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Research progress of naturally fermented yogurt with lactic acid bacteria in Xinjiang: a review of anti-constipation probiotics

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Abstract
Xinjiang is a multi-ethnic region in China, traditional fermented yogurt is the main food of local herdsmen. This study aimed to summarize the literature data in recent years and data on the constipation-inhibitory effect of probiotics isolated from naturally fermented yogurt in Xinjiang, China. Xinjiang naturally fermented yogurt is rich in microbial resources, of which many in the food industry have been or are being developed and utilized as probiotics. *Lactobacillus*, naturally fermented yogurt of Xinjiang, has been verified to have a good constipation-inhibitory effect. Lactic acid bacteria isolated from naturally fermented yogurt in Xinjiang, China, has a good effect in terms of improving the symptoms of constipated experimental animals and could be used as probiotics. Some in-depth studies found that these lactic acid bacteria had target effects in regulating the stem cell factor (SCF)/stem cell factor receptor (c-Kit) signaling pathway and nitric oxide synthase expression and thus played a role in inhibiting constipation. The constipation-inhibitory effect of Xinjiang naturally fermented yogurt probiotics is also better than that of general commercial probiotics and can be used as high-quality probiotics to improve constipation. This study summarized available findings, provided some research ideas, and gave some directions for future research.

Keywords: constipation; lactic acid bacteria; probiotics; Xinjiang; SCF/c-kit signaling pathway.

Practical Application: Xinjiang is an area with special geographical conditions and mixed ethnic groups in China, with good microbial diversity. This study summarizes and summarizes the research on lactic acid bacteria in Xinjiang natural fermented yogurt, which provides theoretical knowledge for scholars who are carrying out relevant research and intend to carry out similar research.

1 Introduction

Xinjiang Uygur Autonomous Region, as the largest provincial-level administrative region in China, has vast natural grasslands and rich forage resources. The grassland area is 4.8×10^7 hm^2, which is one third of the total area of Xinjiang and one of the five largest pastoral areas in China. In addition, the unique ecological environment of Xinjiang, with sufficient sunlight, sparse population, and weak mobility, is not prone to diseases; the vast territory, rich forage resources, and low cost of dairy cattle breeding ensure the development of animal husbandry in Xinjiang in many aspects. It is the source of milk in China. It is one of the top 10 main producing areas of China; it is also one of the high-quality milk sources and even the golden milk source area recognized by the world.

As an important animal husbandry base in China, many ethnic groups in Xinjiang have long maintained the habit of consuming livestock milk and dairy products. For example, Kazakhs, Mongolians, and Russians have the habit of consuming goat milk, milk, milk tea, cheese, and other dairy products for three meals a day; it is more common for Hui and Uyghur people to drink homemade yogurt. The unique food culture and habits due to multi-ethnic mixing have extensively promoted the development of dairy products. Smart herdsmen not only have rich breeding experience but also have skilled dairy product processing technology. They use livestock milk as a raw material to make unique and ethnic dairy products, such as cheese, cattle yogurt, yak yogurt, horse yogurt milk wine, kefir grains, milk cakes, sour goat milk, fermented camel milk, and so forth. A wide variety of dairy products not only extend the shelf life of milk and facilitate savings but also offer unique flavors and nutrients. The quality of naturally fermented yoghurt is completely affected by external natural conditions. Different additives, different herdsman families, and even products fermented at different times contain different microorganisms. Therefore, the diversity is very good, and there is a great possibility of probiotics with good biological activity (El-Shafei et al., 2020; Lucatto et al., 2020; Pena et al., 2021). However, with the development of industrial science and technology, traditional processes are constantly being replaced by new technologies and the valuable lactic acid bacteria resources in naturally fermented yogurt are gradually disappearing.

Xinjiang has an excellent milk source base and a unique ecological environment. Traditional naturally fermented yogurt, as one of the favorite dairy products of local herdsmen, is rich in protein, fat, vitamins, minerals, and nutrients such as organic acids and lactose. In addition, animal milk serves as a pure, natural medium for cultivating lactic acid bacteria in yogurt

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into a large number of excellent biological resources due to factors such as differences in climate and milk sources in the long-term fermentation process.

