


Review

Limosilactobacillus reuteri Regulating Intestinal Function: A Review

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Abstract: Probiotics have extensive use in daily life, due to the function of the changing intestinal metabolism and material conversion processes, wherein they remodel the intestinal microbiota, regulate the intestinal function and affect the organism's health. *Limosilactobacillus reuteri* (*L. reuteri*), originally discovered in breast milk and currently reported to be present within the gut of almost all vertebrates and mammals, is an intestinal probiotic with prebiotic efficacy. Most *L. reuteri* have good intestinal colonization and bacteriocin secretion abilities, which can increase the expression of the mucin (mucoprotein) genes 2 MUC2 and MUC13, which in turn promote the development and maturation of intestinal organoids, and augment mucin secretion. In enteritis patients, *L. reuteri* downregulates α Tumor necrosis factor- α , (TNF- α), Interleukin-6 (IL-6), IL-8, and IL-12 expression to attenuate inflammation. It also induces the host's production of immunoglobulin A (IGA), which manipulates the intestinal microbial community, inhibiting the growth of pathogens. *L. reuteri* has been widely used in daily life. with in-depth studies having been conducted on the prebiotic effects of *L. reuteri*. However, the complexity of its application in a clinical setting is still unclear because the pathogenesis of various diseases still requires a large amount of data and theoretical support.

Keywords: *Limosilactobacillus reuteri*; physiological function; gut flora; inflammation; immunomodulation



Citation: Jiang, J.; Li, K.; Xiao, Y.; Zhong, A.; Tang, J.; Duan, Y.; Li, Z. *Limosilactobacillus reuteri* Regulating Intestinal Function: A Review. *Fermentation* **2023**, *9*, 19. <https://doi.org/10.3390/fermentation9010019>

Academic Editor: Marikunte Yanjarappa Sreenivasa

Received: 25 November 2022

Revised: 21 December 2022

Accepted: 22 December 2022

Published: 26 December 2022



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1. Source and Diversity of *L. Reuteri*

L. reuteri is a Gram-positive bacterium of heterotypic lactic-acid fermentation and is a facultative anaerobic organism. The morphology shows a slightly irregular campylobacter with a rounded end. It was first isolated in breast milk in 1962. Its suitable culture environment is 35~40 °C, with a pH of between 6.7 and 7.0. Its metabolites include lactic acid, carbon dioxide, formic acid, ethanol, acetic acid, higher alcohols, etc. [1]. It has good biocompatibility with lactic acid bacteria in the intestines of most vertebrates and mammals and is non-toxic to human beings, without causing disease. It has been proven to be one of the resident flora of the human gastrointestinal tract [1]; thus, it has a high theoretical research and production application value.

Currently, *L. reuteri* is commonly used for screening and amplification cultures of lactic acid bacteria, such as MRS and M17, and some researchers have chosen LRIM medium with cottonseed sugar as the carbon source to screen and culture it from feces [2].

L. reuteri was first found in breast milk. It is often distributed in the intestines and feces of animals, and it is found in some fermented products. *L. reuteri* from different sources has diverse physiological characteristics, with strong adhesive capacity. Most *L. reuteri* can colonize intestinal mucosa to form site competition, effectively resist harmful bacteria colonization, regulate intestinal flora, and avoid intestinal diseases. Its characteristics are summarized in Table 1.

Table 1. Distribution, sources and characteristics of *L. reuteri*.

