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Review Article

The impact of probiotics on gut health via alternation of immune status of monogastric animals

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ABSTRACT

The intestinal immune system is affected by various factors during its development, such as maternal antibodies, host genes, intestinal microbial composition and activity, and various stresses (such as weaning stress). Intestinal microbes may have an important impact on the development of the host immune system. Appropriate interventions such as probiotics may have a positive effect on intestinal immunity by regulating the composition and activity of intestinal microbes. Moreover, probiotics participate in the regulation of host health in many ways; for instance, by improving digestion and the absorption of nutrients, immune response, increasing the content of intestinal-beneficial microorganisms, and inhibiting intestinal-pathogenic bacteria, and they participate in regulating intestinal diseases in various ways. Probiotics are widely used as additives in livestock and the poultry industry and bring health benefits to hosts by improving intestinal microbes and growth performance, which provides more choices for promoting strong and efficient productivity.

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1. Introduction

The livestock and poultry industry is an important part of the economy and lifestyle for many countries and people. With the increasing demand for animal-derived food, the livestock and poultry industry needs to be more healthy and rapidly developed to keep up with the pace of demand (Hu et al., 2017b). Maintaining intestinal health is critical to the livestock and poultry industry. The intestine is composed of a single layer of intestinal-epithelial cells (IEC). Maintaining its healthy state can ensure the digestion and absorption of nutrients, the integrity of the intestinal barrier function, and the balance of intestinal microecology (Ji et al., 2019). The intestines of animals, especially those in their infancy or weaning period, are particularly vulnerable to pathogens from different sources (feeding environment, diet, and even the mother).

The application of probiotics can reduce the spread of pathogens in livestock and poultry, improve the digestion and absorption of intestinal nutrients, and maintain a healthy microecological state. In addition, the use of antimicrobial drugs used in veterinary therapeutics to prevent and treat diseases in recent decades has led to drug resistance of pathogenic bacteria, causing the treatment of antimicrobial drugs to be questioned (Nava et al., 2005). Therefore, antibiotics have been banned on a large scale and replacements are urgently needed. The utilization of probiotics has been considered to fill this gap and has had some success (Gadde et al., 2017; Nava et al., 2005). In this review, we summarize that probiotics maintain intestinal health by improving the digestion and absorption of nutrients, improving intestinal morphology and immune response, altering the intestinal-microbial composition and inhibiting intestinal-pathogenic bacteria. Moreover, probiotics play a vital role in regulating diarrhea and promoting the colonization of microorganisms in intrauterine growth retardation (IUGR) piglets.

2. Probiotics

Probiotics were first described as substances produced by one protozoan and stimulated by another and later described as animal-feed additives that can have beneficial effects by affecting intestinal microbes in host animals (Lilly and Stillwell, 1965). In 2002, the

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Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) defined probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" (Bielecka, 2006). More precisely, probiotics are non-toxic and non-pathogenic living microorganisms that can be administered through the digestive route to bring beneficial effects to the host (Guillot, 1998). The probiotics commonly used are *Lactococcus*, *Enterococcus*, *Bacillus*, and yeast, and have been incorporated into human probiotics products (Markowiak and Śliżewska, 2017). In recent years, a large number of animal models and clinical intervention studies have provided strong evidence to explore the potential prevention and treatment of probiotics in many diseases (Yu and Li, 2016).

Probiotics are very important for maintaining barrier function in epithelial cells, which is affected by strengthening tight junctions (Rhayat et al., 2019). Furthermore, gut-associated-lymphoid tissues (GALT) are also the main sites of interaction between probiotics and hosts. GALT are mainly composed of Peyer's plaques and lymphocytes/plasma cells scattered throughout the intestinal mucosa, and its main function is immune monitoring. Immune cells in this location, such as dendritic cells or macrophages, can present antigens and directly affect T-cell and B-cell or M-cell-mediated responses (Hitotsumatsu et al., 2005; Kamada et al., 2013). In addition to direct contact with mucosa, soluble molecules produced by the metabolism of probiotics are involved in the development of host diseases (Hevia et al., 2015). For instance, butyric acid, produced by fermented dietary fiber from obligate anaerobic bacteria such as *Clostridium clusters*, *Bacteroides thetaiotaomicron*, and *Faecalibacterium prausnitzii*, is one of the main energy sources of IEC (Kau et al., 2011; Louis et al., 2014; Roediger, 1980). Butyrate in the colon is mainly consumed by colonoscopy cells that differentiate at the top of the crypt (Roediger, 1980).