At present, lactic acid bacteria in fermented milk mainly include *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, *Enterococcus*, *Leuconostoc*, *Streptococcus, Pediococcus*, and other genera (Zhang, 2015). Many research reports are available on the diversity of lactic acid bacteria in fermented yogurt. The common separation and identification methods mainly include 16S rDNA sequence homology analysis, 16S rRNA amplified fragment base difference analysis, rRNA transcription spacer sequence analysis, DNA fingerprinting technology, multi-locus sequence typing, regularly clustered interspaced short palindromic repeats, gene network construction phylogenetic tree, second- and third-generation sequencing technology, and metagenomic sequencing technology. A total of 706 strains of lactic acid bacteria, including 8 genera and 27 species or subspecies, were isolated from 86 dairy products collected from herdsmen's homes in 4 areas of Ili Kazakh Autonomous Prefecture, Xinjiang. As shown in Table 1, the dominant genera were *L. delbrueckii* subsp. *bulgaricus*, *L. fermentum*, and *L. helveticus*, together accounting for 52.7% of the total isolates (Zhu et al., 2008). Twenty-six samples of homemade dairy products were collected from around Urumqi, Xinjiang, and in Yili, including cheese, yogurt, horse milk, milk lumps, ghee, primer, camel milk, and so forth. Thirty-five strains of lactic acid bacteria were isolated from these foods, including 22 strains of bacilli and 13 strains of cocci (Dong et al., 2013). Based on the sequencing and splicing of 10 traditional fermented yogurts from Xinjiang Artush and Ushi, 7 phyla were detected at the level of 16S rRNA. Firmicutes was the dominant phylum, with 43 genera and *Lactobacillus* and *Streptococcus* being the predominant genera. At the level of ITS sequencing, five phyla were detected, of which *Bursa*, *Basidiomycetes*, and *Zygomycetes* were the dominant phyla. At the genus level, 43 fungal genera were detected; *Kluyveromyces* and *Saccharomyces* were the dominant genera (Ahat et al., 2018). A total of 92 strains of lactic acid bacteria were isolated from 41 traditional yogurt samples collected in Kashgar, Xinjiang, including 10 strains of *L. delbrueckii*, 16 strains of *L. fermentum*, 7 strains of *Pediococcus lactis*, 36 strains of *Enterococcus faecium*, 14 strains of *Enterococcus dudus*, and 1 strain of *Leuconostoc membranae*. *E. faecium* has the largest number and can be regarded as the dominant strain in Kashgar (Gou et al., 2022). Seven yogurt milk samples and eight yogurt camel milk samples collected from Kazakh people in the Tacheng area were separated with five different culture media. A total of 683 pure cultures were obtained, and 502 Gram-positive strains were obtained through preliminary screening. Five strains of lactic acid bacteria and one strain of *Lactococcus* were obtained through further identification: *Lactobacillus fermentum*, *L. acidophilus*, *L. plantarum*, *L. parabrevis*, *L. casei*, and *Lactococcus garvieae* (Jiang et al., 2015). The composition and quantity of microorganisms in traditional fermented dairy products in Xinjiang are affected by factors such as the local environment, climate change, fermentation temperature and time, and personal production methods, implying that the microbiota in yogurt products in different regions of Xinjiang was quite different.

Table 1. The main lactic acid bacteria in Xinjiang dairy products (3).

Latin name of the strain	Latin name of the strain
Enterococcus durans	*Lactobacillus brevis*
Enterococcus faecalis	*Lactobacillus coryniformis subsp. torquens*
Enterococcus faecium	*Lactobacillus delbrueckii subsp. bulgaricus*
Enterococcus italicus	*Lactobacillus fermentum*
Lactococcus garvieae	*Lactobacillus graminis*
Lactococcus lactis subsp. cremoris	*Lactobacillus helveticus*
Lactococcus lactis subsp.lactis	*Lactobacillus kefiranofaciens subsp. kefiranofaciens*
Leuconostoc citreum	*Lactobacillus kefiri*
Leuconostoc lactis	*Lactobacillus paracasei*
Leuconostoc mesenteroides	*Lactobacillus plantarum*
Lactobacillus acidophilus	*Lactobacillus casei*
Leuconostoc pseudomesenteroides	*Lactobacillus sakei*
Pediococcus pentosaceus	*Weissella confuse*
Pediococcus acidilactici	*Weissella cibaria*
Vagococcus carniphilus	*Streptococcus thermophilus*

Constipation is a syndrome characterized by gastrointestinal symptoms, such as difficult or infrequent bowel movements. It may occur alone or secondary to another underlying disorder (e.g., Parkinson's disease). Many physicians consider constipation to be synonymous with reduced stool frequency, but some physicians consider defecation strain, hard stools, incomplete defecation, anorectal obstruction, and even manual manipulations as constipation (Sandler & Drossman, 1987). In addition, factors such as differences in patients' understanding of the degree of constipation and different symptom descriptions hinder the clinical diagnosis and treatment of constipation. According to the pathological mechanism and clinical manifestations of patients, constipation can be divided into slow transit constipation (STC), outlet obstructive constipation, and mixed constipation according to abnormal motility. According to the severity, constipation can be categorized into mild constipation, moderate constipation, and severe constipation (Li & Yu, 2011). According to the Rome III criteria, functional gastrointestinal disorders related to defecation abnormalities are divided into two syndromes: irritable bowel syndrome (IBS) and functional constipation. The main clinical manifestation of IBS is recurrent abdominal pain with persistent abdominal distension (Spiller & Thompson, 2010). According to epidemiological studies, IBS is a global disease. The incidence rate of IBS in North America (about 15%–20%) is higher than that in Asia (5%-10%). The prevalence rate in women is higher than that in men (Zhang et al., 2014; Li et al., 2013; Cuomo et al., 2014; Turnbull et al., 2015). Functional constipation is defined as the symptoms that have appeared for not less than 6 months before diagnosis and treatment. The symptoms in the last 3 months should meet two or more of the following criteria, and the frequency of each symptom should be greater than or equal to 1/4: (1) defecation requires excessive force; (2) the stool is a lump; (3) patients have a feeling of incomplete evacuation after defecation; (4) defecation is less than three times per week; (5) patients experience anorectal obstruction or a sense of obstruction; and (6) patients need hand assistance in defecation. Long-term constipation and stool retention in the intestines lead to unbearable pain and psychological anxiety, and cause an effect on the quality of life, accumulation of intestinal contents, and metabolism of harmful bacteria producing a large amount of toxic substances, such as hydrogen sulfide, indole, ammonia, and so forth. If constipation stays for a long time, the toxic substances are reabsorbed into the blood circulation. In severe cases, it can increase the load on the liver, causing nausea, headache, and even rectal cancer (Lu & Chen, 2014). The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) jointly define probiotics as living microorganisms that can benefit health when ingested in an appropriate amount (Zendeboodi et al., 2020). Since the 21st century, the term "probiotics" has become the focus of attention of researchers in various fields at home and abroad. Probiotics are a class of active microorganisms and their metabolites that colonize the host's gut, reasonably improve the host's gut microbial balance, and perform beneficial functions for the host. Probiotics have been widely sold in supplements and foods. Improving the function of probiotics so that they can be better used in supplements or fermented foods is also the focus of research (Champagne et al., 2018). As a typical representative of probiotics, lactic acid bacteria have gradually become a popular research object. The lactic acid bacteria in the naturally fermented dairy products of Xinjiang have also attracted the attention of many researchers, including the intervention effect of these lactic acid bacteria on constipation.

