The current research status and progress of the impact of Lactobacillus on intestinal diseases.

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Abstract

In recent years, the application of probiotics has garnered increasing attention. This surge in interest is largely attributed to an expanding body of research revealing the positive role of probiotics in enhancing human health. Specifically, the gut microbiome—a complex ecosystem dominated by bacteria—exerts significant influence on host health through microbial interactions and inter-species crosstalk. Despite Lactic Acid Bacteria (LAB) constituting a relatively minor proportion of the gut microbiome, numerous studies have confirmed their pivotal role in intestinal health. Historically, LAB have been integral to foods and pharmaceuticals, exhibiting beneficial effects on various human body systems. For instance, certain strains of LAB are involved in addressing neurological issues through the microbiota-gut-brain/liver/lung axis, highlighting their probiotic characteristics. However, in-depth research into the intrinsic mechanisms of LAB, along with assessments of their dietary safety and scientific value, remains imperative. A deeper understanding of how LAB influences and modulates the molecular mechanisms of intestinal diseases will aid in the development of innovative microbial therapeutic strategies in biology and medicine. This paper aims to review the latest research advancements in LAB's promotion of intestinal health.

Introduction:

Lactic Acid Bacteria (LAB) constitute a homogenous group characterized predominantly by lactic acid production through carbohydrate fermentation. These Gram-positive and catalase-negative microorganisms mainly originate from the Lactobacillales order. LAB exhibit adaptability across diverse environments, thriving in temperatures ranging from 10 to 45 and salt concentrations up to 6.5% NaCl(Garbacz, 2022).

The fermentation types of LAB can be classified into homolactic and heterolactic. The former primarily produces lactic acid, while the latter synthesizes additional products such as acetic acid, alcohol, and carbon dioxide(Zúñiga, Pardo, & Ferrer, 1993). As ubiquitous microorganisms, LAB are widespread in milk, dairy products, plant-derived materials, fermented dairy, vegetables, meat and fish products, sourdough, silage, and fermented beverages(Klaenhammer, 1988). Additionally, they colonize various habitats within humans and animals, such as the oral cavity, ileum, colon, and vagina in females, and the gastrointestinal tracts of fish, amphibians, reptiles, and birds(Garbacz, 2022).

In the food industry and biotechnology sector, Lactic Acid Bacteria (LAB) represent one of the most pivotal microbial groups, commonly employed as fermenting agents in dairy products and fermented plant-derived products(Walter, 2008). Beyond enhancing the flavor and texture of products, LAB inhibit the growth of spoilage-causing bacteria by synthesizing lactic acid and reducing environmental pH. Additionally, LAB produce other antimicrobial substances including bacteriocins, hydrogen peroxide, and diacetyl(De Vuyst & Leroy, 2007). Due to their health benefits, LAB have been designated as "Generally Recognized As Safe" (GRAS) and are extensively utilized in dairy products(Naidu, Bidlack, & Clemens, 1999; Tachedjian, Aldunate, Bradshaw, & Cone, 2017).

LAB are a key component of the human gut microbiome. An adult's intestine houses a complex ecosystem, with approximately 10^12 microbes per gram of intestinal content, encompassing around 1000 different species(Sekirov, Russell, Antunes, & Finlay, 2010). The colonization of gut bacteria begins immediately after birth and continues for several years, with its final composition being influenced by various factors, leading to an individual-specific microbiota. LAB in the gut exhibit significant metabolic and enzymatic activities, participating in the metabolism of exogenous and endogenous compounds and synthesizing various bioactive substances. Their main characteristics include the ability to adhere to mucosal surfaces and colonize intestinal crypts without posing infection risks, and self-regeneration in disturbed conditions (e.g., antibiotic treatment)(Reid & Burton, 2002).

The impact of LAB on the immune system is primarily associated with their specific activation of Pattern Recognition Receptors (PRRs) on the surface of intestinal cells and dendritic cells, particularly Toll-like Receptors (TLRs). These receptors recognize LAB-specific Microbial Associated Molecular Patterns (MAMPs), triggering intracellular signaling responses, especially the NF-kB transcription factor, which then synthesizes endogenous antimicrobial factors, defensins, pro-inflammatory cytokines, and chemokines(Rakoff-Nahoum, Paglino, Eslami-Varzaneh, Edberg, & Medzhitov, 2004).

The stability of the gut microbiota is linked to the development of tolerance in the gut immune system. LAB, a commonly used probiotic, constitutes 6% of the total bacteria in the human duodenum and 0.3% in the colon(Almonacid et al., 2017; Nistal et al., 2016). The prevalence of Lactobacillus genus and species varies significantly across different host intestines, reflecting specific health needs(L. Wang et al., 2020; Zorron Cheng Tao Pu et al., 2020). Certain LAB strains can improve biological processes, such as pathogen clearance(Stones & Krachler, 2016; Ternent, Dyson, Krachler, & Jabbari, 2015), enhancement of intestinal barrier function(Z. Liu et al., 2011; S. Wang et al., 2020), immunomodulation(H. Gill & Prasad, 2008), anti-cancer activity(Uccello et al., 2012), and modulation of host metabolism(Y. Liu et al., 2020). Furthermore, LAB play a crucial role in preventing or ameliorating intestinal diseases like diarrhea(Gutierrez-Castrellon et al., 2014), inflammatory bowel disease(Zocco et al., 2006), and irritable bowel syndrome(Martoni, Srivastava, & Leyer, 2020; Seong et al., 2020; Skrzydło-Radomańska et al., 2020).Animal and clinical studies of different lactic acid bacteria strains in alleviating different intestinal inflammatory diseases are summarized in Table 1(Supplementary material:Table 1).

1. Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD), encompassing Ulcerative Colitis (UC) and Crohn's Disease (CD), represents a group of chronic mucosal immune-related disorders(Molodecky et al., 2012; Ng et al., 2017). UC affects the entire gastrointestinal tract, while CD primarily targets the intestinal epithelium(Francescone, Hou, & Grivennikov, 2015). The exact etiology of IBD remains elusive, yet it's known to involve multiple factors, including intestinal barrier dysfunction, pathogen invasion, oxidative stress, abnormal immune responses, and altered levels of inflammatory mediators(Goyal, Rana, Ahlawat, Bijjem, & Kumar, 2014; Yulan Liu et al., 2017; Ng et al., 2017; Schreiber et al., 1991). IBD predominantly manifests as diarrhea, rectal bleeding, ulcers, anemia, and weight loss, potentially leading to severe complications such as colorectal cancer(Beaugerie & Itzkowitz, 2015). Traditional treatments, such as aminosalicylates, steroids, immunomodulators, and biologics, are widely used for IBD management but offer limited efficacy and potential adverse effects like infections, fever, allergies, and hepatorenal syndrome(Celiberto et al., 2018; Feuerstein, Akbari, Tapper, & Cheifetz, 2016; Guidi, Pugliese, & Armuzzi, 2011). Given the high recurrence rate of IBD, the development of new dietary-based therapeutic approaches with fewer side effects and better preventive outcomes is crucial(Burisch & Munkholm, 2015).

