Effects of probiotics on lactose intolerance

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Abstract: Globally, the prevalence rate of lactose intolerance is over 60%. Lactose intolerance is caused by the deficiency of the intestinal enzyme lactase, which is responsible for lactose digestion. Subsequently leading to the colonic fermentation of undigested lactose, resulting in clinical symptoms of lactose intolerance including diarrhea, abdominal cramps and pain, flatulence, and so on. The supplementation of probiotics shows beneficial effects in alleviating these symptoms by modulating the composition of intestinal microbiota. Extensive preclinical studies have indicated promising therapeutic effects of probiotics for lactose intolerance management. In this article, lactose metabolism in the gastrointestinal tract is first introduced and the causes of lactose intolerance are explained. It focuses on the beneficial effects of probiotics in the treatment of lactose intolerance and the mechanisms by which probiotics are used to relieve gastrointestinal symptoms. Finally, commonly used probiotic species or strains and fermented foods containing probiotics are discussed. Through this article, the understanding of the treatment of lactose intolerance is further deepened, in order to help clinicians and others to make better clinical decisions.

1. Introduction

Lactose intolerance is one of the most common types of food intolerance worldwide, it is a digestive disorder caused by the impaired ability to digest lactose, the main sugar found in dairy products, due to the deficiency of an intestinal enzyme called lactase-phlorizin hydrolase, also known as lactase. There is up to 60% of the global population possesses a reduced activity of enzyme lactase [1]. Regions like Africa, Asia, and South America have the highest prevalence rates of lactose intolerance, which is approximately 65%-90% of their countries' population [1-3]. Lactose intolerance is characterized by gastrointestinal (GI) clinical symptoms such as diarrhea, abdominal cramps and bloating, nausea, and vomiting, resulting from the malabsorption of lactose inside the small intestine due to the deficiency of enzyme lactase, which further results in the fermentation of lactose within large intestine - colon. There are several factors that can modify and affect these GI symptoms, which include the dose of lactose, expression of remanent lactase, concurrent intake of other dietary ingredients, gut-transit time, and colonic microbiome composition [2, 4].

Clinical signs and symptoms of lactose intolerance can be avoided by reducing the consumption of dairy products or not eating at all. However, fully eliminating dairy foods is not appropriate owing to a more desirable effect on health. Dairy products provide a variety of nutrients, such as calcium, potassium, proteins, and Vitamin B and D. Lack of these essential nutrients may result in bone fracture, osteoporosis, and malnutrition [2]. Aside from these problems, it was discovered that people with lactose intolerance have a higher risk of getting a variety of extra-intestinal diseases, such as memory deterioration and cancers [5]. Therefore, it is substantial to exploit adequate treatment for lactose intolerance. In recent years, probiotics have gained considerable interest as they are considered a potential treatment for lactose intolerance to alleviate the corresponding symptoms. Probiotics are defined as live bacteria or yeast that act as supplements to the gastrointestinal microbiota [1]. However, present understanding of the exact effects of probiotics is limited and the mechanisms behind the association between probiotics and lactase deficiency are still relatively undeveloped. The latest studies indicated that probiotics could be applied to symptomatic therapies due to their ability to

modulate the gut flora and increase lactase digestion and colonic compensation [2]. Extending our knowledge of the possible interactions between probiotics and lactose intolerance treatment.

In this paper, we specifically focus on the effects of probiotics on lactose intolerance, highlight their contributions to the alleviation of lactose intolerance symptoms, and discuss some of the biological mechanisms thought to be used by probiotics to perform their functions. We will investigate some probiotic products which have already been applied to treat lactose intolerance and propose putative therapies that could be exploited in future preclinical studies to either prevent lactose intolerance or relieve its corresponding symptoms.

2. Lactose metabolism, biological mechanism of lactose intolerance and its diagnosis

In lactose intolerant individuals, due to the insufficient lactase expression and down-regulated activity of lactase, there is a change in the site of the digestive tract for lactose metabolism. For instance, normally all of the lactose molecules can be properly digested in the small intestine, because the enzyme responsible for digesting lactose, known as lactase, is exclusively expressed by the enterocytes on the microvilli of the small intestine, with the highest production level in the jejunum [3]. Lactase is a β-galactosidase that can hydrolyze the disaccharide lactose into two monosaccharides, glucose, and galactose. The two simple sugars are able to be absorbed by intestinal absorptive cells and go into the bloodstream. Glucose can be used as an energy source by our bodies, while galactose can be converted into a component of glycoproteins and glycolipids [3]. In addition, there is little bacterial fermentation that occurs in the small intestine/jejunum, owing to the low concentration of bacteria [3].