Source	Strain	Feature or Function	References	
Fermented foods	Highland barley wine	WHH1689	No lactose fermentation, no post-acidification caused by storage at room temperature, high bacterial survival rate, good resistance, strong adhesion to HT-29 cells, can effectively inhibit <i>Escherichia coli</i> , <i>Shigella flexneri</i> , <i>Salmonella</i> β paratyphoid, and gold <i>Staphylococcus aureus</i> activity	[3]
	Fermented dough	81	With 4,6- α -glucanotransferase properties, it can produce malto-oligosaccharides with immunomodulatory effects	[4]
		100-23	Contains three glutaminase enzymes which can promote the conversion of glutamine into glutamic acid and improve the flavor of fermented products	[5]
		TMW1.656	Resists proteolysis in dough and heat inactivation in baking, inhibits <i>Streptomyces</i> ’ growth and extends shelf life, and produces the bacteriocin Reutericyclin	[6]
Humans	Stool	DSM0016	Good dehydrogenation ability of ethanol and promotes the mutual conversion of aldehydes, alcohols, and ketones	[7]
		FXZ014	Produces higher amounts of 3-HP and 1,3-PD	[8]
		LR6	Has antagonistic activity against different targeted pathogens and, has cholesterol-lowering activity and anti-hypercholesterolemia effects	[9]
	Breast milk	ATCC557 (Mother plant); DSM 17938	Effectively reduces pathogen colonization, improves intestinal health, reconstructs intestinal flora, has the ability to convert glycerol into 3-HP and 1,3-pdo, and effectively reduces constipation in infants and young children	[10]
		JCM 1112 ^T	Produces reuterin and vitamin B12	[11]
		IRT-5	Immunomodulation of hyperimmune diseases and is a treatment for rheumatoid arthritis, atopic dermatitis, and inflammatory bowel disease	[12]
	Vaginal	RC14	Inhibits the adhesion of pathogenic bacteria, inhibits the gene expression of <i>Staphylococcus</i> superantigen protein, and reduces the inflammatory response caused by <i>Candida albicans</i>	[13]
	Gut	DSM20016	Produces spirosin, reduces serum SUA levels in hyperuricemic rats, relieves the symptoms of hyperuricemia, and produces Roy’s protein	[7,14]
Pigs	Manure	NCIMB 30242	Improves gastrointestinal health, inhibits sterol absorption, increases average circulating 25-hydroxyvitamin D	[15]
		DSMZ 20056	Promotes murine secretion	[16]
		ZLR003	Positive effects on the regulation of feed intake, weight gain, gut microbiota composition, and immune performance in weanlings, growing–finishing sows, and lactating sows	[17]
	Intestines	Probio-16	Resistant to low pH and bile, inhibits enteric bacterial pathogens and rotavirus, has antibacterial and antiviral activity, and has an inhibitory effect on the Zika virus	[18]
		I5007	Interacts with Caco-2 cells, has strong adhesion to porcine intestinal mucus and the host cells IPEC-J2 and IEC-6, can produce large amounts of exopolysaccharides, inhibits <i>Salmonella</i> Typhimurium and <i>Escherichia coli</i> growth, and positively regulates piglet immune function	[19]

Table 1. Cont.

Source		Strain	Feature or Function	References
Mice	Droppings	R28	Good colonization effect, and can effectively reduce diarrhea and enteritis	[20]
		TD1	Does not produce Reutericyclin	[21]
Rats	Internal organs	DSMZ 17509	Contains acid urease gene cluster, and can remove urea in rice wine	[22]
Chickens	Chicken	ATCC 55148	Anaerobic; can be used to treat bacterial intestinal infection in poultry, and it delays and improves chronic enteritis	[23]
	Intestines	KUB-AC5	Effectively resists <i>Salmonella</i> and prevents poultry <i>Salmonella</i> infection, produces large amounts of exopolysaccharides, and has potential technical applications and uses for improving food properties	[24]
		SKKU-OGDONS-01	Using antiviral protein as carrier as feed additive	[25]
		BBC5	Good tolerance, good adhesion to Caco-2 cells, and can significantly enhance chicken macrophages involved in immune regulation	[26]
Bees	Gut	LP4	Good antibacterial properties, can regulate the expression of the antimicrobial peptide mRNA in the guts of adult oriental honey bees and worker bees, and increases the survival rate of bees	[27]
Uncertain	/	GMNL-263	Improves renal fibrosis and insulin resistance, improve liver steatosis and hyperlipidemia, and enhances white adipose tissue browning	[28]
	/	ATCCPTA 6475	Reduces osteoclast activity, and improves bone health in estrogen-deficient conditions	[29]

2. Physiological Role of *L. Reuteri*

Probiotics can regulate intestinal microbial communities and inhibit the growth of harmful microorganisms by inducing the host to produce bacteriocins and immunoglobulins [30]. Probiotics can also fortify the intestinal barrier through maintenance of the tight junctions and induction of mucin production, and they can mediate immune regulation, which may occur through the secretion of cytokines mediated by signaling pathways, such as nuclear factor kappa-B (NF- κ B), which affects the proliferation and differentiation of immune cells or epithelial cells. Many studies have proven that *L. reuteri* has an important regulatory effect on animal growth, intestinal microflora composition and metabolism, and intestinal immune function [1,31].