Against this backdrop, extensive research has focused on assessing the potential value of probiotics in IBD treatment, with Lactobacilli and Bifidobacteria being the most extensively studied genera(Gionchetti et al., 2000; Leccese et al., 2020). The intestinal epithelial barrier, composed of Intestinal Epithelial Cells (IECs) and tight junctions, segregates the luminal microbiota from the sterile underlying layer, maintaining intestinal balance and preventing infection(Slifer & Blikslager, 2020). IECs can recognize specific components of pathogens, triggering downstream anti-infection inflammatory pathways(Takeuchi & Akira,

2010). For instance, TLR4 on endothelial cell surfaces recognizes lipopolysaccharides, subsequently initiating rapid activation of NF-ϰB and thus promoting the synthesis of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6(Bruno et al., 2009). Studies have shown that probiotics, by inhibiting TLR4/NF-ϰB and PI3K/Akt/NF-ϰB signaling pathways, reduce pro-inflammatory cytokines (such as TNF-α and IL-1β) and increase anti-inflammatory factors like IL-10, thereby aiding in the maintenance of UC remission(Shen et al., 2018). Additionally, activation of NF-ϰB can enhance NLRP3 transcription(He, Hara, & Núñez, 2016). The NF-ϰB signaling pathway plays a crucial role in regulating stimuli signals and cytokines, serving as a central mediator in inflammatory responses(Barnabei, Laplantine, Mbongo, Rieux-Laucat, & Weil, 2021). The NLRP3 inflammasome, an essential component of the immune system, counters microbial infection by regulating Caspase-1 activation and pro-inflammatory cytokines IL-1β/IL-18 secretion(Kelley, Jeltema, Duan, & He, 2019). However, overexpression of NLRP3 can lead to inflammatory diseases. Studies have discovered that inhibiting the NLRP3 inflammasome can alleviate issues caused by endothelial gap junction dysfunction(Xing Zhou et al., 2019). The activation of the NLRP3 inflammasome can be regulated by upstream NF-ϰB signaling pathways or directly activated by intracellular toxins perceived by Caspase (Caspase-4 and Caspase-5 in humans, Caspase-11 in mice)(He et al., 2016). Experiments found that Lactobacillus ATCC 393 and its metabolites alleviate ulcerative inflammation in the intestines of mice through the NLRP3-Caspase-1/IL-1β signaling pathway(Dou et al., 2021).

Extensive literature has confirmed that Lactic Acid Bacteria (LAB) positively impact Inflammatory Bowel Disease (IBD) by improving the intestinal mucosal barrier, regulating the gut microbiota, and modulating immune pathways. Studies on animal models of intestinal inflammation induced by Dextran Sulfate Sodium (DSS) have revealed the significant effects of various Lactobacillus species, such as Lactobacillus plantarum(Ding, Yan, Fang, Jiang, & Liu, 2021; Hu et al., 2021; Khan et al., 2022; Pan et al., 2021; Y. Wu et al., 2022), Lactobacillus rhamnosus(Han, Liao, Si, Bai, & Gai, 2022; Yeo et al., 2020), Lactobacillus acidophilus(Hu, Wang, Xiang, Mu, & Zhao, 2020; W.-K. Kim et al., 2021), Lactobacillus casei(W.-Q. Zhang et al., 2022), Lactobacillus salivarius(Iyer et al., 2022), Bifidobacterium bifidum(Xun et al., 2022), Lactobacillus curvatus(X. Wang, Li, Meng, Kim, & Oh, 2022), Lactobacillus reuteri(G. Wang, S. Huang, et al., 2020), and fermented whey prepared by Lactobacillus fermentum(Kaur, Gupta, Kapila, & Kapila, 2022), in improving the intestinal mucosal barrier, reducing inflammation, improving the Disease Activity Index (DAI), inflammatory factors, histopathological scoring, and the transcriptional expression of tight junction genes. Additionally, these lactobacilli can reduce oxidative stress, restore gut microbiota diversity, and increase the abundance of bacteria associated with Short Chain Fatty Acid (SCFA) production. Research by Meiling Liu and colleagues first reported that DSS treatment significantly reduced the acetylation levels of histone H3K9, while supplementation with Lactobacillus LH23 restored the acetylation levels of histone H3K4 in the colon tissue(M. Liu et al., 2020). Moreover, certain metabolic products of LAB, such as exopolysaccharides (EPS) produced by Lactobacillus rhamnosus ZFM231, significantly increased the levels of the anti-inflammatory factor Transforming Growth Factor-β in colonic cells of mice, while significantly reducing the levels of the pro-inflammatory factor Tumor Necrosis Factor-α(C. Wan et al., 2022).

Intestinal epithelial tight junctions (TJs) are the uppermost connecting complexes, acting as functional and structural barriers against harmful luminal antigens and preventing intestinal inflammation(Kaminsky, Al-Sadi, & Ma, 2021). Defects in the intestinal epithelial TJ barrier or increased intestinal permeability due to intestinal leakiness are key pathogenic factors in Inflammatory Bowel Disease (IBD) and other intestinal inflammatory conditions, such as necrotizing enterocolitis and celiac disease(Turner, 2006). Clinical studies have found that persistently increased intestinal permeability in IBD patients after clinical remission may indicate poor clinical outcomes and early relapse of the disease. Normalization of intestinal permeability is associated with sustained long-term clinical remission(Berezov, Pinskiĭ, & Bratslavskiĭ, 1975). Increasing evidence suggests that defects in the intestinal TJ barrier play a crucial role in exacerbating and prolonging intestinal inflammation in IBD. Studies have discovered that a particular strain of Lactobacillus acidophilus LA1 significantly enhances the function of the intestinal TJ barrier. LA1 attaches to the apical membrane of intestinal epithelial cells in a TLR-2 dependent manner, causing a rapid increase in TLR-2 membrane expression and strengthening the intestinal TJ barrier function through TLR-2/TLR-1 and TLR-2/TLR-6

heterotypic complex formation. Oral administration of LA1 rapidly strengthens the intestinal TJ barrier in mice, counteracts the increase in intestinal permeability caused by DSS, and prevents DSS-induced colitis in a TLR-2 and intestinal TJ barrier-dependent manner(Al-Sadi et al., 2021).

The NF-κB signaling pathway is widely considered a central pathway in the pathogenesis of Inflammatory Bowel Disease (IBD)(McDaniel, Eden, Ringel, & Allen, 2016). Under physiological conditions, inhibition of this pathway is achieved through proteasomal degradation and the regulation of the phosphorylation stability of IκB-α (Inhibitor of κB-α)(Kanarek, London, Schueler-Furman, & Ben-Neriah, 2010; McConkey & Zhu, 2008). Recent studies have shown that certain Lactic Acid Bacteria (LAB) effectively ameliorate intestinal inflammation in mice induced by Dextran Sulfate Sodium (DSS) by inhibiting the NF-κB signaling pathway. For instance, treatment with the Lactobacillus casei Shirota strain (LcS) significantly inhibits NF-κB activation and enhances the stability of its inhibitor IκB-α(Wong et al., 2022). Fermented lactobacillus ZS40 reduces the mRNA and protein expression of NF-κB p65, IL-6, and TNF-α, while upregulating IκB-α expression(Z. Chen et al., 2021). Additionally, Lactobacillus plantarum and Lactobacillus rhamnosus modulate gene expression related to the NF-κB signaling pathway, improving intestinal inflammation(Y. Li et al., 2020; Yu, Ke, Guo, Zhang, & Li, 2020).Lactobacillus Royale stimulated the proliferation of intestinal epithelial cells to repair epithelial damage by increasing the expression of R-responsive proteins, thereby activating the Wnt/β-catenin pathway, which reduced pro-inflammatory cytokine secretion in the intestines and the concentration of LPS in the serum, and furthermore, the activation of the Wnt/β-catenin pathway induced the differentiation to Paneth cells. Corroborating that LAB is effective in maintaining intestinal epithelial regeneration and homeostasis as well as repairing intestinal damage after pathological injury, and is therefore a promising alternative treatment for intestinal inflammation(Wu et al., 2020).