However, under the deficiency of lactase, the intake of lactose cannot be adequately digested in the small intestine. The undigested form of lactose passes through the digestive system and goes into the large intestine. Colonic fermentation of lactose mainly happens in the colon, which is the longest part of the large intestine. Colonic microbiota plays an important role in this process, it is an important player in human digestive physiology. During this process, microbiota itself can acquire energy, and meanwhile, it converts lactose into a high production of short-chain fatty acids and gas, mainly hydrogen (H2), carbon dioxide (CO2), and methane (CH4) [6]. Excessive gas can irritate the lining of the intestine and result in the following digestive symptoms, such as diarrhea, abdominal bloating and pain, nausea, and vomiting. A schematic diagram of the metabolic mechanisms of lactose inside the gastrointestinal tract is shown in Figure 1.

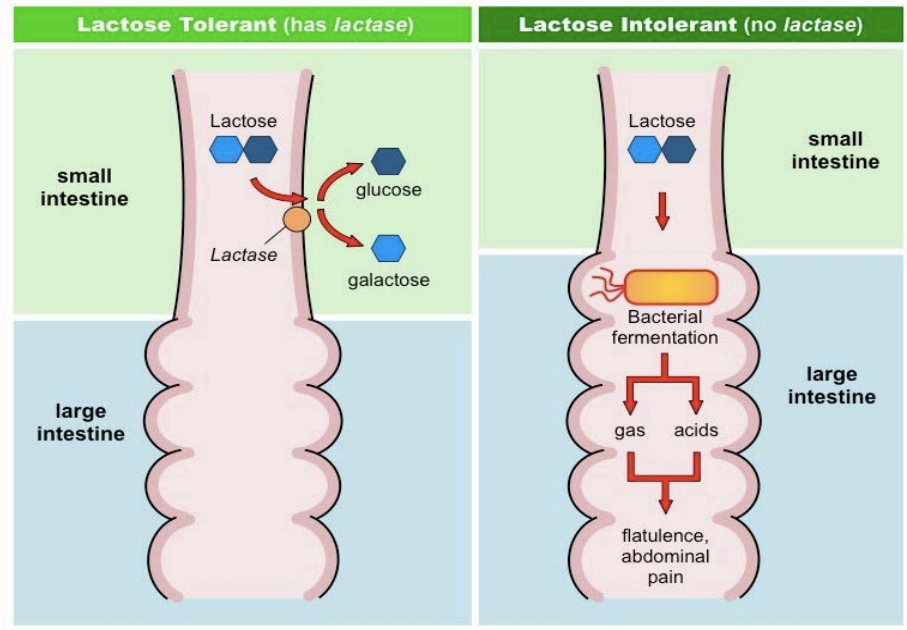

Figure 1. Lactose metabolism inside the gastrointestinal tract: two different biological mechanisms of lactose tolerance and lactose intolerance (https://ib.bioninja.com.au).

A proper diagnostic method is important to the treatment of lactose intolerance and to investigate the potential functions of other factors and therapies, such as probiotics. Hydrogen breath test (HBT) is the most commonly used approach for lactose intolerance diagnosis, owing to its high sensitivity and specificity, non-invasiveness, simple manipulation, and its low cost [2, 3, 5]. This test measures and compares the concentrations of exhaled hydrogen of each individual under the conditions of fasting and subsequent intaking of lactose (usually 25-50g). HBT utilizes the circumstance that the undigested lactose accumulates in the colon and undergoes bacterial fermentation by the gut microbiota, resulting in the formation of gas, including hydrogen [5]. If the exhaled hydrogen concentration after lactose ingestion is 20 ppm (parts per million) higher from the baseline value, it is suggested to be lactose intolerance [3, 5]. Hence, the results collected from HBT can be used to evaluate and predict the possible impacts of different therapeutic options such as probiotics on lactose malabsorption.