2.1. Improvement of Intestinal Physiological Function

2.1.1. Modulation of Gut Flora

Probiotics are able to influence the diversity, composition, and metabolic function of the gut microbiota. Proper supplementation of *L. reuteri* can promote the gut microbiota to enhance inosine production, which can reduce Th1/Th2 cells and their related cytokines under the action of adenosine A_{2A} receptor, and the *L. reuteri* intestinal microbiota inosine adenosine A_{2A} receptor axis can be used as a potential treatment for Treg cell-deficient diseases. *L. reuteri* C10-2-1 has been shown to regulate the diversity of intestinal microbiota in rat ileum [32], and the addition of *L. reuteri* DMS17938 to the diet of infants improves their intestinal health by reducing pathogen colonization, the expression levels of enterohemorrhagic *E. coli* virulence genes and deleterious bacteriotoxic effects [33].

2.1.2. Improvement of Intestinal Structure

L. reuteri can promote the development of intestinal villi, increase the expression of intestinal defense peptides and tight junction proteins, and increase the integrity of the intestinal barrier. Other studies have compared and analyzed the effect of *L. reuteri* on the miRNA expression profile of piglet jejunum, and they found that it significantly up-regulated jejunal miR-423-5p. *L. reuteri* can affect the intestinal immune function of piglets by inhibiting the synthesis of the immunoglobulin λ light chain C region [34], and *L. reuteri* 15007 can increase the height of the ileum villi and reduce the depth of duodenal crypts in piglets, significantly improving the intestinal development of newborn piglets, promoting the expression of intestinal epithelial cell proteins, and enhancing the mechanical barrier function of a piglet's intestinal mucosa [35,36].

2.2. Inhibition of the Growth and Colonization of Intestinal Pathogenic Bacteria

2.2.1. Production of Antimicrobial Metabolites

L. reuteri is a heterotype lactic-acid fermentation that can produce lactic acid, acetic acid, ethanol, short-chain fatty acid, and other metabolites. At the same time, some *L. reuteri* also produce bacteriocin Reuterin or Reutericyclin, Reuterin 6, and Ap48-MapA to effectively inhibit the growth of harmful microorganisms.

Metabolites

L. reuteri metabolites such as lactic acid can inhibit the growth of harmful microorganisms by changing the permeability of the pathogenic bacteria cell membrane, chelating metal ions and reducing the pH of the growth environment [37].

Secretion of reuterin

Reuterin's main components are monomers, hydrates, and the cyclodimers of 3-Hydroxypropionaldehyde (3-HPA), which are associated with glycerol metabolism. The antibacterial activity of reuterin, with its stronger stability, is not destroyed by nuclease, protease, and lipase [38,39]. It also has broad-spectrum antimicrobial properties and can inhibit the growth of some Gram-positive bacteria, Gram-negative bacteria, *Saccharomyces*, *Aspergillus*, and *Fusarium fungi*. However, its mechanism of action is tentatively unclear, and the current explanation is that reuterin can inhibit harmful microbial RNase activity [40,41]. It interacts with thiol genes in cells [42] to inhibit the growth and reproduction of harmful bacteria.

Secretion of Reutericyclin

Reutericyclin is a tetrachloric acid derivative, and its main component, 1,3-diacetylpyrrolidine-2,4-dione compounds, can be produced by some *L. reuteri* strains. It is a class of proton carrier with broad-spectrum antimicrobial properties, but it is ineffective against Gram-negative bacteria, acting through the protons and into the cytoplasm and acidic cytoplasmic-effect transmembrane pH gradient dissipation and the inhibition of harmful microbial growth [42,43]. At present, it is mostly used in the preservation of food, as it can inhibit protein hydrolysis in dough and the thermal inactivation caused by baking, and it inhibits the growth of streptomyces [6].

Secretion of Reuterin 6

Reuterin 6 is a Class II bacteriocin, which is derived from *L. reuteri* LA6 and screened from infant feces. Reuterin 6 has strong hydrophobicity, good thermal stability, and has bactericidal and dissolving effects on sensitive bacteria [44,45]. It can destroy the integrity of the cell membranes of harmful microorganisms through depolarizing the membranes and exuding cell fluid, leading to cell death and achieving antibacterial effects [46,47].

Production of antibacterial peptide Ap48 MapA

Peptide Ap48 MapA is composed of 48 amino acids. It is an antimicrobial peptide with a PI of 9.63, and it has a good antibacterial effect [48].