Patients with colitis exhibit changes in the composition of intestinal metabolites, particularly lower levels of Short Chain Fatty Acids (SCFAs) compared to normal controls(Jing et al., 2018; K.-Y. Sun et al., 2017; Mingming Sun, Wu, Liu, & Cong, 2017). SCFAs, such as acetate, propionate, and butyrate, are products of the gut microbial community's metabolism of fibrous materials and are crucial for various host functions, including fluid absorption, energy provision, mucosal epithelial cell protection, regulation of T-regulatory cell differentiation, and alleviation of inflammatory responses through the G-protein-coupled receptor 43 signaling pathway(Arpaia et al., 2013; Furusawa et al., 2013; Maslowski et al., 2009; Scheppach, 1994). Lactobacillus acidophilus plays a regulatory role in the production of SCFAs, aiding in the improvement of intestinal barrier dysfunction by activating the NLRP3 inflammasome pathway. Additionally, PCR analysis reveals that the regulation of SCFA production by Lactobacillus acidophilus may be achieved through the activation of G-protein-coupled receptors(P. Li et al., 2022).

In the Dextran Sulfate Sodium (DSS) induced colitis model, an increase in the expression of Toll-like receptors (TLRs) was observed compared to the control group(Jawhara & Poulain, 2007). Studies indicate that TLR2 must form a heterodimer with TLR1, where TLR2/TLR1 promotes inflammatory immune responses, while TLR2/TLR6 induces Treg responses(DePaolo et al., 2012; Netea, van de Veerdonk, Verschueren, van der Meer, & Kullberg, 2008). The TLR-mediated PI3K/Akt signaling pathway plays a crucial role in cell cycle regulation and proliferation of intestinal epithelial cells(Way et al., 2016). Moreover, the improvement in connexin expression is closely related to the activation of the Akt signaling pathway, which mediates protein synthesis in intestinal epithelial cells(Hao Wang et al., 2015). Lactobacillus acidophilus PIN7, through regulating the immunomodulatory TLR6 signal and the composition of the gut microbiome, ameliorates colitis induced by DSS(Kye et al., 2022).

Treg cells are a subset of T cells with negative immunoregulatory functions.Treg cells play a crucial role in maintaining immune balance and inducing peripheral immune tolerance.Treg cells can participate in inflammation in vitro through cell contact-dependent mechanisms.Treg cells can also participate in the pathogenesis of UC by regulating the release of inhibitory cytokines (such as IL-10), and a decrease in their number or dysfunction can lead to the occurrence of the disease(Haribhai, Chatila, & Williams, 2016; Jang et al., 2019; Zou, He, & Chen, 2019).Juan Huang et al. found that Lactobacillus paracasei R3 exerts a protective effect against DSS-induced colitis in mice by modulating the balance between Th17 and Treg

cells(Huang et al., 2021). Certain Lactobacillus plantarum also improve colitis by modulating mouse T cells(D. H. Kim et al., 2020).

The JAK-STAT signaling pathway plays a crucial role in both innate and adaptive immunity, participating in cellular processes such as growth, survival, and migration(Olivera, Danese, & Peyrin-Biroulet, 2017).Administration of Lactobacillus plantarum-12 can enhance immunity by activating the Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway and by upregulating the expression of mucin 2 (MUC2) protein to strengthen the intestinal barrier function affected by DSS(Mengying Sun et al., 2020).In vitro studies have also found that lactic acid bacteria can modulate the JAK/STAT signaling pathway, exhibiting anti-inflammatory effects on HT-29 cells(Aghamohammad et al., 2022).Lactobacillus paracasei L9 inhibits the IL-6/STAT3 signaling pathway by increasing the abundance of bacteria producing butyrate, thereby alleviating the development of DSS-induced colitis and offering new therapeutic targets for alleviating IBD(Deng et al., 2021).

hen lactic acid bacteria are used in combination, the improvement of symptoms related to DSS-induced colitis is more significant compared to the effect of a single lactic acid bacteria strain. Limin Xu et al. found that a probiotic consortium composed of Lactobacillus rhamnosus, Lactobacillus casei, Lactobacillus acidophilus, and Lactobacillus bifidus exhibits superior effects in inhibiting inflammation and accelerating recovery compared to those observed with the use of single strains(L. Xu et al., 2022).

LPS is an important glycoprotein derived from the outer cell membrane of Gram-negative bacteria, composed of hydrophobic (lipid A) and hydrophilic (polysaccharide O antigen and carbohydrate core) components. It can trigger pro-inflammatory reactions, causing significant relaxation and permeability of the intestinal wall, leading to "leaky gut," which further allows bacteria and their metabolites, such as toxins, to translocate to other extraintestinal organs.The binding of LPS to TLR-4 triggers the activation of mitogen-activated protein kinase (MAPK) and NF-κB pathways(Kawano et al., 2016). Lactic acid bacteria with high and low adhesive capabilities exert positive effects on immune modulation in LPS-stimulated mice(Gao et al., 2016). Ruchika Bhatia et al. evaluated the protective effects of five strains of indigenous LAB on lipopolysaccharide-induced intestinal barrier injury in C57BL/6 mouse models, finding that plant-derived lactobacilli can reduce the levels of inflammatory factors, correct dysbiosis induced by endotoxins, and enhance the expression of intestinal tight junction proteins(Bhatia, Sharma, Bhadada, Bishnoi, & Kondepudi, 2022).Compared to mice induced with LPS alone, the administration of a mixture of Lactobacillus plantarum (Lactobacillus plantarum KLDS 1.0318, Lactobacillus plantarum KLDS 1.0344, and Lactobacillus plantarum KLDS 1.0386) significantly increased the numbers of immune cells (CD4+ T cells, IgA plasma cells) and the expression of tight junction proteins (Claudin1 and Occludin), while downregulating intestinal protein expression of TLR4, P-IκB, and NF-κB p65, leading to a marked improvement in intestinal injury(J. Dong et al., 2022).

In a C57BL/6J mouse model induced by Citrobacter rodentium, it was shown that administration of Lactobacillus johnsonii effectively modulates the mice's inflammatory response and endoplasmic reticulum stress, thereby alleviating colitis caused by Citrobacter rodentium(Y. Zhang et al., 2021). Additionally, the Lactobacillus acidophilus strain BIO5768 not only improves colitis induced by Citrobacter rodentium but also shows efficacy in colitis induced by 2,4,6-Trinitrobenzenesulfonic Acid (TNBS)(Hrdý et al., 2022).