2 Evaluation and research status of functional lactic acid bacteria in naturally fermented milk yogurt in Xinjiang, China

2.1 Lactic acid bacteria in dairy products in Xinjiang

Studies have reported that lactic acid bacteria in Xinjiang dairy products have the functions of acid production, exopolysaccharide production, tolerance to gastric acid bile salts, anti-oxidation, enhancement of immune regulation, and lowering of blood lipids and cholesterol. *Lactobacillus plantarum*, *L. casei*, *L. pentosus*, and *L. deutsch* were isolated from naturally fermented yogurt in Korla and Kashi, Xinjiang, China (Table 2). Some lactobacilli also showed good resistance to artificial gastric acid and bile salts (Table 3), and had the potential to serve as probiotics.

Twenty-one strains of lactic acid bacteria were isolated from yogurt milk collected from Shuixigou and Ili in Xinjiang. Two strains of lactic acid bacteria with high production of exopolysaccharides were detected and identified as *Lactobacillus casei* using the phenol-sulfuric acid method. The culture conditions were optimized, and the final exopolysaccharide synthesized amount reached 151.76 mg/L (Jin et al., 2017). Using 15 samples of yogurt milk collected from the Tacheng area in Xinjiang as the source of isolation, 502 Gram-positive strains were isolated and analyzed for their drug resistance profiles. The results showed that 84% of the strains were resistant to three to seven strains. Two of three strains were resistant to gentamicin, 25 strains were sensitive to rifampicin, and 2 strains were resistant to erythromycin; all strains could effectively use glucose, lactose, and fructose (Jiang et al., 2015). *In vitro* antioxidant tests were conducted on 20 strains of lactic acid bacteria screened from Xinjiang yogurt and cheese. The results showed that all strains had certain antioxidant activities (Jiang et al., 2015). Further, 15 strains of *Lactobacillus plantarum* with a better antioxidant effect were selected to examine the liver protection effect in the carbon tetrachloride–induced mouse acute liver injury model. Lactic acid bacteria could significantly inhibit the generation of free radicals, reduce the activity of related antioxidant enzymes, promote gastrointestinal peristalsis, prevent liver cell damage, and effectively protect the liver. By isolating fermented camel milk samples collected from the pastoral areas of Altay and Changji in Xinjiang, 10 strains of lactic acid bacteria were obtained. Then, BALB/c mice were injected with cyclophosphamide intraperitoneally to induce low immune function in mice. After functional verification, it was found that *Lactobacillus* No. 10 could increase the levels of IL-4 and IFN-γ in the live or heat-killed state, activate Th2 and Th1 cells, and then enhance the cellular

Table 2. The 16S rDNA sequence analysis of microorganisms isolated from natural fermented yoghurt in Xinjiang.

Strain number	Latin name of the strain	Homology (%)	Gene Bank accession number	Source
KFY02	*Lactobacillus plantarum strain*	99.66%	MT473372.1	Korla
KFY03	*Lactobacillus plantarum strain*	99.93%	MK049960.1	Korla
KFY04	*Lactobacillus plantarum strain*	99.86%	MK049960.1	Korla
KFY05	*Lactobacillus plantarum strain*	99.86%	MF369880.1	Korla
KFY06	*Lactobacillus plantarum strain*	99.86%	MG754568.1	Korla
KFY07	*Lactobacillus casei strain*	97.06%	GQ131243.1	Korla
KSFY01	*Lactobacillus plantarum strain*	99.73%	MT515964.1	Kashgar
KSFY02	*Lactobacillus pentosus strain*	99.59%	MT898576.1	Kashgar
KSFY03	*Lactobacillus plantarum strain*	99.79%	MH681604.1	Kashgar
KSFY04	*Lactobacillus plantarum strain*	99.86%	MT510328.1	Kashgar
KSFY05	*Lactobacillus plantarum strain*	100.00%	MW279239.1	Kashgar
KSFY06	*Lactobacillus plantarum strain*	99.86%	MW279239.1	Kashgar
KSFY07	*Lactobacillus delbrueckii subsp. bulgaricus*	99.66%	MT545085.1	Kashgar
KSFY08	*Lactobacillus delbrueckii subsp. bulgaricus*	99.79%	MT613595.1	Kashgar
KSFY09	*Lactobacillus plantarum strain*	100.00%	MG890195.1	Kashgar