3. Clinical effects of probiotic supplementation on lactose intolerance and limitations of studies

Many clinical trials showed that probiotics performed significant and beneficial effects on alleviating the signs and symptoms of lactose intolerance and HBT results. According to Leis, R., et al (2020), they collected a total of seven clinal studies which assessed the effects of probiotics on symptoms of lactose intolerance by either recording the disappearance rate of abdominal cramps or rating the level of gastrointestinal symptoms based on standardized scales, for example, 0-1, or 0-100, after the supplementation of probiotic to each participant. Six out of seven clinal trials indicated that there is an advantageous impact of the probiotic intervention on mitigating the symptoms of lactose intolerance, and only one trial did not observe a significant relationship between the intervention and alleviation of symptoms. In addition to that, there were five clinical studies in which the evaluation of lactose metabolism was conducted by HBT. All of the experiments reported a notable effect of probiotics on decreasing the exhaled hydrogen concentration of HBT results [2].

However, there are some factors that need to be taken into account. Firstly, the duration of probiotic intervention. A clinal study that conducted a six-week intervention of probiotics is the sole trial that reported no significant association between probiotic supplementation and lactose intolerance alleviation. However, in the same study, experimental results collected two weeks after the probiotic intervention indicated that probiotic supplementation played a significant role in preventing and relieving abdominal cramps and diarrhea [2]. This proved that the different durations of the intervention may affect the persistence and efficacy of probiotics, a long-term trial is needed to fully study the application of probiotics, to fully evaluate the persistence of the effects of probiotics and the drawbacks of probiotic administration.

The second factor is the dose of probiotic supplementation [2, 3, 5]. These clinical studies also suggested that there is a significant difference in probiotic effects upon applying high doses or low doses. It is important to note that when supplying probiotics, the dose is a significant parameter since the changes in the composition of the gut microbiota are dependent on the minimum number of microorganisms required for colonization. The significance of dose selection was also stressed by the joint working group of the FAO/WHO in 2002, which suggested defining the probiotics as live microorganisms that provide a health benefit on the host when administered in sufficient amounts.

Thirdly, it is must be considered that the HBT is likely to produce false-negative results and false-positive results. The HBT has a 5%–15% chance to detect false-negative results [5]. This kind of phenomenon can be caused by some actions or conditions that may lead to alterations in normal gut microbiota, for instance, the use of probiotics [5], physical exercise, and recent administration of oral antibiotics [3, 5]. Apart from that, the false-positive results are considered to be caused by the small intestinal bacterial overgrowth (SIBO), smoking, and intake of some food such as corns and beans [3, 5]. Smoking can increase the production of hydrogen because when combusting tobacco, it can lead to an increase in gases, which include hydrogen. The digestion process of some foods like corn and beans can also cause an increase in hydrogen production. Therefore, in order to increase the validity

of the HBT, participants are recommended not to smoke and eat hydrogen-generating foods such as corns and beans on the day of the test, and to avoid using antibiotics in recent weeks before the test.

4. The roles of probiotics in alleviating gastrointestinal symptoms

Lactose intolerance is usually accompanied by a variety of gastrointestinal symptoms. For instance, diarrhea, abdominal cramps and bloating, flatulence, vomiting, and nausea. These symptoms of lactose intolerance are the results of bacterial fermentation of undigested forms of lactose inside the colon. This colonic fermentation leads to the production of gas and short−chain fatty acids, followed by acidification of intestinal contents, which can further increase the osmotic load of the intestine. Together with the generation of gas, they can irritate the lining of the intestine and speed up its transit time [5]. Aside from these typical symptoms, clinical research found that a large portion of individuals with lactose intolerance have also developed symptoms of depression, anxiety, and fatigue [7], because of the intention of patients to restrict their food intake in order to avoid the occurrence of gastrointestinal symptoms and suffering from the abdominal pain [8]. Additionally, It has been discovered that these lactose-intolerant subjects are more likely to develop certain extra-intestinal diseases such as memory deterioration, headache [5], and certain types of cancer [9], owing to the alteration of the gut microbial compositions and the extra synthesis of the toxins caused by the gastrointestinal symptoms of lactose intolerance. However, probiotics have recently been suggested that they may act on the symptoms of lactose intolerance through altering the metabolic activity of colonic microbiota [1, 2, 3, 5, 10]. Hence, it is essential to study the mechanisms utilized by probiotics in the alleviation of lactose intolerance, to better understand the roles and beneficial effects played by probiotics.