To further explore the mechanisms of lactic acid bacteria in intestinal inflammation, extensive in vitro studies have been conducted. In caco-2 intestinal epithelial cells exposed to Escherichia coli, an increase in pro-inflammatory cytokines such as IL-8, TNF-α, IFN-γ, and IL-23 was observed. Interventions with Lactobacillus fermentum MTCC-5898 and Lactobacillus rhamnosus MTCC-5897 demonstrated the ability to modulate cytokines, including IL-10 and TGF-β, pattern recognition receptors TLR-2 and TLR-4, and the transcriptional expression of genes related to key inflammatory regulators NF-κB and SIGIRR, thus reducing the inflammatory response induced by Escherichia coli(T. Gupta, H. Kaur, S. Kapila, & R. Kapila, 2021; Taruna Gupta, Harpreet Kaur, Suman Kapila, & Rajeev Kapila, 2021). The intervention of Lactobacillus plantarum in IPEC-1 intestinal cells of pigs exposed to Escherichia coli was found to inhibit the inflammatory response in IPEC-1 cells by modulating the MAPK and NF-κB signaling pathways(J. Yang et al., 2021). In caco-2 cells induced by Lipopolysaccharides (LPS), significant increases in reactive oxygen species (ROS),

lactate dehydrogenase, and inflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α were observed. Intervention with Lactobacillus rhamnosus CY12 at a concentration of 10ˆ8 cfu/mL significantly alleviated cell toxicity, apoptosis, oxidative stress, and expression of pro-inflammatory cytokines, and inhibited the TLR4/NF-ϰB signaling pathway. Additionally, gene expression of antioxidant enzymes and mRNA and protein expression of Tight Junctions (TJs) proteins were significantly improved(Zheng et al., 2022).

2.Colorectal Cancer

Colorectal cancer is a malignancy with high incidence and mortality rates, posing a significant threat to human health and life(Arnold, 2018). It ranks third in cancer incidence among both men and women globally(Tang & Evans, 2021). In China, there are up to 400,000 new cases of colorectal cancer annually, with about 10 million new cases worldwide each year(S.-N. Jia, Han, Yang, & Yang, 2022). Early stages of colorectal cancer may present no noticeable symptoms, while advanced stages may manifest as abdominal bloating, indigestion, changes in bowel habits, abdominal pain, or blood in the stool(Pacal, Karaboga, Basturk, Akay, & Nalbantoglu, 2020). Some patients with colorectal cancer can be treated surgically, though the risks are high and postoperative complications can be severe(Wahab, Alshahrani, Ahmad, & Abbas, 2021).

Inflammation is a natural defense response to injury, but uncontrolled chronic inflammation is closely linked to the development and metastasis of cancer(Schmitt & Greten, 2021). Inflammatory diseases such as colitis, pancreatitis, and hepatitis are associated with increased risks of colorectal, pancreatic, and liver cancers, respectively. Clinical investigations have shown that many cancer patients have a history of chronic inflammatory diseases(Beckmann et al., 2019). Generally, the gut microbiota plays a crucial role in protecting the colon, but when its population is reduced by more than 50%, its ability to defend against carcinogens is compromised(Xueyan Zhou et al., 2020). Gut microbes regulate intestinal health through the release of metabolites, and dysbiosis is a characteristic of colorectal cancer (CRC), leading to inflammation, tumor growth, and treatment responses(Bell et al., 2022). Clinical studies suggest a potential correlation between ulcerative colitis and colorectal cancer, with inflammatory cells found in tumor biopsy specimens(Q. Wang et al., 2021). Research indicates that long-term consumption of DSS solution can cause colitis, and the intake of lactic acid bacteria shows preventive effects against DSS-induced colorectal cancer(C. Z. Wang et al., 2018). Probiotics have anti-cancer effects, functioning through the production of anti-cancer compounds, enhancing the immune system, improving the intestinal barrier, inhibiting cancer cell proliferation, and inducing apoptosis. Potential mechanisms of probiotics may include altering the gut microbiome, lowering intestinal pH, and changing tumor metabolism, such as producing Short Chain Fatty Acids (SCFAs) and conjugated fatty acids(C.-C. Chen et al., 2012).

The combined stimulation of AOM and DSS can induce colorectal cancer(Jeon et al., 2018). Lactic acid bacteria show various forms of resistance to colorectal cancer, including live and dead strains, strain components, and metabolic products of live strains. Research focusing on inducing apoptosis in colorectal cancer cells using lactic acid bacteria has become a hot topic. Under the influence of pro-inflammatory factors and tumor necrosis factors, the NF-ϰB signaling pathway regulates the expression of various genes, such as interleukin 2 related genes and downstream apoptotic factors, thereby increasing the immune evasion capabilities of pre-cancerous cells. Therefore, chronic inflammation is considered a triggering factor for tumorigenesis, with NF-ϰB playing a vital role in the development of inflammatory tumors. Research has confirmed that Lactobacillus fermentum ZS40 can reduce the expression of TNF-α and IL-1β, as well as the expression of key proteins IϰBα and p65 in the NF-ϰB signaling pathway, leading to a decrease in the expression of target protein COX-2 and reducing levels of colorectal cancer markers CD34 and CD117, thereby decreasing the number of histological abnormalities in colon tissue(J. Liu, Wang, Yi, Long, & Zhao, 2022). Furthermore, studies have found that Lactobacillus acidophilus KLDS1.0901 inhibits the proliferation of HT-29 and Caco-2 cells in a dose-dependent manner, associated with the NF-ϰB and PI3K-AKT signaling pathways(Yue et al., 2021). Yuanchun Yue and colleagues discovered that the Lactobacillus plantarum strain YYC-3 significantly inhibits two types of colorectal cancer cell lines (HT-29 and Caco2). In vivo studies revealed that strain YYC-3 prevents colorectal tumors and mucosal damage in APCMin/+ mice on a high-fat diet, inhibiting

the activation of NF-ϰB and Wnt signaling pathways and restoring the altered gut microbiome composition to resemble that of wild-type mice(Yuanchun Yue et al., 2020).

In the colorectal cancer mouse model induced by Azoxymethane (AOM) and Dextran Sulfate Sodium (DSS), extensive research has confirmed the anti-cancer abilities of Lactic Acid Bacteria (LAB). Specifically, the treatment with Bulgarian Lactobacillus and fermented Lactobacillus V3 significantly inhibited the overall volume and average size of tumors and alleviated the clinical symptoms of intestinal inflammation. This resulted in decreased levels of IL-6, TNF-α, IL-17, IL-23, and IL-1β in the intestines and tumors, thereby demonstrating these LAB's ability to modulate inflammatory responses and prevent colon cancer(Chou, Ho, Chen, Wu, & Pan, 2020; Silveira et al., 2020).