Table 3. Survival rate of strains in pH 3.0 gastric acid and 0.3% bile salt.

Strain number	Colony count in pH 3.0 gastric acid (CFU/mL)			Survival rate in 0.3% bile salt(%)
	0 h	3 h	Survival rate (%)	
KFY02	1.19×10^9	1.11×10^9	93.46 ± 1.45	24.67 ± 1.25
KFY03	9.08×10^9	2.03×10^9	23.42 ± 9.11	13.75 ± 2.21
KFY04	7.65×10^7	4.18×10^7	54.55 ± 2.23	8.27 ± 1.07
KFY05	4.65×10^9	3.75×10^8	8.18 ± 2.24	8.34 ± 1.25
KFY06	1.31×10^{10}	1.19×10^9	9.11 ± 0.18	9.78 ± 0.52
KFY07	1.17×10^9	9.13×10^8	78.63 ± 11.14	9.03 ± 1.54
KSFY01	6.65×10^8	5.80×10^8	86.94 ± 25.80	13.27 ± 0.88
KSFY02	7.68×10^8	5.68×10^8	73.88 ± 2.93	13.25 ± 1.93
KSFY03	6.08×10^8	5.20×10^8	85.93 ± 8.83	10.96 ± 1.51
KSFY04	8.23×10^8	7.50×10^8	91.34 ± 7.83	7.34 ± 3.87
KSFY05	1.17×10^9	6.63×10^8	58.08 ± 14.29	11.67 ± 14.29
KSFY06	7.80×10^9	1.35×10^9	17.24 ± 1.13	8.44 ± 1.01

and humoral immunity of mice (Latipa et al., 2014). Ten strains of lactic acid bacteria isolated from Xinjiang camel yogurt were studied. Through enrichment culture, lactic acid bacteria that could decompose cholesterol were selected. The cholesterol content of lactic acid bacteria after culture was measured using cholesterol as the only carbon source and energy. The cholesterol degradation rate of the three strains was more than 60% (Zeng & Sun, 2010). A *Lactobacillus* strain with a cholesterol-lowering effect was isolated from the cheese made by Kazak nationality in Xinjiang. The results showed that the contents of triglyceride and total cholesterol in the serum of rats fed a high-fat diet were higher at different times of gavage, which decreased to varying degrees in the fat diet group but increased in the high-density lipoprotein cholesterol group. The lactic acid bacteria served as a highly effective probiotic for reducing blood lipid levels (Tian & Zhan, 2012). Lactic acid bacteria isolated from naturally fermented yogurt in Korla and Kashgar, Xinjiang, were proved to have a constipation-inhibitory effect (Mu et al., 2020; Gan et al., 2020), but the related studies were few. The research and development of the constipation-inhibitory effect of probiotics isolated from naturally fermented yogurt in Xinjiang is still in its infancy.

2.2 Mechanism of constipation

Constipation is a complex syndrome, and its etiology and pathology are complex. In recent years, many research reports have been published on constipation, but its pathogenesis is inconclusive. The possible etiological factors are as follows.

2.3 Intestinal nervous system disorders

The physiological function of the gastrointestinal tract is mainly regulated by the central nervous system (CNS) and the enteric nervous system (ENS). As the "gastrointestinal brain," ENS independently regulates the activities of the gastrointestinal tract and the secretion, absorption, blood circulation, and movement of the digestive system (Alvarez et al., 2013). Glial cell–derived neurotrophic factor (GDNF) is an extracellular protein that plays a key role in the survival of ENS. As a neurotrophic factor, GDNF can regulate the expression of mature ENS neurons and promote the proliferation, differentiation, maturation, and migration of developing neurons (MacEachern et al., 2011). GDNF plays an important role in patients with functional constipation. The STC model was established by the intragastric administration of rhubarb, and recombinant human GDNF was injected into the tail vein of STC rats. The expression of GDNF mRNA in the gastric wall of the STC model group was found to be lower, and the expression of GDNF mRNA in the gastric wall of model rats injected with GDNF significantly increased. It showed that the low expression of GDNF in the gastric wall caused pathological changes in gastrointestinal plexus and hindered gastric motility (Fang et al., 2010). Some scholars found that the protein and mRNA expression levels of GDNF in constipation model mice were significantly lower than those in normal mice and mice treated with electroacupuncture at large intestine acupoints (Sun et al., 2018).