Probiotics are defined as live bacteria or yeasts that are capable of acting as the supplementation of gut microbiota [11]. Promoting the intestinal colonization of certain probiotic species or strains, such as Bifidobacterium longum and Lactobacillus rhamnosus, can help to achieve the modulation of gut microbial composition, which can largely increase the intolerance of small amounts of lactose present in dairy food [11], with a long-lasting effect and with considerable benefits for the lactose intolerant individuals' quality of life [3]. Apart from that, supplementing certain species of probiotics is able to increase the enzymatic activity of lactase. Experiments showed that the lactase activity was increased significantly during the supplementation of B. longum [2]. Generally, gastrointestinal symptoms of lactose intolerance only occur when the activity of lactase is less than 50%. Therefore, probiotic supplementation can effectively alleviate lactose intolerance.

These beneficial effects of probiotics acting on lactose intolerance treatment could be explained by the following mechanisms:

(1) probiotics act as compensation for lactase deficiency. Probiotics serve as a source of lactase in the intestinal tract upon reaching the digestive system, to increase the overall hydrolytic capacity of the gastrointestinal tract and increase the colonic fermentation of lactose [1, 5].

(2) probiotics perform antagonistic effects inside the GI tract. Probiotics produce antagonistic substances to act on heterofermentative bacteria which produce a large amount of gas, including hydrogen, carbon dioxide, and methane that can irritate the lining of the intestine, resulting in diarrhea and abdominal cramps. In this way, probiotics are capable of positively modulating the permeability of the intestinal barrier and microbial environment by inhibiting the growth of harmful microorganisms [5, 12].

(3) Probiotics can stimulate host immune responses against infections, owing to their ability to strongly adhere to the intestinal mucosa [1, 5].

5. Requirements for the selection of probiotic species or strains applied to lactose intolerance management

More and more relevant studies and evidence have suggested that clinical symptoms and signs of lactose intolerance can be alleviated and improved by the use of probiotics. However, it has been

demonstrated that not all of the species and strains can be applied to lactose intolerance management. Researchers found that the probiotics utilized in the treatment of lactose intolerance should meet the following requirements.

Firstly, the applied probiotics should perform β-galactosidase enzymatic activity [3, 10, 13]. As mentioned previously, β-galactosidase is capable of digesting the disaccharide lactose into glucose and galactose. Probiotics with β-galactosidase activity can aid in lactose digestion [3] and exert a positive effect on gastrointestinal activity and the microbial environment [10]. According to preclinical and clinical studies, probiotic strains of both Lactobacillus and Bifidobacterium have shown the capability of expressing β-galactosidase activity [3]. Thus, some specific β-galactosidase expressing probiotics can be applied to facilitate lactose digestion and help to improve the lactose intolerant individuals' quality of life. A comparison of the level of β-galactosidase activity expressed by certain species and strains of probiotics is shown in Table 1.

Table 1. Comparisons of the β-galactosidase activity expressed by several probiotic species and certain strains [2].

Probiotic species	Strains	Level of β-galactosidase activity
Bifidobacterium lactis	W52	****
Bifidobacterium lactis	W51	***
Lactobacillus acidophilus	W22	*****
Lactobacillus acidophilus	W70	*****
Lactobacillus brevis	W78	*
Lactobacillus casei	W20	*
Lactobacillus casei	W79	**
Lactobacillus rhamnosus	W71	*
Lactobacillus salivarius	W24	*****
Lactococcus lactis	W19	*
Streptococcus thermophilus	W69	*****

Note: * represents the intensity of β-galactosidase activity.

Secondly, the applied probiotics should be tolerant to the intestinal environment. For example, the adaptation to the pH value and temperature of the gastrointestinal tract, the ability to adhere to the intestinal mucosa, and the competitive ability to expel the pathogens [2]. According to Leis, R et. al. [2], there are six species of probiotics, including Lactobacillus acidophilus, Lactobacillus reuteri, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Streptococcus thermophilus, and Bifidobacterium longum, showed to meet all the criteria and are effective in alleviating the gastrointestinal symptoms of lactose intolerance. Different species have varying degrees of efficacy but an overall positive relationship between probiotics and lactose intolerance in relation to specific strains and concentrations.