Lactobacillus rhamnosus LS8 and rod-shaped Lactobacillus MXJ32 were effective in inhibiting tumor formation. Additionally, LAB enhanced the intestinal barrier by preventing the loss of goblet cells and promoting the expression of tight junction proteins ZO-1, occludin, and claudin-1. LAB also improved imbalances in the gut microbiome, which favored the growth of beneficial bacteria like Faecalibaculum and Akkermansia, leading to an increase in Short Chain Fatty Acids (SCFAs) and a decrease in Lipopolysaccharides (LPS). Furthermore, LAB alleviated intestinal inflammation by suppressing the TLR4/NF-ϰB signaling pathway, pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-6, IL-γ, and IL-17a), and chemokines (such as Cxcl1, Cxcl2, Cxcl3, Cxcl5, and Cxcl7)(T. Wang, L. Zhang, et al., 2022; T. Wang, J. Zheng, et al., 2022).

Lactobacillus rhamnosus M9 inhibited the formation of tumors in the colon by regulating the intestinal environment and improving inflammation(H. Xu et al., 2021). Early colonization of Lactobacillus rhamnosus GG (LGG) might influence the diversity of intestinal tumors by inhibiting the Wnt signaling and promoting tumor cell apoptosis(X. Liu et al., 2022). The supernatant of Lactobacillus rhamnosus also exhibited anti-cancer effects, inhibiting the growth of HT-29 cancer cells in a dose- and time-dependent manner, leading to the upregulation of pro-apoptotic genes such as caspase-3, caspase-9, and Bax, and downregulation of Bcl2 and cell cycle genes cyclin D1, cyclin E, and ERBB2(Dehghani, Tafvizi, & Jafari, 2021).

In the rat colorectal cancer model induced by Dimethylhydrazine (DMH), it was confirmed that the administration of Lactobacillus casei X12 and DTA81 could prevent severe weight loss in rats treated with DMH and also proved that the administration of Lactobacillus casei could prevent tumor incidence, cellular proliferation, and inhibit tumor growth(da Silva Duarte et al., 2020; Mousavi Jam et al., 2020). Lactobacillus salivarius Ren, isolated from centenarians in Bama, China, demonstrated anti-cancer effects in an oral cancer animal model. Oral administration of LS effectively inhibited the formation of Colorectal Cancer (CRC) induced by DMH. Furthermore, the metabolic products of LS inhibited the growth of HT-29 cells, blocked the cell cycle, and induced apoptosis. After LS treatment, phosphorylation of Protein Kinase B (AKT) and downstream proteins cyclinD1 and Cyclooxygenase-2 (COX-2) were significantly downregulated in both in vivo and in vitro tests, indicating that LS inhibits the occurrence of CRC by suppressing the AKT signaling pathway, thereby inhibiting cell proliferation and inducing apoptosis(Y. Dong, Zhu, Zhang, Ge, & Zhao, 2020).

Formyl Peptide Receptors (FPR1, FPR2, and FPR3) are innate immune sensors for pathogens and symbiotic bacteria, playing a role in the homeostasis of the colonic mucosa. Previous studies found that FPR1 is a tumor suppressor in gastric cancer cells, as it maintains anti-angiogenic inflammatory responses. Research shows that Lactobacillus rhamnosus GG can promote intestinal epithelial homeostasis and subsequent MAPK signaling activation through FPR1, and observed pro-degradative, anti-angiogenic, and homeostatic functions in colorectal cancer cell lines(Liotti et al., 2022).

4. Intestinal Damage Caused by Pathogens or Harmful Substances

Salmonella typhimurium, a Gram-negative bacterium capable of intracellular replication, is a significant zoonotic pathogen causing intestinal infectious diseases worldwide(Ferrari et al., 2019). This strain disrupts the tight junctions of Intestinal Epithelial Cells (IECs), facilitating its invasion and spread, and eliciting strong inflammatory responses(N. Dong et al., 2020). Enteric Salmonella not only resides in animals but is also common in humans, causing symptoms like fever, intestinal inflammation, and diarrhea(G.-Y. Yang

et al., 2017). Given the rise in multi-drug resistance and limitations of antibiotic treatments(Ungaro et al., 2014), probiotics have emerged as an effective alternative for the prevention and treatment of Salmonella infections.

In piglet diarrhea models and Caco-2 cell models, Lactobacillus johnsonii L531 has demonstrated the ability to alleviate intestinal structural and ultrastructural damage caused by enteric Salmonella. Post-infection, there is a significant increase in the expression of NOD (Nucleotide-binding Oligomerization Domain) pathway-related proteins (such as NOD1/2, RIP2), autophagy-related key proteins (like ATG16L1, IRGM), and endoplasmic reticulum stress markers (such as GRP78, IRE1). Pretreatment with Lactobacillus johnsonii L531 effectively mitigates intestinal damage caused by enteric Salmonella through inhibiting the activation of the NOD pathway, modulating endoplasmic reticulum stress, and promoting autophagic degradation(L. Yang et al., 2022).

Salmonella is a common pathogen causing gastroenteritis and systemic infections in chickens(Yingyu Liu et al., 2021). Lactobacillus rhamnosus significantly reduces the diarrhea rate in chicks infected with Salmonella typhimurium, improving daily weight gain and survival rates. It enhances intestinal mucosal immunity by reducing cell apoptosis and effectively suppresses intestinal inflammation. The strain also balances the expression of IL-1β and IL-18, mitigates levels of endotoxins and D-lactic acid, and expands the levels of tight junction proteins like Zonula occludens-1 and Claudin-1, enhancing the functionality of intestinal mucosal epithelial cells(Peng et al., 2022).

In a C57BL/6 mouse model infected with Salmonella typhimurium, Lactobacillus rhamnosus reduces weight loss, mortality, and intestinal inflammatory responses caused by the pathogen. Moreover, it limits the spread of Salmonella typhimurium to the liver and spleen. The strain is found to offer protection against Salmonella typhimurium infection by modulating M1 macrophage polarization(Duan et al., 2021). Lactobacillus acidophilus increases the survival rate of infected mice and reduces the secretion of TNF-α. Additionally, Lactobacillus acidophilus mitigates the overexpansion of goblet and Paneth cells induced by Salmonella typhimurium, preventing over-depletion and improving the pathogen's excessive activation of the Wnt/β-catenin pathway, thereby affecting epithelial proliferation(X. Lu, Xie, Ye, Zhu, & Yu, 2020).

Lactobacillus reuteri SLZX19-12, isolated from Tibetan pig feces and sensitive to common antibiotics, exhibits strong resistance. Mice pretreated with a high dose of SLZX19-12 and then challenged with Salmonella typhimurium SL1344 show disrupted colonic microbiota, colon inflammation, and potential apoptosis due to the S100A8/S100A9-NF-kB pathway, with pathogen translocation to extraintestinal organs. However, post-treatment, the internal organs have lower Salmonella loads, less colon inflammation, and higher barrier integrity. Importantly, Lactobacillus reuteri SLZX19-12 stabilizes the colonic microbial ecosystem(J. Wu et al., 2022).

In the IPEC-J2 cell model infected with Salmonella typhimurium, Lactobacillus johnsonii L531 (Lactobacillus johnsonii L531) alleviates tight junction damage induced by the pathogen by inhibiting the TLR4/NF-ϰB/NLRP3 inflammasome signaling pathway, enhancing the expression of ZO-1, Occludin, and Claudin-1(S. Chen et al., 2021).