2.2.2. Site Competition with Pathogenic Bacteria through Colonization

Probiotics are a type of living bacteria that can promote the ecological balance of intestinal flora. By adhering to the host's intestinal tract, they form a biological barrier

with normal flora, releasing active antibacterial substances or blocking the combination of pathogenic bacteria with cell receptors through space, which affects the colonization, occupation, and reproduction of pathogenic bacteria. Probiotics produce biological enzymes, active peptides, and metabolites in their host, which can prevent the infection and colonization of pathogenic bacteria in the body, playing the role of a chemical barrier and achieving the purpose of preventing gastrointestinal mucositis (see Figure 1)

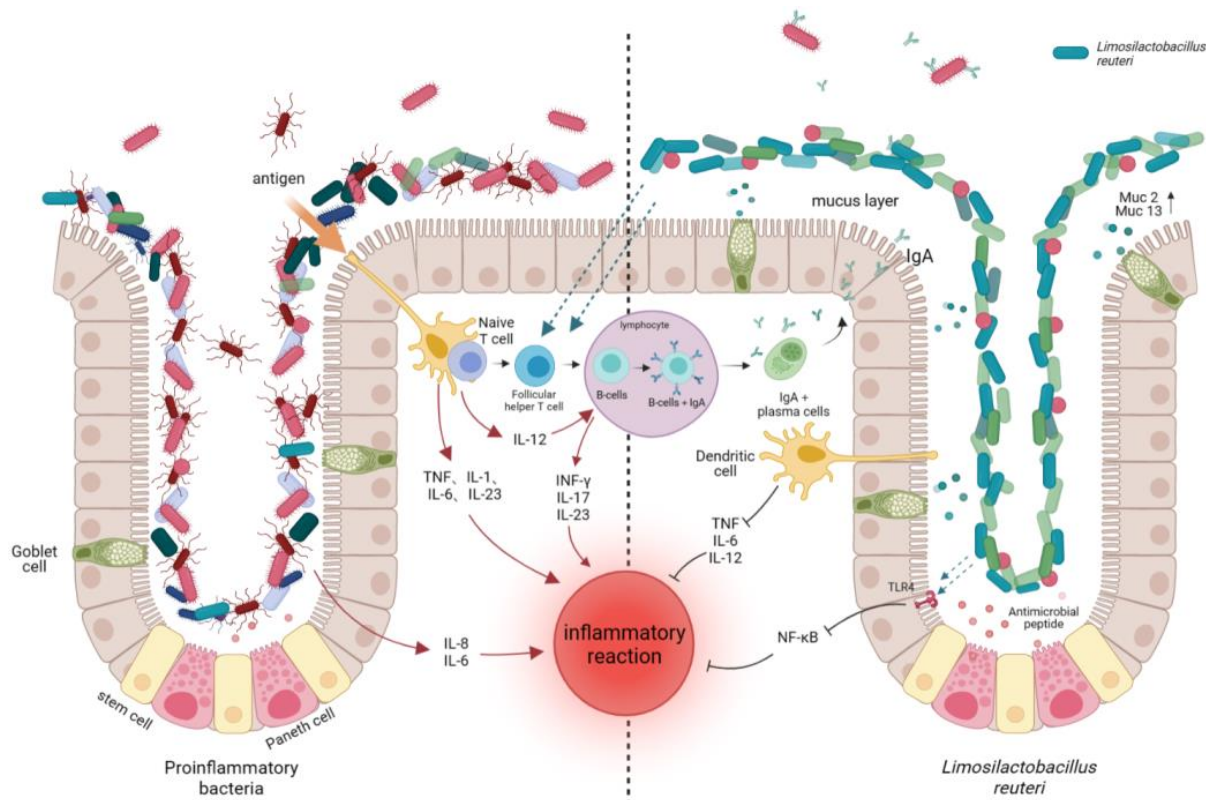


Figure 1. Immune regulation of *L. reuteri* in intestinal tract. IL-1: Interleukin 1; IL-6: Interleukin 6; IL-23: Interleukin 23; IL-12: Interleukin 12; INF- γ : γ Interferon; IL-17: Interleukin 17; IL-8: Interleukin 8; NF- κ B: κ -light chain enhancement in nuclear factor-activated B cells; mucus layer; MUC2: Mucin gene 2; MUC13: Mucin gene 13.

