobacterium adolescentis			
Note – compiled based on the source[21,24,25,26]			

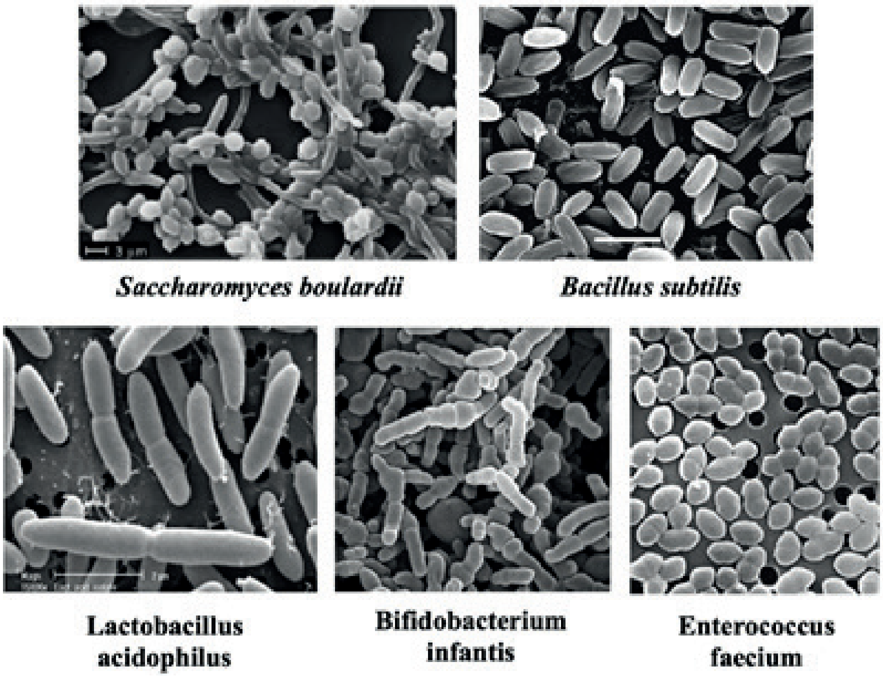

Figure 1. Probiotic microorganisms [21, 24, 25, 26]

The central part of probiotics are lactobacilli. These are facultative anaerobic, non-spore-forming gram-positive bacteria. They are rod-shaped or coccoid bacteria located singly or in chains; lactobacillus strains differ in the fermentation process, the production of hydrogen peroxide and bacteriocin. These various features make them a versatile group suitable for various conditions. In the intestine, the adhesion of lactobacilli to the mucous layer of the intestinal wall is mediated by a protein surface layer called the S-layer. In addition, some strains of lactobacilli produce antioxidants, and also have probiotic potential - the ability to immunomodulate human cells to achieve an anti-inflammatory response [27]. In the gastrointestinal tract, lactobacilli live in its various departments: starting from the oral cavity and ending with the large intestine at a pH of 5.5-5.6. *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus short, Lactobacillus fermentum, Lactobacillus parabuchneri, Lactobacillus delbrueckii* subsp. *bulgaricus, Lactobacillus rhamnosus* GG are the most commonly used species for commercial purposes, as in production of probiotics, and during fermentation of various types of food products [27]. All these types have proven their effectiveness in the treatment of various types of diseases. For example, *Lactobacillus acidophilus* can be used for travelers' diarrhea, Lactobacillus casei - for constipation and rheumatoid arthritis, *Lactobacillus brevis* - for diseases of the biliary tract, *Lactobacillus Lactobacillus delbrueckii* subsp. *bulgaricus* improves immune status, *Lactobacillus rhamnosus* GG also improves immune status, especially in viral infections [28].

Bifidobacteria are frequently employed in the manufacture of probiotics. These are strictly anaerobic gram-positive bacteria, usually look clubby or branching and may have bifurcations, some species sometimes exhibit swollen coccoid forms. They are located mainly singly, in pairs or in the form of a chain [29]. Usually, bifidobacteria live in the colon. The main function of bifidobacteria is to create a protective barrier of the intestine and thus prevent the penetration of pathogenic microorganisms and toxins [30]. Therefore, with the balance of microbiota, bifidobacteria account for about 90-95%. Probiotic bacteria, such as *L. acidophilus* and *Bifidobacterium* spp., produce β-d-galactosidase, which breaks down lactose and improves lactose tolerance [31].

Researchers have recently become interested in exploring the potential of probiotics and their ability to regulate the structure of the gut microbiota, leading to the production of probiotic products. The use of probiotics to treat diseases associated with the intestinal microbiota aims to restore intestinal balance through beneficial microbes [32]. Modulating the gut microbiota using probiotic cultures is now a recognized method for treating human diseases [33]. Bifidobacteria, lactobacilli, lactococci, and streptococci are the most frequently employed probiotic strains in current probiotic products. Other probiotic strains showing promise are bacterial genera such as *Bacillus, Escherichia*, and *Propionibacterium*, as well as some yeast genus - *Saccharomyces*. Overall, probiotics are deemed safe for human health, with minimal side effects [34,35].