The high-altitude environment, characterized by low air pressure and low oxygen levels, profoundly impacts organ physiology and state, posing a significant challenge(Z. Jia et al., 2020; Wen, Zhang, Nie, Zhong, & Sun, 2014). Early studies indicate that the gut microbiota of animals living at high altitudes is unique, aiding their adaptation to such environments(Ma et al., 2019; Z. Zhang et al., 2016). This suggests that studying gut microbiota can provide insights into altitude-related gastrointestinal issues. A novel strategy for addressing intestinal damage caused by the low-oxygen environment at high altitudes involves using probiotics to modulate the composition of the gut microbiome. Research has shown that exposing C57BL/6 mice to hypoxic conditions in a low-pressure oxygen chamber for 14 days, followed by daily administration of saline and Lactobacillus johnsonii YH1136, effectively mitigates the damage to the intestinal barrier caused by the high-altitude low-oxygen environment and reduces the likelihood of pathogen infection via the intestinal barrier, positively regulating the gut microbiome. These findings reveal the beneficial role

of Lactobacillus johnsonii YH1136 in preventing intestinal dysfunctions potentially caused by endogenous pathogens in high-altitude environments(Z. Wan et al., 2022).

Clostridioides difficile Infection (CDI) is a common hospital-acquired infection posing a significant public health threat. Vancomycin is the preferred drug for treating CDI, but its therapy is associated with recurrence rates. Lactobacillus rhamnosus, as an adjunctive therapy for gastroenteritis and diarrhea, functions by modulating immune responses and repairing the intestinal barrier. Zhengjie Wu and others developed primary and recurrent CDI models and administered Lactobacillus rhamnosus to C57BL/6 mice. The probiotic improved mortality rates, significantly reduced weight loss, and mitigated colon damage. Combined treatment with Lactobacillus rhamnosus and vancomycin inhibited the growth of enterococci and counteracted the side effects of vancomycin treatment, promoting the recovery of the intestinal microbiota. This suggests that oral administration of Lactobacillus rhamnosus has the capacity to resist primary and recurrent infections in CDI mouse models, demonstrating the potential of probiotics in treating gastrointestinal diseases(Z. Wu et al., 2022).

Clostridium perfringens, a Gram-positive, spore-forming, anaerobic rod-shaped bacterium(Hassan et al., 2015), can be isolated from natural environments (such as soil) and the intestines of humans and animals, forming part of the normal microbial community(Lindström, Heikinheimo, Lahti, & Korkeala, 2011). However, Clostridium perfringens is an opportunistic pathogen that can cause various intestinal diseases under certain conditions, such as overgrowth or disruption of the gut microbiota(Charlebois, Jacques, Boulianne, & Archambault, 2017). Clostridium perfringens secretes various toxins or enzymes, which are its primary virulence factors. Studies have reported that probiotics, especially lactobacilli, provide protection against Clostridium perfringens infections in vivo and in vitro. For instance, Lactobacillus acidophilus and Lactobacillus fermentum inhibit the growth and alpha-toxin production of Clostridium perfringens in vitro(Guo et al., 2017). In Clostridium perfringens-infected porcine intestinal epithelial cell lines (IPEC-J2), Lactobacillus plantarum Lac16 significantly inhibits the growth of Clostridium perfringens, accompanied by a decrease in pH level, reducing the adherence of Clostridium perfringens to IPEC-J2 cells, alleviating cell toxicity, and intestinal barrier damage caused by Clostridium perfringens. Furthermore, Lactobacillus plantarum Lac16 significantly suppresses the expression of pro-inflammatory cytokines and Pattern Recognition Receptors (PRRs) genes induced by Clostridium perfringens in IPEC-J2 cells(W. Wang et al., 2022).

In the treatment of tuberculosis, isoniazid (H) and rifampin (R) are the main anti-tuberculosis drugs, known for their specific identification and effective elimination of Mycobacterium tuberculosis(Suárez et al., 2019). However, as antibiotics, these drugs may cause gastrointestinal adverse reactions, a common issue in anti-tuberculosis treatment, including symptoms such as nausea, vomiting, indigestion, loss of appetite, and diarrhea, with an incidence rate ranging from 3.45% to 29.4%(El Hamdouni et al., 2020; Farazi, Sofian, Jabbariasl, & Keshavarz, 2014). Antibiotic-induced gastrointestinal adverse reactions are primarily related to the disruption of the gut microbiota(Dethlefsen, Huse, Sogin, & Relman, 2008). Lactobacillus casei can prevent intestinal damage caused by anti-tuberculosis drugs by regulating the gut microbiome and the metabolism of short-chain fatty acids and restore the reduction in goblet cell numbers and low expression of MUC2 caused by anti-tuberculosis drugs(Y. Li et al., 2022).

Necrotizing enterocolitis (NEC) is among the gastrointestinal diseases with the highest morbidity and mortality rates, primarily affecting neonates, especially preterm infants weighing less than 1000 grams, with an incidence rate of approximately 15% to 20% (Battersby, Santhalingam, Costeloe, & Modi, 2018)and an average mortality rate of 15% to 30%, reaching as high as 75% to 85% in the most severe cases(P. W. Lin, Nasr, & Stoll, 2008). Cronobacter sakazakii, a conditional pathogen related to severe outbreaks of NEC in preterm and full-term infants, suggests its potential role in the pathogenesis of NEC(Henry & Fouladkhah, 2019). Currently, due to the potential of probiotics in preventing and treating NEC, they have garnered significant attention(Seghesio, De Geyter, & Vandenplas, 2021). Early use of probiotics can improve intestinal health, promote intestinal development, and alleviate intestinal damage by promoting intestinal motility and absorption, enhancing intestinal barrier integrity, stimulating the maturation of the immune system, and balancing the gut microbiota. Probiotics antagonize pathogens directly (by competing for nutrients or

epithelial adhesion sites) or indirectly (by releasing metabolic products like organic acids). Clinical studies have confirmed the beneficial effects of probiotics, including Bifidobacterium species. Novel probiotics like Lactobacillus salivarius YL20, isolated from breast milk, alleviate NEC in animal models by increasing the survival rate of neonatal mice, reducing pathological scores, and downregulating pro-inflammatory cytokines. Additionally, in vitro, this strain promotes the proliferation of intestinal epithelial Caco-2 cells, rescues damaged epithelial cells, prevents the reduction in mRNA levels of LGR5, ZO-1, and Occludin, and reverses the low expression of MUC2 induced by Cronobacter sakazakii(Y. Zhou et al., 2021).

Mycotoxins are widespread and unavoidable environmental contaminants with intestinal toxicity, immunotoxicity, and neurotoxicity, posing a severe threat to human and animal health(Robert et al., 2017; C. Yang, Song, & Lim, 2020). Deoxynivalenol (DON) is one of the most common and hazardous mycotoxins. Acute exposure to DON in various animal species leads to vomiting, while long-term exposure to low doses of DON can cause anorexia and weight loss(L. Chen, Peng, Nüssler, Liu, & Yang, 2017). Exposure to DON may also induce intestinal inflammation, damage the integrity of the intestinal barrier, and reshape the gut microbiome. In a piglet model contaminated with DON, Lactobacillus rhamnosus mitigates intestinal inflammation caused by DON, primarily through inhibiting the TLR4/NF-κB signaling pathway. Additionally, the addition of Lactobacillus rhamnosus enhances the relative abundance of beneficial bacteria (such as Collinsella, Lactobacillus, Ruminococcaceae, and anaerobes), reduces the relative abundance of harmful bacteria (such as Pseudomonas and Campylobacter), and promotes the production of short-chain fatty acids(Bai et al., 2022).