L. reuteri, as the primary bacterium in human and most animal intestines, has good tolerance to the low pH of gastric acid and bile salt [49], and it has the ability to reject and replace pathogenic bacteria in intestinal cell adhesion. *L. reuteri* ATCC 55730 has been proven to adhere to Caco-2 human intestinal epithelial cells and combine with intestinal epithelial cells to form site competition, reduce the colonization of harmful bacteria, and inhibit the gene expression of pathogenic bacteria [50].

The ability of probiotics to inhibit the adhesion of pathogenic bacteria mainly depends on the specific adhesins of *Lactobacillus* and pathogenic bacteria and the carriers on the cell surface. The adhesins mainly include secreted proteins, glycoproteins, and adhesive polysaccharides. *L. reuteri* contains gene-encoding proteins and collagen-binding proteins related to the adhesion of type collagen [51], which is conducive to its colonization in the intestinal tract. Some *L. reuteri* fermentation supernatants and their bacteria have the ability to inhibit the adhesion of pathogenic bacteria [52]. Through experiments, researchers have proven that *L. reuteri* can adhere to intestinal epithelial cells, form a biological barrier, and prevent the adhesion and colonization of pathogenic bacteria in intestinal epidermis. These findings further support the assumptions of the adhesion mechanism of *L. reuteri*.

2.2.3. Promotion of Mucus Secretion and Reduction in the Colonization of Harmful Microorganisms

The surfaces of intestinal epithelial cells are covered with a layer of mucus, which is mainly composed of mucin secreted by goblet cells. The mucus layer separates intestinal epithelial cells from the intestinal cavity environment, providing a habitat for obligate or facultative anaerobic microorganisms, attachment sites, and growth substrates for intestinal symbiotic flora [53]. It can also promote the colonization of probiotics in the intestinal tract and inhibit the growth and reproduction of harmful microorganisms (see Figure 1)

The genes related to mucin secretion that are stimulated by *L. reuteri* are *muc2*, *muc3A*, *muc13*, *muc17*, *clca1*, *fcgfp*, *zg16*, *tff3*, etc. Ye Seul Son et al. [54]. found through immunofluorescence staining that *L. reuteri* can promote intestinal organoid maturation and mucin secretion by increasing the expression of mucin barrier formation and the secretion of the gel-associated mucin MUC2 and mucin MUC13 that protect the mature gut from inflammation. *L. reuteri* I5007 can restore the number of goblet cells and repair damaged tissues by stimulating the gene expression of the mucin MUC2, and it can also promote the expression of proteins related to cell structure and vitality, as well as lipid metabolism in jejunal mucosal proteins [55]. In addition, the metabolites of *L. reuteri*, such as short-chain fatty acids, modulate the integrity of the epithelial barrier and tight junctions, which enhances mucus release and promotes the differentiation of intestinal epithelial cells.

2.3. Immunomodulatory Effects

Gut immune regulation is realized by the interaction of trillions of microorganisms and many model receptor gene products, and the gut microbiota drive immune system function and development, thus maintaining the homeostasis of the gut.

2.3.1. Influence on the Production of Immunoglobulin A

The presence of probiotics can affect the production of immunoglobulin A (IgA), whose metabolites, such as short-chain fatty acids, aryl hydrocarbon receptor ligands, and polyamines, communicate with their host and secrete outer membrane vesicles containing microbial-associated patterns vesicles. They can pass through the epithelial barrier or directly recognize pattern recognition receptors, promoting polymeric immunoglobulin receptors and transmembrane mucins to mediate the transformation of B cells into plasma cells and produce IgA, thus reducing the interaction between pathogens and the surface of intestinal epithelial cells, thereby reducing the corresponding exposure, colonization, and inflammatory damage [56]. It has been proved that various strains of *L. reuteri* can induce intestinal IgA production and modulate gut microbiota diversity in a strain-dependent manner [32]. However, whether they affect IgA levels through the direct regulation of B cells requires further study.

2.3.2. Regulation of TREG Cells

Regulatory T cells (Treg) are T lymphocytes with high immune tolerance that have a negative feedback regulation function. The decrease in the activity of Treg cells usually leads to abnormal immune activation. *L. reuteri* has been shown to modulate anti-inflammatory Treg cells, which can help them exert probiotic effects in a variety of disease and non-disease conditions [1]. *L. reuteri* CCFM1072 and CCFM1040 can regulate Treg cell effects. The modulation of gut microbiota in allergic asthmatic mice reduces airway inflammation [57]. *L. reuteri* DSM 17938 can promote the development or migration of Treg cells, reduce the generation of effective memory T cells (Tem), and suppress immunity in the necrotizing enterocolitis (NEC) model of the small intestine's activated and reduced inflammatory response [33]. Studies have shown that *L. reuteri* can also inhibit an excessive inflammatory responses by inhibiting Toll-like receptors (TLR) 4 and NF- κ B in small intestinal epithelial cells, intervening in the balance between Treg cells and Tem cells to make the immune system remain immune and to interrupt and avoid excessive immunity and exert anti-inflammatory effects [33,58,59]. It should be noted that *L. reuteri* is not helpful for all