2.4 Gastrointestinal motility disorder

The study found that the level of gastrointestinal hormones had a significant correlation with gastrointestinal motility and an inevitable relationship with the occurrence of constipation in the body. The smooth progress of gastrointestinal motility depends on the gastrointestinal hormone levels of the body, messenger receptor regulators, and coordination of the ENS. Gastrointestinal hormones include excitatory gastrointestinal hormones (acetylcholine, endothelin, gastrin, motilin, and substance P) and inhibitory gastrointestinal hormones (vasoactive peptide, nitric oxide, and somatostatin). Motilin is an important indicator of gastrointestinal motility, which promotes the motility of various parts of the gastrointestinal tract; a decrease in motilin release reduces the frequency of gastrointestinal motility (Chen et al., 2019). Gastrin, one of the most important gastrointestinal hormones, has a large impact on the gastrointestinal tract, stimulating gastric secretion, enhancing gastrointestinal motility, promoting pyloric sphincter relaxation, and accelerating gastric emptying (Xin et al., 2018). Substance P is an excitatory transmitter of gastrointestinal motor neurons, which promotes the contraction of smooth muscle in the gastrointestinal tract, stimulates the secretion of water and electrolytes in the mucosa of the small intestine and colon, and promotes gastrointestinal motility (Zhuang et al., 2019). Endothelin maintains normal intestinal function by maintaining vascular tone and cardiovascular stability, while somatostatin inhibits the release of gastrointestinal hormones, reducing the rate of gastric emptying and the frequency of smooth muscle contractions, thereby accelerating constipation. When inulin and isomaltooligosaccharides were used to treat constipated rats, the levels of motilin and substance P were found to be the lowest in the serum of rats in the model group. After treatment, the levels of gastrointestinal motility–related hormones increased (Lan et al., 2020a). The effect of resistant starch on Institute of Cancer Research (ICR) mice with constipation found that the serum levels of motilin (MTL), gastrin (Gas), endothelin (ET), acetylcholinesterase (AChE), substance P (SP), and vasoactive intestinal peptide (VIP) significantly increased, while the level of somatostatin (SS) decreased in constipated mice treated with resistant starch (Qian et al., 2013). By treating slow transit constipation (STC) rats with traditional Chinese medicine decoction, it was found that the contents of SP, MTL, and Gas in the serum of the constipated rats significantly decreased ($P < 0.05$), and the contents of SP, MTL, and Gas significantly increased after treatment ($P < 0.05$) (Zhu et al., 2019).

2.5 Intestinal flora imbalance

The predominant flora in the feces of constipated patients is significantly less than that in healthy people; the changes in *Bifidobacterium* and *Lactobacillus* are the most obvious. At the same time, the number of opportunistic pathogens (fungi, *Enterococcus*, and *Enterobacter*) in the intestines of constipated patients increases. The more obvious the adverse trend changes, the higher the degree of constipation (Khalif et al., 2005). Differences exist in the structure of intestinal microbes in each person, which are mainly affected by diet, drugs, and living environment. In healthy people, intestinal microbes and the body mutually benefit each other. The human body provides a comfortable growth environment for intestinal microbes. The digestion and breakdown of food and its metabolites coordinate homeostasis such as host gastrointestinal hormones. A number of related studies have shown that the intestinal flora can enhance the biological barrier of intestinal mucosa, improve immunity, regulate the function of the brain–gut axis, and promote intestinal peristalsis (Distrutti et al., 2016; Wang & Wang, 2016; de Meij et al., 2016). When exploring the mechanism of intestinal flora and the occurrence and development of chronic constipation, it was found that the colonic flora of constipated patients was scattered and the abundance reduced; the flora structure was completely different from that in healthy people. increased, leading to intestinal dysbiosis (Lan et al., 2020b). When the extracts of *Aloe vera*, American ginseng, and senna leaves were combined for treating constipated mice, the combination could effectively improve the richness and diversity of intestinal flora, inhibit the proliferation of harmful bacteria, and regulate the intestinal microecology, thereby improving constipation (Chen et al., 2020).

2.6 Other factors

Besides the aforementioned factors, the influencing factors for 203 children with functional constipation, aged 2–7 years, were analyzed (Bao et al., 2020). In a study of 1138 college students suffering from functional gastrointestinal diseases, 119 students suffered from functional constipation with the highest incidence, followed by functional dyspepsia. The main causes were overeating, lack of sleep, anxiety, and depression (Wu et al., 2020). The functional constipation caused by diet in 50 elderly patients with constipation was analyzed. The main factors for constipation were summarized as follows: low intake of dietary fiber and water and difficult intestinal peristalsis. The elderly patients were unable to move, stayed in bed for a long time, and reduced the amount of exercise. Also, long-term medication for geriatric diseases also caused constipation. (Wang et al., 2008).

3 Experimental verification of commonly used methods for constipation

The etiology of constipation is complex, and the specific pathogenesis is not completely clear at present. It is necessary to establish a constipation animal model in basic research (Table 4). The establishment method and success of the constipation animal model have a direct impact on the follow-up experiments. Common constipation modeling methods include the drug modeling method and nondrug modeling method. Commonly used drug modeling methods include loperamide method, compound diphenoxylate method, montmorillonite powder method,

Table 4. Comparison of different inducers of constipation.