5.Constipation and Diarrhea

Constipation is a globally prevalent condition with rising incidence rates, significantly impacting patients' quality of life(Daniali, Nikfar, & Abdollahi, 2020). Due to the accelerated pace of life, changes in diet and habits, as well as social and physiological factors, the prevalence of constipation is continually increasing. Insufficient dietary fiber intake is one of the main causes of constipation(S. K. Gill, Rossi, Bajka, & Whelan, 2021). There are various types of constipation, including functional constipation (FC), irritable bowel syndrome with constipation, opioid-induced constipation, and functional defecation disorders, with FC being the most common(Yoshida, Uchino, & Sasabuchi, 2022). FC is characterized by colonic functional impairment and transit abnormalities, leading to reduced intestinal transport capability and potentially causing a series of severe complications(Barberio, Judge, Savarino, & Ford, 2021). Traditional treatments for constipation primarily rely on osmotic and secretory laxatives. However, these methods often fail to cure constipation effectively, and the misuse of laxatives may damage the colonic nervous system, exacerbating constipation symptoms(Camilleri & Brandler, 2020).

The gut microbiome plays a key role in maintaining intestinal health and affects various pathophysiological activities of the host. Establishing and maintaining a beneficial balance between the gut microbiome and the human body is essential for normal intestinal function(Markowiak-Kopeć & Śliżewska, 2020). Clinically, it is suggested to alleviate constipation by using probiotics to improve the composition of the gut flora(Vriesman, Koppen, Camilleri, Di Lorenzo, & Benninga, 2020). The main mechanisms of action of probiotics include: (1) regulating the balance of the gut microbiome, whose metabolites (such as bile acids, short-chain fatty acids, hydrogen sulfide, and methane) affect intestinal motility by acting on the intestinal wall(S.-K. Kim et al., 2019); (2) participating in the production of neuroendocrine factors and gastrointestinal hormones (such as motilin, Substance P, gastrin, vasoactive intestinal peptide, and 5-hydroxytryptamine), which, along with the nervous system, regulate the movement, secretion, and absorption of digestive organs(Dinan & Cryan, 2017); Also, the gut microbiota interacts with the enteric nervous system and enteric neurotransmitters. In particular, glial cell-derived neurotrophic factors are important for innervation and ganglion cell function in the muscular layer of the colon(Morel, Domingues, Zimmer, & Michel, 2020). Transient receptor potential vanilloid 1 (TRPV1) regulates intestinal motility by mediating 5-HT release. (3) The intestinal mucosa is exposed to a large number of antigens and the intestinal microbiota., intestinal immune homeostasis depends on the synergistic action of the gut microbiome, intestinal epithelial cells, and gut-associated lymphoid tissue (GALT). Tight junction proteins, such as claudin and ZO-1(Pickard, Zeng, Caruso, & Núñez, 2017), play a

crucial role in the normal function of the intestinal mucosal barrier. Therefore, using probiotics to alter the composition of the gut microbiome is an effective approach to improve constipation. Probiotics exert their effects by influencing the composition and/or activity of the gut microbiome and have been proposed as a treatment method. However, developing safe and effective probiotic products remains an unresolved issue.

Several independent studies have confirmed the effectiveness of various lactobacilli and bifidobacteria in alleviating symptoms of functional constipation (FC) in animal models and humans(Anzawa et al., 2019; Ibarra, Latreille-Barbier, Donazzolo, Pelletier, & Ouwehand, 2018; Ojetti et al., 2014). For instance, mice gavaged with Lactobacillus plantarum Lp3a for 15 days showed significant improvement in intestinal motility, shorter time to first defecation, and increased stool volume after being induced with constipation using a 25% diphenoxylate solution(C. Zhang et al., 2022). Another study isolated Lactobacillus plantarum KFY02 from naturally fermented yogurt in Kuerle, Xinjiang, showing positive effects in treating mice with constipation induced by a low-fiber diet. This strain significantly improved the water content of feces, intestinal transit capability, and defecation time in constipated mice, while maintaining the diversity and structure of the gut microbiome in balance and increasing the serum levels of neuroendocrine factors related to intestinal motility, regulating the expression of genes related to intestinal motility in the colonic tissue(Yi, Zhou, Liu, Xue, & Yang, 2022).

Lactobacillus plantarum PS128 intervention in loperamide-induced constipated mice improved the mice's weight, fecal quantity, and water content, increased colonic mucin levels, and the small intestine propulsion rate. Additionally, this strain significantly altered the expression levels of genes related to 5-HT signal transduction, such as TPH1, CHGA, SLC6A4, and Htr4, promoting intestinal motility and 5-HT signaling, thereby alleviating constipation symptoms(C.-M. Chen et al., 2022). Lactobacillus rhamnosus modulates 5-HT to promote MUC2 production and regulate the gut microbiome, improving the defecation function in mice(Gu et al., 2022). Researchers like Gang Wang suggest that the anti-constipation effects of different Lactobacillus rhamnosus strains are related to gastrointestinal regulatory peptides, neurotransmitters, neurotrophic factors, and the gut microbiome, but not directly related to the levels of short-chain fatty acids (SCFAs) in the colon(G. Wang, S. Yang, et al., 2020).

5-HT plays a crucial role in promoting intestinal motility and effectively alleviating constipation(Cao et al., 2017). Increasing research indicates that the gut microbiome regulates the biosynthesis of 5-HT(Yano et al., 2015). Approximately 90% of 5-HT is synthesized and distributed by enterochromaffin cells (ECs) in the gut, but the specific molecular mechanisms by which probiotics regulate the secretion of 5-HT by ECs and how they stimulate signal transmission to the nervous system are not yet fully understood. Lactobacillus paracasei F34-3 induces ECs to express CgA, increases the secretion of catecholamines, activates the CgA/α2A adrenergic receptor (Adrα2A) cascade signal, and regulates the Trp/α-OR pathway, thereby promoting the secretion of 5-HT by constipated mice's ECs(Y. Lu et al., 2021).

Gastrointestinal infections caused by pathogenic bacteria present a significant global public health challenge. According to the World Health Organization (WHO), there are approximately 2 billion cases of diarrhea annually worldwide due to pathogenic bacteria. In developing countries, diarrhea caused by Escherichia coli is a major contributor to increased morbidity and mortality in children(Brubaker et al., 2021).

Rotavirus infection is the most common and severe form of acute gastroenteritis in infants and young children globally(Lo Vecchio et al., 2017). The severity of rotavirus is related to a combination of molecular events over time that lead to secretory and osmotic diarrhea(De Marco et al., 2009). In the early stages of infection, rotavirus directly induces the secretion of active chlorine and water into the intestinal lumen through the enterotoxic effect of its non-structural protein nsp4, increasing intracellular calcium ion concentrations and triggering chloride ion secretion(Buccigrossi et al., 2014; Ousingsawat et al., 2011). Moreover, rotavirus infection results in severe damage to the intestinal villi structure, cell death, and subsequent loss of epithelial integrity, leading to osmotic diarrhea due to poor nutrient absorption(Medici et al., 2011).