patients with inflammation. In lupus erythematosus patients, *L. reuteri* can intervene in the TLR7 pathway to affect immune regulation, making lupus-susceptible hosts more susceptible to disease and aggravating the patient's condition [60].

2.3.3. Inhibition of the Production of Pro-inflammatory Factors

Some *L. reuteri* have been found to reduce the production of pro-inflammatory factors, as it is a common genus of *Lactobacillus* with therapeutic properties [61]. Anukam et al. [62] found that *L. reuteri* RC-14 downregulated TNF- α , IL-6, IL-8, IL-12, and other levels, and it relieved some symptoms of cystitis. *L. reuteri* GMNL-263 can reduce the levels of MCP-1, TNF, and IL-6 in mice fed a high-fat diet [63]. In addition, some *L. reuteri* also inhibit pro-inflammatory motor-protein cells in rodent models [64].

2.3.4. More Studies

Some *L. reuteri* can affect the production of inflammatory factors through their special structures and metabolites.

Exopoly saccharides (EPSs): EPSs are a type of carbohydrate compound secreted outside the cell wall of lactic acid bacteria during the growth and metabolism processes. They have the effect of inhibiting the pro-inflammatory immune response of macrophages. High levels of capsular polysaccharides can protect against intestinal innate immune factors [65], such as antimicrobial peptides. Enterotoxins released by enterotoxigenic *Escherichia coli* can induce the upregulation of CAMKII and cAMP in intestinal cells and destroy the electrolyte homeostasis of intestinal cells, leading to intestinal cell dehydration and diarrhea [66]. *L. reuteri* L26 can secrete an EPS (MW = 8.2×10^5 Da) composed of α -D-glucose (1 \rightarrow 3) and (1 \rightarrow 6) glycosidic bonds [67], which can interfere with the overexpression of calmodulin-dependent protein kinase II and the cAMP-dependent kinase protein-related gene PRKAR1A, which is induced by enterotoxigenic *Escherichia coli*. Additionally, it reduces the effect of enterotoxigenic *Escherichia coli* on the tight junction of intestinal epithelial cells, preventing the development of diarrhea in piglets infected with enterotoxigenic *Escherichia coli* [68]. EPSs are important factors in the induction of T cells by *L. reuteri*. *L. reuteri* 100-23 produces EPSs by decomposing sucrose. This EPS is a levan (β -2, 6-linked fructan), and it can induce the proliferation of regulatory T cells in the spleen, affecting the immune response [69–71].

Surface layer proteins (SLPs): SLPs are part of the complex structure of the cell wall of *L. reuteri*. With the exception of its adhesive function, understanding the other functions of SLPs is still in the hypothetical stage. It has been experimentally demonstrated that SLPs can be recognized by dendritic cell-specific intercellular adhesion molecules combined with non-integrin molecules and induce a pro-inflammatory cytokine profile in the human dendritic cell DSC92 [72].

Histamine: Histamine in the metabolites of *L. reuteri* can stimulate the host H2 histamine receptor, derive histamine to inhibit THP-1 cells, produce tumor necrosis factor (TNF), and inhibit TNF production by transcriptional regulation [73].

Tryptophan catabolite can activate aromatic hydrocarbon receptors, promote innate lymphocytes, and produce local IL-22 [74].

In conclusion, *L. reuteri* has a good immunomodulatory effect, which can exert an immune effect by affecting the expression of mucin genes, producing antibodies and inflammation-related factors (as shown in Figure 1). However, some studies have shown that *L. reuteri* has little effect on immunity, and single use of *L. reuteri* does not improve immunity and has a negative effect on some diseases. Therefore, the adjustment and improvement of *L. reuteri* on the body's immunity is still controversial.