Inducer	Common dose	Modeling method	Advantages and disadvantages
Loperamide	1.5–50 mg/(kg·d)	Subcutaneous injection, oral gavage, and mixed in feed	Simple operation, low cost, and short molding time
Compound diphenoxylate	3.3–50 mg/(kg·d)	Oral gavage	Easy operation, high repeatability, and short modeling time
Montmorillonite	30 mg/(kg·d)	Oral gavage	Simple operation, low cost, high safety, and short molding time
Morphine	2.5 mg/(kg·d)	Subcutaneous injection	Morphine is a strictly regulated drug, and it is difficult to purchase
Phenethylpiperidine	8 mg/(kg·d)	Mixed in feed	Easy operation, strong repeatability, and long experimental cycle
Activated carbon	1 mg/(kg·d)	Oral gavage	Easy operation, low cost, and short molding time

morphine injection method, phenethylpiperidine method, and so forth. Loperamide is an opioid receptor agonist, which can combine with the opioid receptor on the intestinal wall to prevent the release of acetylcholine, thus blocking intestinal peristalsis, increasing the residence time of contents in the intestine, and resulting in less defecation and dry stool. It can be used to treat chronic acute diarrhea with good safety (Huang et al., 2020b). The mice were given loperamide at a concentration of 9.6 mg/kg, two times a day, for 12 h to establish a constipation model in mice. The results showed that the time of feces in the intestinal passage of the mice in the model group was prolonged, the frequency of defecation reduced, and the water content of feces decreased. Compound diphenoxylate is a commonly used inducer in the study of functional constipation animal models. It can directly act on smooth muscle, inhibit the sensitivity of mucosal receptors, reduce the frequency of intestinal peristalsis, and also promote intestinal water absorption and dry feces (Ji et al., 2019). The method of compound diphenoxylate–induced rat constipation model was optimized. It was found that the rat constipation model was induced using 15 mg/(kg·d) compound diphenoxylate for 7 days, which was maintained for 7 days. The rat defecation volume and the water content of the feces were reduced. The method was reproducible and safe (Gu et al., 2019). Montmorillonite powder is an intestinal mucosal protective agent, which can combine with mucus glycoprotein to cover the intestinal mucosa and stop diarrhea. The oral administration of montmorillonite powder does not affect the blood system, and it can be discharged directly through the digestive tract. A certain dose can lead to constipation (Wu, 2014). Besides this pharmacological effect, the powder can be used to construct an animal model of constipation. The results showed that the mice with constipation caused by montmorillonite powder took the longest time to excrete black stool, and the levels of gastrointestinal-related hormones significantly decreased (Li et al., 2015). While evaluating the alleviating effect of *L. plantarum* KSFY06 on montmorillonite powder–induced constipation, it was found that KSFY06 shortened the time of excreting the first black stool in constipation model mice from 182 min to 87 min; the fecal moisture content and fecal excretion were significantly higher than those in mice with montmorillonite powder–induced constipation (Gan et al., 2020). Morphine, an opioid, is mostly used to induce STC in animal models. Constipation was induced in mice by the subcutaneous injection of 2.5 mg/kg morphine hydrochloride every day for 45 days. It was found that the quality of feces in mice decreased, and the small intestinal propulsion slowed down. Phenylpiperidine acts primarily on intestinal smooth muscle, hindering peristalsis and leading to constipation (Xu et al., 2004). The rats were fed a diet containing 8 mg/kg body weight of compound phenepine for 120 days. The results showed that the content in the intestinal tract of the model rats stayed longer, the number of defecations decreased, the time it took to expel the first black stool increased, and the colonic slow wave showed bidirectional changes with increased frequency and unstable waveform (Liu et al., 2004). Also, nondrug modeling methods, such as low-fiber diet, water restriction, ice water stimulation, and activated carbon ice water obstruction, are commonly used (Xie et al., 2016). Constipation was induced in mice by the gavage of 0.2 mL of activated carbon ice water with a mass concentration of 100 g/L for five consecutive days; the activated carbon propulsion rate was found to be the lowest, and the first black stool excretion time was found to be the longest (Feng & Zhao, 2016). The constipation model of mice induced by montmorillonite powder is simple. Combined with the pharmacological effect of montmorillonite powder, oral gavage has no effect on the blood system. Also, the powder can be discharged directly through the digestive tract, does not affect drug absorption, is highly safe, and is recognized by researchers at home and abroad. It can be used to test the improvement effect of lactic acid bacteria on constipated mice. Animal studies also used montmorillonite powder and activated carbon to verify the inhibitory effect of lactic acid bacteria isolated from Xinjiang naturally fermented yogurt on constipation. However, the effect of lactic acid bacteria isolated from Xinjiang naturally fermented yogurt on people has not been explored.