The mechanisms of action of probiotics are primarily associated with the modulation of the microbiota of the gastrointestinal tract of the body. The first of the proposed methods of action is a barrier effect directed against pathogenic bacteria, preventing or limiting their colonization. Bacterial inhibition may be due to the production of bacteriocins of a wide spectrum of inhibition, metabolites, for example, short-chain fatty acids, causing a decrease in pH, unfavorable for bacterial growth, biosurfactants with antimicrobial activity. In addition, probiotics play a role in improving the barrier function of the intestinal mucosa. This barrier function is related to the quality of dense connections between intestinal epithelial cells. In addition to probiotics, Paneta cells producing antimicrobial peptides (defensins, lysozyme) and goblet cells producing mucus also participate in this barrier function; mucus acts as a protective layer preventing any direct contact with bacteria in the intestinal lumen. Thus, probiotics can act at the level of signaling pathways resulting in the augmentation of the mucus layer or to the production of defensins, as well as on proteins of dense compounds, improving their physiological barrier function.

One of the widely studied mechanisms of action of probiotics is alteration of the immune system's activity. More than 70% of immune cells are located at the intestinal level, particularly in the small bowel, forming intestinal-associated lymphoid tissue (GALT), where the immune system is activated [19, 36].

Therefore, the regulation of the intestinal microbiome through multiple factors plays a crucial role in preventing and treating diseases. The effectiveness of probiotics may depend on the type, dose and disease, and the duration of therapy depends on clinical indications. There are many studies that confirm that probiotics are effective in diarrhea associated with antibiotics, acute infectious diarrhea, and Clostridium difficile , ulcerative colitis, hepatic encephalopathy, irritable bowel syndrome, functional gastrointestinal disorders, and necrotizing enterocolitis [18, 37].

Low-lactose probiotic fermented milk products: characteristics, use, and prospects

Fermented milk is an important part of our food. In ancient times, people understood that fermentation was taking place, without knowing, however, its causes. In the beginning, milk was fermented through a process of natural fermentation, and the practice of reusing fermentation tanks and tools helped to establish a level of consistency and stability in the fermentation process. This has led to the use of specific microorganisms for the manufacture of more or less refined products. Different countries or even different parts of the same country developed their own fermented milk. The most famous product is thermophilic fermented milk yogurt, which has been increasingly popular in the last three decades. The role of living microorganisms in fermented dairy products have attracted significant attention from both manufacturers and consumers [38].

In 1974, it was proposed that dairy products would be useful for lactose intolerance, although at the time it was assumed that this was due to low lactose content [39]. However, when rats were fed natural yogurt (live culture), they absorbed galactose more efficiently and had more intestinal lactase activity than rats fed pasteurized yogurt or an imitation yogurt recipe. In addition, yogurt bacteria survived for 3 hours in the gastrointestinal tract of rats, and the authors suggested that the bacteria contributed to the hydrolysis of lactose [40]. These data obtained from experimental animals suggested that this was not due to a low dose of lactose.

The first human study was conducted in 1982. Unlike skimmed milk, a trial drink made from yogurt or acidophilic milk did not cause any symptoms in people with lactose intolerance.

This was due to a decrease in the amount of lactose in yogurt, since the dose of lactose in the tested beverages was higher in low-fat milk -24.6 g than in acidophilic milk -18.1 g or yogurt - 11.4 g. The author suggested that microorganisms (in particular bifido/lactobacilli) contained in yogurt may be active in the intestinal tract, participating in the hydrolysis of lactose [41].

Presently, fermented milk items have become functional food products worldwide due to their advantageous effects on human health [42]. To help individuals with minor symptoms of lactose intolerance adjust to lactose, small amounts of milk/dairy products may be gradually introduced [43]. Introducing fermented dairy products into diet, like mixing milk porridge with rice, can help some people tolerate their food better. For those with lactose intolerance, hard cheeses such as cheddar, parmesan, and hollandaise are often better tolerated than a glass of milk because they contain very little lactose. When a person consumes more than 12 grams of lactose per day, their symptoms can become worse. As more people become lactose intolerant, there are now more lactose-free and low-lactose fermented milk products available. These products are nutritionally similar to regular dairy products but are treated with lactase to reduce lactose levels. Lactase breaks down lactose into glucose and galactose, which makes the product sweeter.