3. Gut immunity of monogastric-production animals

The intestinal tract is an important interface between the host and its environment, playing an important role in the digestion and absorption of nutrients, tolerance to harmless and beneficial microorganisms, and appropriate immune responses, in addition to preventing the transfer of intestinal microorganisms to sterile sites (Farhadi et al., 2003; Neu, 2007; Zou et al., 2019). From another point of view, IEC are a selective-permeability barrier that not only completes the absorption of nutrients and electrolytes but also effectively blocks the invasion of antigens such as bacteria and potential allergens (Groschwitz and Hogan, 2009). The mucus layer is the first line of defense of the "intestinal barrier," the IgA secreted by plasma cells can inhibit the adhesion of intestinal bacteria, and the antimicrobial peptides (AMP) secreted by Paneth cells play an important "defense" role in defending against the invasion of antigens (Stokes, 2017). The glycocalyx, which consists of a mucus layer and AMP, possesses the capacity to capture/remove microorganisms that attempt to invade under the action of peristalsis (Stokes, 2017). IEC are composed of a dense, stable layer of cells on the outer surface, thus acting as a barrier, while barrier function is maintained by an apical–junction complex composed of tight junctions (Balda and Matter, 2008), adherens junctions (Harris and Tepass, 2010), desmosomes (Hatzfeld et al., 2017), and gap junctions (Kumar and Gilula, 1996).

The wall of the small intestine is mainly composed of mucosa, submucosa, muscularis propria, and serosa. The innermost mucosa mainly includes epithelium, mucous muscularis, and lamina propria in the middle. The mucosa is the site for nutrient absorption in the body, and the intestinal wall of the submucosa is composed of dense hoofed tissue, whose dense structure plays an important role in the integrity of the intestinal tissue barrier. Lymphatics including Peyer's patches are present in this layer of the intestinal wall (Campbell et al., 2019; Lv et al., 2018). The lymphoid tissues in the intestine such as Peyer's patches and mesenteric lymph nodes contain a large number of immune cells, such as dendritic cells, natural killer cells, macrophages, and CD4^{+}and CD8^{+}T cells (Coombes and Powrie, 2008). Intestinal-dendritic cells are involved in maintaining the tolerance of harmless antigens and producing a protective immune response to pathogens (Mann and Li, 2014). The mucosal-dendritic cells located in the fornix of Peyer's patches receive M-cells to obtain antigens and then activate naive T-cells to produce interleukin (IL)-4 and IL-10 (Mathers and Cuff, 2004). Animals are closely related to huge and diverse microbiota, and most of their members live in the gastrointestinal tract with two gradients, the proximal–distal axis and the tissue–tube axis (Sommer and Bäckhed, 2013). The mucosal immune system can control pathological microorganisms, limit microbial overgrowth, and secrete IgA to deal with microorganisms that break through the intestinal chemical and physical barriers, ensuring the composition of beneficial microbiota. The innate immune system recognizes microbial infections by identifying pathogen-associated molecular patterns through germline-encoded pattern-recognition receptors (Hajishengallis and Lambris, 2011). However, microbiota play an important role in the development and regulation of host immune tissues, immune cells, and immune mediators.