4 Research status of lactic acid bacteria in preventing constipation

With economic development, people's dietary structure, living habits, psychological factors, and other factors have led to an increase in the incidence of constipation every year. At present, traditional Chinese medicine, Western medicine, surgery, and intestinal microecological adjustment are the main ways to treat constipation (Li et al., 2019). However, drug treatment has potential side effects, and long-term consumption is prone to drug dependence. Therefore, finding an efficient and safe treatment method for constipation has become a major issue for human beings. Probiotics are live microorganisms beneficial to the human body. A certain amount of probiotics colonizing the intestine can promote the health of the body and exert a probiotic effect. *Bifidobacterium*, *Lactobacillus*, and *Streptococcus thermophilus* have been reported as probiotics commonly used in the treatment of constipation (Zhang & Zhou, 2021). *Bifidobacterium* can be more effective in relieving constipation by improving the amount of water, propionate, and butyrate in the stool, and also overall transit time in the gastrointestinal tract. Meanwhile, from the perspective of fecal flora, *Bifidobacterium* relieves constipation mainly by increasing the relative abundance of genera (*Bifidobacterium*, *Lactobacillus*, and *Prevotella*) involved in rapid defecation. Constipation was induced in mice by loperamide, and the relieving effect of adherent *Bifidobacterium* on constipation was evaluated (Wang et al., 2019). *L. rhamnosus* strains isolated from five different sources were administered to mice with loperamide-induced constipation, and the effects of these strains on constipation-related indicators were evaluated. The main effects of different *L. rhamnosus* strains in relieving constipation are related to the gastrointestinal tract, including gastrointestinal regulatory peptides, neurotransmitters, neurotrophic factors, and intestinal flora (Wang et al., 2020). The effect of pentose from *Pseudomonas pentosus* B49 isolated from human colostrum on loperamide-induced constipation in mice was explored. The results showed that the treatment of *P. pentosus* B49 could alleviate the constipation of mice by shortening the defecation time and increasing the passing rate of GI and the production of feces (Huang et al., 2020a). The serum levels of inhibitory neurotransmitters (vasoactive intestinal peptide and nitric oxide) and excitatory neurotransmitters (acetylcholinesterase, motilin, and gastrin) were elevated. Also, the concentrations of cecal short-chain fatty acids (SCFAs) increased. The analysis of the cecal microbiota showed that *P. pentosaceus* B49 colonized the gut of constipated mice, increased the abundance of beneficial SCFA-producing bacteria (i.e., *Lactobacillus* and *Bacteroides*), and reduced the abundance of potential pathogenic bacteria (i.e., *Staphylococcus* and *Helicobacter pylori*) to alter the cecal microbiota.

5 Mechanism of lactic acid bacteria isolated from Xinjiang yogurt in preventing constipation

The research shows that the lactic acid bacteria isolated from Xinjiang yogurt can significantly improve the constipation symptoms of mice. These strains increase the fecal moisture content of constipated mice, shorten the discharge time of the first black stool of constipated mice, improve the small intestinal propulsion rate of constipated mice, and alleviate the damage of experimental constipation to small intestinal villi. They can also significantly increase the activities of total superoxide dismutase (T-SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) enzymes in mouse serum, reduce the content of MDA, and then slow down the degree of oxidative damage in constipated mice (Mu et al., 2020; Gan et al., 2020). They can significantly increase the levels of VIP, MTL, gastrin, AChE, and SP cytokines in mouse serum, reduce the contents of SS and ET-1, stimulate intestinal peristalsis by regulating gastrointestinal hormones, shorten the transport time of food in the small intestine, and promote defecation. These results show that the lactic acid bacteria isolated from Xinjiang yogurt can obviously alleviate constipation and significantly regulate the levels of gastrointestinal hormones. Many probiotics have been found to regulate the levels of hormones in the body and play a variety of bioactive roles, including inhibiting constipation, reflecting the involvement of probiotics in intestinal regulation, including regulating the levels of intestinal hormones. Lactic acid bacteria isolated from Xinjiang yogurt also showed similar intestinal hormone regulation, indicating their basic activity as probiotics. In addition, the lactic acid bacteria isolated from Xinjiang yogurt also showed an effect on oxidative stress, which was similar to the general antioxidant effect of probiotics. To sum up, the lactic acid bacteria isolated from Xinjiang yogurt had the basic biological activity of common probiotics.

At the gene level, the mRNA expression of c-Kit, SCF, GDNF, endothelial nitric oxide synthase (eNOS), and neuronal nitric oxide synthase (nNOS) in the small intestine was significantly upregulated, while the mRNA expression of TRPV-1 and inducible nitric oxide synthase (iNOS) were decreased. At the same time, probiotics increased the abundance of beneficial bacteria *Bacteroides*, decreased the abundance of harmful bacteria Firmicutes, and increased the abundance of *Akkermansia* by regulating the richness and diversity of intestinal microbial communities in constipated mice. They also improved the intestinal environment and inhibited the occurrence and development of constipation.