Yogurt is a thick sour cream—like product with a sour taste, composed of all the same elements as milk, but with a lower amount of lactose. During the process of bacterial fermentation, lactic acid is produced, which changes the milk's pH and converts lactose into lactic acid. The traditional microorganisms used to culture milk into yogurt are *Lactobacillus delbrueckii subsp . bulgaricus* and *Streptococcus thermophilus*. Yogurt is a great source of nutrients such as protein, calcium, vitamin D, riboflavin, vitamin B_6, and vitamin B_{12}. Additionally, yogurt may contain probiotics, which are live microorganisms that benefit the gut, as well as prebiotics, which are compounds formed during fermentation that positively impact the gut microbiota and overall health. The production of fermented milk products is a significant area of fermentation, with cultured bio-yoghurts and probiotic drinking yoghurts being the fastest growing dairy sector between 1998 and 2003 [44]. Nowadays, a few international manufacturers dominate over 50% of the global yogurt market in Western countries by creating cultured bio-yogurts and fermented milk blends. This range of items comprises extra types of microorganisms such as *Bifidobacteria* and *Lactobacillus acidophilus*, which are believed to enhance their prebiotic properties and provide additional health benefits.

Conclusion

Research on different human illnesses demonstrates the crucial involvement of gut microbiota. It is essential to comprehend how gut microbiota affects the overall health of the body to devise strategies that aim to manipulate it, particularly in cases where there are irregular microbial patterns. Probiotics play a significant role in achieving health benefits for the body through various mechanisms, with a focus on modifying the intestinal microbiota being noteworthy. With the help of probiotics, it is possible to enrich the intestinal microbiota with bifido / lactobacilli, which will break down the milk sugar entering the body in people with lactose intolerance [45].

Lactose intolerance is a prevalent ailment worldwide these days. Nevertheless, a majority of individuals suffering from lactose intolerance retain some lactase activity, and therefore, they can consume different quantities of lactose in their diet without experiencing any symptoms. Consequently, individuals have adapted to lactose intolerance by adjusting their diet within their physical capabilities, enhancing their ability to consume lactose by adapting their microbiome, and generating a diverse range of dairy products that are low in lactose. Research has demonstrated that people have difficulty digesting fresh milk, but can consume certain dairy products, such as cheese, yogurt, without discomfort. These products are prepared using fermentation processes that break down most of the lactose in milk. It has been proven that probiotic cultures, such as *L. acidophilus* and *Bifidobacterium* spp., synthesize β-d-galactosidase, which breaks down lactose and helps to reduce lactose in fermented milk products, which improves lactose tolerance.

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Лактозаға төзбеушілік кезінде ішек микробиотасын модуляциялаудағы пробиотиктердің рөлі

Аңдатпа. Лактозаға төзбеушілік – тамақтанудың ең көп таралған бұзылыстарының бірі. Бұл бұзылысқа ұшыраған адамдар лактаза ферментінің генетикалық төмен экспрессиясына байланысты лактозаның көп мөлшерін сіңіре алмайды. Адамның ішек микробиотасы ішек денсаулығына, иммунологиялық тепе-теңдікке әсер ететін және лактозаны метаболиздейтін көптеген микробтық қауымдастықтарға ие. Бұл бұзылыспен күресудің бір әдісі – пробиотиктерді қолдану. Пробиотикалық микроорганизмдер адам денсаулығына пайдалы әсеріне байланысты бүкіл әлемде функционалды тағам ретінде қолданылатын тірі ашытылған сүт өнімдерінде көп мөлшерде кездеседі. Сонымен қатар, әлемдік нарықта төмен лактоза/лактозасыз ашытылған сүт өнімдері бар, олар адам ағзасына жағымды әсер етумен қатар, лактозаның ыдырауына және азаюына ықпал етеді, осылайша лактозаны оңай тасымалдауға көмектеседі. Бұл шолу сүт өнімдерін тұтыну кезінде лактазаның адам денсаулығына жағымсыз әсерін жоюға қабілетті маңызды әзірлемелерге бағытталған.

Түйін сөздер: ішек микробиотасы, лактоза, пробиотиктер, лактаза, ашытылған сүт өнімдері.

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Роль пробиотиков в модуляции кишечной микробиоты при непереносимости лактозы

Аннотация. Непереносимость лактозы является одним из наиболее распространенных пищевых расстройств. Люди, подверженные этому расстройству, не могут усваивать большое количество лактозы по причине генетически низкой экспрессии фермента лактазы. Микробиота кишечника человека обладает большинством разнообразных микробных сообществ, которые оказывают влияние на здоровье кишечника, иммунологическое равновесие, и в том числе метаболизирует лактозу. Одним из методов борьбы с этим расстройством является использование пробиотиков. Пробиотические микроорганизмы в большом количестве содержатся в живых кисломолочных продуктах, которые применяются в качестве функциональных продуктов питания во всем мире из-за их благотворного воздействия на здоровье человека. К тому же на мировом рынке имеются низколактозные/безлактозные кисломолочные продукты, которые, помимо положительного воздействия на организм человека, способствуют расщеплению и снижению количества лактозы, тем самым помогают легче переносить лактозу. Настоящий обзор фокусируется на важных разработках, способных нивелировать неблагоприятный эффект лактазы на здоровье человека при потреблении молочной продукции.

Ключевые слова: микробиота кишечника, лактоза, пробиотики, лактаза, кисломолочные продукты.

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