6. Various species of probiotics in fermented food products

Recent works demonstrated that probiotic-containing foods have a variety of beneficial effects on promoting human health. Probiotics have been linked to the promotion of lactose digestion and

improvement of lactose tolerance in people who consume these fermented foods regularly [14]. Clinical studies demonstrated that probiotic supplementation significantly relieved gastrointestinal signs and symptoms, such as abdominal pain, diarrhea, and flatulence, in people with lactose intolerance [1, 2, 3, 5]. Actually, these health-promoting fermented foods are very common and accessible in our lives. A few probiotics-containing fermented foods that can be used to alleviate lactose intolerance are introduced below.

6.1 Yogurt

Yogurt is produced through the fermentation of milk. Typically, the consumption of yogurt causes fewer symptoms than milk consumption. It is traditionally fermented by certain lactic acid bacteria, such as Lactobacillus bulgaricus and Streptococcus thermophilus [13]. These bacteria are proved to be effective in alleviating clinal symptoms of lactose intolerance, as mentioned previously [2]. Other probiotic strains can also be added in order to produce probiotic yogurt, for example, lactobacilli and bifidobacteria. These probiotics all express the β-galactosidase activity, which can hydrolyze the disaccharide lactose into glucose and galactose [3] while simultaneously lowering the pH of yogurt [13].

6.2 Kefir

Kefir is produced from fermented milk, it is considered a probiotic drink with a creamy texture, sour taste, and subtle effervescence. It is produced from grains called kefir grains, which are composed of symbiotic lactose-fermenting yeasts such as Kluyveromyces marxianus and non-lactose fermenting yeasts such as Saccharomyces cerevisiae and Saccharomyces unisporus, along with probiotics which can produce lactic and acetic acid [15]. A variety of probiotic species have been identified to present within kefir grains, including Lactobacillus brevis, Lactococcus lactis, Streptococcus thermophilus, Saccharomyces cerevisiae, Kluyveromyces marxianus, and so on [15]. meet all the criteria for becoming compensation for colonic microbiota. For example, they have a high resistance to the extreme environment in the gastrointestinal tract, such as low pH and bile salts; and they have the capability to adhere to the intestinal mucosa. In addition, the microbiota present in kefir can produce antagonistic substances, such as organic acids and bacteriocins, these can be used to compete with pathogens inside the intestinal mucosa by interfering with the adherence of pathogens [14].

Clinical research have shown that subjects with lactose intolerance showed a good intolerance to kefir because kefir consists of probiotics that express the β-galactosidase activity, for example, Kluyveromyces marxianus. It can trigger the hydrolysis of lactose, therefore the lactose concentration present in kefir is decreased. Besides that, Kefir contains a much higher level of β-galactosidase (about 60%) than the yogurt, meanwhile, during the fermentation of milk, part of lactose has been degraded in kefir, converting into glucose and galactose, then probiotics present in kefir will convert glucose into lactic acid [7]. In this way, the concentration of lactose in kefir is about 30% lower compared to general milk [15].

Therefore, for those individuals who are lactose intolerant, in order to avoid lactose intolerance symptoms, and meanwhile meet the nutritionally balanced requirement, they can choose to intake the above food products as an alternative to milk, to get the recommended amount of protein and minerals daily.

7. Conclusions

Clinical research indicated that probiotics exhibit beneficial effects on lactose intolerance treatment, supported by the evidence that alleviations in abdominal cramps, diarrhea, vomiting, and flatulence during the supplementation of probiotics or after intake of probiotic-containing dairy products. These certain strains or species of probiotics should possess β-d-galactosidase to aid in lactose breakdown, also possess the ability to modulate the gastrointestinal microbiota. Probiotics can be administered independently or added to some food products, for example, yogurt and kefir. They can be considered as an alternative to milk for lactose intolerant individuals, and help them to maintain a well-balanced

diet and at the same time, avoid the corresponding symptoms of lactose intolerance. In the future, relevant studies could focus on finding some particular species or strains of probiotics that can boost the production of β-galactosidase, because clinical research indicates that adding such probiotics to diverse food products appears to be the most efficient way to alleviate lactose intolerance. Furthermore, new investigations on the selection of probiotic species and strains, their preparation, dose, and the time of intervention should be conducted to help us fully understand the therapeutic relationship between probiotics and lactose intolerance.

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