Pro-inflammatory microorganisms (shown on the left side of the figure) can directly or indirectly interact with immune cells and intestinal epithelial cells to produce pro-inflammatory factors such as IL-6, IL-8, etc. In addition to B lymphocytes producing IgA, various stimulated proinflammatory cytokines produced by epithelial cells, monocytes, and lymphocytes also elicit an immune stimulatory response. *L. reuteri* can directly or indirectly

alter gut microbiota through its metabolites, adhesion mechanisms, and gene regulation, reducing pro-inflammatory bacterial colonization and attenuating inflammatory responses (shown on the right side of the figure).

2.4. Amelioration of Obesity

Current studies suggest that low-grade systemic inflammation is the main mechanism leading to insulin resistance in obese individuals, and the correlation between gut microbiota and obesity has been well documented. *L. reuteri* is significantly associated with the development of obesity. In a high-fat diet (HFD)-induced obesity mouse model, through treatment with *L. reuteri* GMNL-263, the weight, fat, tissue, and liver, as a percentage of body weight, decreased significantly [74]. Li-Han Chen [28] and others have found that *L. reuteri* 263 supplementation triggered the remodeling of energy metabolism in white adipose tissue and enhanced browning-related genes including *pparγ*, *prdm16*, *bmp7*, *fgf21*, etc., promoting the conversion of white adipose tissue to faster energy-consuming beige adipose tissue and noticeably ameliorating obesity in HFD-induced obese mice.

2.5. Other Functions

As with many other *Lactobacillus* species, some *L. reuteri* strains produce different types of vitamins, such as vitamins B12 and B9. A recent study by Ker-Ping et al. [75] found that heat-inactivated *L. reuteri* GMNL-263 can activate the IGF-IR signaling pathway to reduce hyperglycemia-induced Fas-dependent, and mitochondria-dependent apoptosis pathways, and at the same time, it can alleviate hyperglycemia-caused heart damage. In addition, *L. reuteri* can lower serum cholesterol levels and is an antidiarrheal [76].

3. Application of *L. Reuteri*

L. reuteri, with its strong intestinal adhesion, widely exists in the intestines of humans and animals, and it can inhibit the reproduction of gastrointestinal pathogens, regulate the immune function of animals, and effectively reduce animal stress responses and feed-to-weight ratios, and thus, it is widely used and applied in daily life.

3.1. Application in the Feed Industry

L. reuteri can effectively inhibit the growth of harmful bacteria and reduce or replace the use of antibiotics in animals in the breeding process, and so it is used to promote the growth of livestock and poultry and weaken the resistance of pathogens caused by antibiotics. In animal husbandry, *L. reuteri* BSA131 causes significant weight gain when introduced into pigs, turkeys, and rats, and it can be isolated at higher concentrations from feces after feeding with probiotics [77]. *L. reuteri* and its mixed preparations can improve the apparent nitrogen digestibility, total energy digestibility, and average daily gain (ADG) of weaned piglets. It can also increase piglet body weight, reduce the proportion of feed materials, and improve animal survival rates [78]. Lei Qingzhi et al. [27] extracted *L. reuteri* LP4 from worker bees, which can inhibit the growth of the enteric pathogens *Salmonella Typhimurium*, *Escherichia coli* and *Shigella flexneri*. By feeding LP4, the survival rates of oriental honeybees to adulthood worker bees can be increased.

3.2. Application in Functional Food

L. reuteri, as a dominant, heterofermentative lactic acid bacteria, is a commonly used probiotic in food production.

The bacteriocin reuterin secreted by *L. reuteri* has strong broad-spectrum antibacterial activity, and it is often used as a biological preservative in food [76]. However, its fermentation effect is not strong and its curdling ability is poor. Therefore, *L. reuteri* is often used as an auxiliary starter in cheese and yogurt to extend the shelf life of food and enhance product performance. At present, the probiotics used in commercial yogurt fermentation have poor acid resistance, bile salt resistance and adhesion, and colonization, which limit their beneficial effects. They do not have an antagonistic effect on *Lactobacillus bulgaricus*

and *Streptococcus thermophilus*, and they can effectively inhibit the growth of *Penicillium* and prolong the shelf life of yogurt. *L. reuteri* LT018 has strong stability and excellent self-polymerization [79]. It can enhance the survival of live bacteria and intestinal colonization in dairy products. The growth state of fermented milk obviously increases the content of riboflavin in fermented milk, and this improves this commodity value.