Clinical trials have shown that Lactobacillus rhamnosus GG (LGG) can rapidly alleviate diarrhea symptoms, with effects observable within hours of treatment initiation(Guarino, Guandalini, & Lo Vecchio, 2015).

LGG's ability to quickly reduce secretory diarrhea suggests its action is related to changes in the microbiota or inflammatory effects(Cox et al., 2010; Pagnini et al., 2018). LGG combats rotavirus-induced diarrhea by inhibiting cytotoxic and enterotoxic mechanisms. LGG demonstrates a direct pharmacological effect by secreting specific components that inhibit chlorine secretion, considered a postbiotic effect. Subsequently, the active bacterial strains function as probiotics, protecting intestinal cell structures(G. Wang, S. Yang, et al., 2020).

On the other hand, Lactobacillus reuteri (LRCC5310) effectively improves clinical symptoms of rotavirus gastroenteritis, including diarrhea and Vesikari scores, by inhibiting rotavirus adhesion and proliferation in the small intestine, demonstrating its potential in treating rotavirus infections(Shin et al., 2020).

Escherichia coli, a Gram-negative bacterium, is known to cause severe diarrhea and rapid dehydration. Its mechanisms include attachment to intestinal microvilli, causing damage, toxin secretion, and reducing trans-epithelial electrical resistance. These processes disrupt tight junctions (TJs), leading to an imbalance in the gut microbiome(Q. Lin et al., 2019; Muza-Moons, Schneeberger, & Hecht, 2004; Philpott, McKay, Sherman, & Perdue, 1996). Lactobacillus paracasei shows potential benefits in regulating the gut microbiome, particularly in addressing diarrhea caused by microbial imbalance. In a mouse model of diarrhea established using E. coli, oral administration of Lactobacillus paracasei cell suspension showed significant therapeutic effects. This includes increasing levels of tight junction proteins (ZO-1, occludin, and claudin-1), enhancing goblet cell expression, reducing intestinal permeability, inducing MUC2 expression, and lowering levels of pro-inflammatory cytokines like IL-6, IL-1β, TNF-α, p65, myosin light chain 2, and myosin light chain kinase. These findings suggest that Lactobacillus paracasei may alleviate diarrhea by inhibiting the activation of the NF-ϰB-MLCK pathway and increasing the abundance of the gut microbiome that produces short-chain fatty acids (SCFAs)(Ren, Chen, Tian, Bai, & Wang, 2022; Ren, Wang, Chen, Lv, & Gao, 2022).

Enterotoxigenic Escherichia coli (ETEC) is a common pathogen causing human diarrhea, particularly in traveler's diarrhea (TD), accounting for 30-60% of TD cases(McFarland, 2007). ETEC is also a pathogen in young animals, such as newborn piglets and calves, with high morbidity and mortality rates(H. Zhang et al., 2018). ETEC produces heat-labile enterotoxins (LT) and heat-stable enterotoxins (ST) that disrupt the integrity of tight junctions, causing inflammation and intestinal dysfunction, affecting the transport of ions, solutes, and water around cells, ultimately leading to diarrhea(Haixiu Wang, Zhong, Luo, Cox, & Devriendt, 2019). Lactobacillus plantarum, a key member of the human intestinal microbiome and an edible probiotic, has shown protective effects against diarrhea caused by ETEC(J. Wang et al., 2018). Lactobacillus plantarum CCFM1143 can lower levels of TNFα, IFNα, IL-6, reduce jejunum damage, enhance the expression of aquaporin AQP3, increase IL-10 levels, reduce heat-stable enterotoxin (ST), and FGDLZ1M5 can reduce the expression of TLR4, demonstrating significant protective effects against ETEC-induced diarrhea(Yue Yue et al., 2020).

6. Prospect

Lactic acid bacteria, a category of probiotics, are widely recognized for their positive impact on host health. Strains belonging to the genus Lactobacillus, in particular, exhibit a range of bioactive functions, demonstrating potential therapeutic applications for various physiological diseases. These bioactivities include antimicrobial, anti-inflammatory, anti-hypertensive, antioxidative, antidiarrheal, antiviral, immunomodulatory, cholesterol-lowering, anti-diabetic, and anticancer effects.

This review reveals the potential applications and underlying mechanisms of probiotic lactic acid bacteria in immunomodulation, anti-pathogenic activity, antioxidation, anticancer activity, and strengthening epithelial barriers. Based on these insights, it is suggested to design dietary plans incorporating appropriate doses of lactic acid bacteria for patients with various emerging or recognized diseases. Undoubtedly, more research is needed to identify the most effective combinations of lactic acid bacteria for treating specific diseases. Moreover, further human and animal trials are required to assess the practical and long-term application of lactic acid bacteria as a protective mechanism for gastrointestinal diseases. Additionally, research should focus on the selection of lactic acid bacterial strains, dosage determination, optimal application methods,

and delivery tools.

Despite the growing application of probiotics, there are still limitations and unknowns regarding their effectiveness in treating and preventing diseases. Research trials often yield contradictory results, leading to opposite conclusions. This phenomenon may be attributed to the highly complex interactions among the host, probiotics, and the microbiome. It is important to recognize that significant individual variations in human microbiome composition due to factors such as age, health status, and dietary habits can influence responses to probiotic interventions, sometimes even leading to adverse effects. To accurately determine the required probiotic strains and dosages for desired health outcomes, it is necessary to delve deeper into the mechanistic properties of probiotics and their interactions with the host.

It is noteworthy that even in healthy individuals, the specific mechanisms of microbe-host interactions should be carefully considered when using probiotics. Studies indicate that the colonization capacity of probiotics in the host is limited, as any changes in the microbiome composition induced by probiotic intake are temporary and depend on continued consumption.

Clearly, there is a long way to go in fully understanding the complexities of the microbiome and its impact on health. More in-depth clinical trials are needed to validate the health claims of commercially available probiotic products. Clarifying the mode of action of probiotics in defined subgroups of the population will help in accurately predicting therapeutic outcomes, improving clinical trial designs, and advancing the development of probiotic health strategies. Furthermore, the expansion of the field of bacterium-derived products, or postbiotics, suggests a more precise, effective, and safer future for the probiotic health market.

Supplementary material

Additional File: Table1.Animal and clinical studies of different lactic acid bacteria strains in alleviating different intestinal inflammatory diseases. Table2.Abbreviation

Authorship contribution statement

Guanru Qian:Conceptualization, Data curation, Writing – review & editing; Jiankang Yu:Data curation,Table drawing; Hui Zang:Data curation; Hao Zhang:Conceptualization; Huibiao Jia:Data curation; Gang Liu:Methodology; Jianping Zhou:Funding acquisition, Resources, Supervision All the authors have read and agreed to the final version manuscript.

Conflict of interest statement

All authors declare that there is no potential conflict of interest.

Data availability statement

All data will be available upon request.

Reference

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