Studies have shown that interstitial cells of Cajal (ICC) are mesenchymal cells with unique functions. The abnormal number of mesenchymal cells and changes in cell morphology and network structure can slow down colonic peristalsis and induce constipation. c-Kit is a specific marker of interstitial cells of Cajal (ICC) (Kim et al., 2019) and a factor in maintaining ICC proliferation and growth under normal conditions (Gamage et al., 2018; Jiang et al., 2015). C-kit protein is expressed in many cells in the body, including ICC and mast cells in the intestine. However, it can be used as one of ICC-specific markers because the morphology and distribution of the aforementioned cells are different. SCF, known as mast cell growth factor, is a natural ligand for the c-kit receptor (Lin et al., 2010). The SCF/c-kit signaling pathway plays an important role in the occurrence, development, and phenotype maintenance of ICC. Constipation is an external manifestation of STC, and the changes in the structure and function of ICC are microscopic changes in STC. Current animal experiments and clinical studies have proved changes in ICC during the pathogenesis of STC (62-64). Animal experiments found that the IIC of each layer in the rat colon significantly reduced and axonal degeneration appeared in the STC rat model (Zhang et al., 2012). At the same time, clinical observations also found that the number of ICCs in each layer of the sigmoid colon decreased in patients with STC. Also, the number of ICCs in the smooth muscle of the surgically resected sigmoid colon in patients with STC reduced, especially the number of ICC-SMBs (Wedel et al., 2002). The expression of c-Kit protein and mRNA decreased to varying degrees in the sigmoid colon of patients with STC compared with the normal population (Ma et al., 2020). These studies confirmed a close relationship between SCF/c-kit signaling pathway, ICC, and STC. The SCF/c-kit signaling pathway can influence the phenotype and function of ICC, and the change in ICC function will inevitably affect intestinal movement, which may eventually lead to the pathogenesis of STC. Therefore, it can be considered that the SCF/c-kit signal pathway is an important signaingl pathway in the occurrence and development of constipation and an important target of constipation treatment. Animal experiments have proved that the lactic acid bacteria isolated from Xinjiang naturally fermented yogurt can significantly regulate the SCF/c-kit signal pathway, thus inhibiting constipation (Mu et al., 2020; Gan et al., 2020). Therefore, it can be judged that the lactic acid bacteria isolated from Xinjiang naturally fermented yogurt can intervene constipation through this target; it may be the most important way to cause intestinal protection and inhibit constipation.

In addition, GDNF plays an important role in constipation. It stimulates the intestinal CNS and is an important factor in regulating gastrointestinal motility (Xie et al., 2020). Stimulating transient receptor potential vanilloid-1 (TRPV1) releases neurotransmitters through prominent globules, which can cause intestinal peristalsis disorder, affect the normal peristalsis of small intestine, cause difficulty in defecation, and cause constipation (66). Intestinal injury caused by gastrointestinal diseases can also increase the expression of TRPV1 in patients with constipation. Therefore, whether the small intestine is damaged can be judged from the expression of TRPV1 (Liu et al., 2019). In the study of intestinal diseases, the changes in the SCF/c-kit signaling pathway also affect the expression of GDNF and TRPV1. The regulation of the expression of these two proteins by lactic acid bacteria isolated from naturally fermented yogurt in Xinjiang also shows synchronous changes with the SCF/c-kit signal pathway (Mu et al., 2020; Gan et al., 2020). Therefore, it can also be considered that the SCF/c-Kit signaling pathway also directly or indirectly affects the expression of GDNF and TRPV1.

Endothelial dysfunction can lead to inflammatory response, and the low bioavailability of NO is an important factor leading to endothelial dysfunction (Ballak et al., 2020). Nitric oxide synthase (NOS) is the only rate-limiting enzyme in the process of NO synthesis. The change in its activity can directly affect the production and biological effects of NO. NOS is involved in regulating gastrointestinal motility. Abnormal NOS leads to an imbalance in the NO level, affects intestinal function, and leads to constipation; a large amount of NO can cause gastrointestinal peristalsis. Three different subtypes of NOS exist: NOS1 (nNOS), NOS2 (iNOS), and NOS3 (eNOS) (Ishizuka et al., 2019). Under normal physiological conditions, NO in vascular endothelial cells mainly comes from eNOS, and its main function is to regulate normal physiological functions. The expression of nNOS decreases significantly in the small intestine of constipated animals. In the quiescent state, iNOS is not expressed, but it can lead to the production of a large number of iNOS and NO in various pathological states (Givvimani et al., 2012). Therefore, controlling the expression of NOS can effectively reduce the content of NO, which is a feasible method to control constipation. The lactic acid bacteria isolated from naturally fermented yogurt in Xinjiang also had a significant impact on the expression of NOS. It can also be judged that these lactic acid bacteria can regulate the expression of NOS and protect the intestine.

6 Conclusions

Lactic acid bacteria isolated from naturally fermented yogurt in Xinjiang, China, have a strong intervention effect on constipation. Besides the conventional intestinal regulation of most probiotics, they can inhibit constipation by regulating the SCF/c-kit signaling pathway and NOS expression. These two aspects of lactic acid bacteria are important in their role as probiotics. The Xinjiang region of China is rich in natural fermentation products and high-quality yogurt. Among these, microbial resources have strong biological activity. Some probiotics have a good constipation-inhibitory effect and hence may be of value in in-depth research and development. This review provided valuable information for researchers.

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