Vitamins are essential trace elements for the human body; however, the body cannot synthesize vitamins by itself. *L. reuteri* is an active vitamin B12-producing bacteria in which cobalamin is involved in the metabolic pathway of methionine, contributing to the production of glutathione and to its anti-oxidation activity [58] and enhancing vitamin B12-related gene pathways in fermented foods mixed with fermented glucose, fructose, and glycerol to increase vitamin B12 production [80]. *L. reuteri* has also been used in the brewing of vinegar and wine, as it can adjust the total acid content of vinegar and improve the flavor [81,82] while also reducing the urea content in liquor-fermented grains and the formation of ethyl carbamate [83]. However, there are relatively few studies on urease in liquor, and the application of *L. reuteri* in liquor production requires further study.

3.3. Clinical Application

With the deepening of antibiotic research, probiotics have been widely studied and applied in clinical medicine. Several studies have shown that the symbiosis of *Lactobacillus* can accelerate the restoration of the host's intestinal microbiota to its original good state, thereby regulating intestinal flora homeostasis in patients with acute diarrhea [76]. It has been proven that *L. reuteri* can significantly improve chronic constipation, colic, and diarrhea in infants, without adverse side effects such as vomiting, bloating, and increased gas [84].

Studies have found that a variety of *L. reuteri* can stimulate immunomodulatory responses, reduce human intestinal inflammation (to varying degrees), and effectively prevent DSS-induced colitis in rats by reducing P-selectin-dependent leukocytes and platelet-endothelial cell interactions. Liu et al. showed that the *L. reuteri* DSM17938 strain may reduce intestinal oxidative stress and increase its antioxidant capacity, thereby reducing the intestinal inflammatory response and reducing the damage caused by small intestinal necrotizing colitis [64,85]. Research has brought new targets for the treatment of patients with enteritis, but the pathogenesis of intestinal inflammation has not been determined, and the specific molecular signaling pathways of *L. reuteri* involved in the inflammatory response by regulating oxidative stress still need to be further explored.

L. reuteri DSM17648 can recognize and adhere to the surface of the adhesion molecules of *Helicobacter pylori*, inhibiting the binding of *Helicobacter pylori* to glycolipid receptors and forming insoluble polymers with them, which are then excreted through the digestive tract [86], reducing gastric inflammation and cancer risk. Currently, the treatment of *Helicobacter pylori* by *L. reuteri* has released in the market, and there are strains (DSM17648, HN019, etc.) being sold on the market.

At present, *L. reuteri* has contributed to new research progress in the treatment of the oral cavity, the regulation of vaginal flora in women, liver failure treatments, and airway inflammation treatment. However, further clinical applications still have a long way to go.

4. Conclusions

L. reuteri, as a common lactic acid bacterium in the intestinal tracts of humans and most vertebrates, is widely used in daily life. *L. reuteri* can effectively improve the intestinal environment, promote intestinal health, and achieve immune function by affecting microbial flora, improving intestinal structures, and regulating the levels of factors such as TNF- α , IL-6, and IL-8. It has broad prospects and research potential in animal breeding and medical treatments.

At present, there are a number of studies on the influence of *L. reuteri* on intestinal flora and the regulation of immunity; however, research on the pathways of postbiotic generation and the physicochemical properties and functions of metabolites requires further study. *L.*

reuteri can produce a variety of bacteriocins which require more research and discussion on the quorum sensing law and on the mechanisms of changes in gut microbiota. The pathogenesis of many diseases is complex and remains unclear, and the potential threat of active probiotics to some diseases is still controversial. The changes in intestinal flora after oral administration, especially the changes in intestinal metabolites, are also not well studied. Therefore, the duration, effectiveness, and safety of *L. reuteri* interventional therapy still requires considerable theoretical knowledge, large samples, and multi-center clinical trials. In the future, *L. reuteri*-related treatment may become a new and safer treatment for inflammatory diseases.

Author Contributions: Conceptualization, J.J. and Z.L.; writing—original draft preparation and software, J.J.; writing—review and editing, Z.L., K.L., and Y.X.; suggestions on revision, A.Z., J.T., and Y.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Key Research Program of Hunan Province (2022NK2040), Hunan Provincial Innovative Construction Special Fund (2021NK4260) and project support of Hunan Province Agricultural Industry Technology system (2022-67).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: We wish to thank the Key Research Program of Hunan Province (2022NK2040), Hunan Provincial Innovative Construction Special Fund (2021NK4260) and project support of Hunan Province Agricultural Industry Technology system (2022-67).

Conflicts of Interest: The authors declare no conflict of interest.

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