4. Probiotics and gut health

The general mechanism of probiotics on the host includes increasing the production of enzymes that are conducive to the digestion and absorption of nutrients, improving the morphology of IEC, and enhancing an immune response, increasing the abundance of favorable microorganisms in the intestine, promoting the barrier function of IEC, and inhibiting the adhesion of pathogens and toxins to IEC (Jäger et al., 2018; Shin et al., 2019; Singh et al., 2019; Wang et al., 2019a). Substantial evidence has shown that probiotics play a significant role in regulating growth performance, immune response, and intestinal health (Table 1).

4.1. The improvement of gut health effected by probiotics via participation in the regulation of nutrient digestion

The intestinal tract is the most densely colonized organ, and dietary habits, stress, and the use of antibacterial drugs have negative effects on the composition of the microbial flora to varying degrees (Jäger et al., 2018). Accumulating evidence highlights a critical role for probiotics in supporting digestion and promoting absorption as nutritionally assisted therapies (Linares et al., 2016; Lv et al., 2018). Probiotics affect the absorption of minerals by changing the pH level of the gut, degrading cholesterol in the gut to lower cholesterol levels, producing digestive enzymes that promote the breakdown of carbohydrates, and even synthesizing important nutrients such as vitamins (Yoo and Kim, 2016). Besides synthesizing nutrients, probiotics may improve the digestion of proteins and lipids and combine with enzymes to break down food substances into simpler forms for digestion and absorption (Ushakova et al., 2015). Moreover, due to the high–fermentation activity of probiotics, intestinal digestion is improved to a great extent, thus the production and activity of intestinal digestive enzymes are increased (Liao and Nyachoti, 2017). One study showed that the supplement of 1 g/kg of *Bacillus coagulans* or *Lactobacillus* in the broiler diet caused the pH value of the cecum to be acidic (Al-Khalaifa et al., 2019). The acidic pH is caused by the production of non-potent volatile fatty acids and antibacterial substances in the cecum, and these antibacterial substances can inhibit or eliminate a variety of pathogens (Wood, 1992). Moreover, the digestion and

Table 1
Effects of probiotics on intestinal health in monogastric animals.

Probiotics	Dosage	Duration of study	Positive performance	Reference
Bacillus coagulans *Lactobacillus*	1 g/kg dried culture	35 d	Inhibits the growth of *Escherichia coli* and *Salmonella*; the pH value of the cecum tends to be acidic	Al-Khalaifa et al. (2019)
Clostridium butyricum *Bacillus subtilis* *Bacillus licheniformis*	5.0×10^{10} CFU/g 5.0×10^{9} CFU/g 5.0×10^{9} CFU/g	28 d	Decreases the levels of AST, ALT, and ALP; improves growth performance, intestinal morphology, and colonic microflora; alters the expression of hypothalamic neurotransmitters	Cao et al. (2019)
Bacillus	$>5 \times 10^{11}$ CFU/kg	35 d	Reduces the population of *E. coli*; increases the population of *Lactobacillus* spp; improves the digestibility of crude fiber; increases the height of villi	Rodjan et al. (2018)
Bacillus amyloliquefaciens SC06	1×10^{8} CFU/g	28 d	Decreases the expression of nuclear factor-κB-P50 and Toll-like receptor 6; reduces the gene expression of *TNF* and *IL-1α* in the intestinal mucosa; reduces the levels of hepatic cytokines IL-4, TNF-α, and IL-1β	Du et al. (2018)
Lactobacillus plantarum 16 and *Paenibacillus polymyxa* 10	10^{8} CFU/kg	21 d	Benefits cell apoptosis and proliferation; enhances the gene expression of *IFN-γ*, *IL-6*, and *IL-10* in the jejunum; reduces the levels of ALP and creatine kinase	Wu et al. (2019)
B. amyloliquefaciens	5.4×10^{9} CFU/g	28 d	Improves morphology; increases the level of IL-10; decreases the level of TNF-α in the small intestine; reduces the abundance of *Escherichia coli* in the jejunum; increases the content of *Lactobacillus* and *Bifidobacterium* in the ileum	Li et al. (2018)
B. subtilis DSM25841	1.28×10^{6} CFU/g	21 d	Reduces *E. coli* F4ac infection; reduces the diarrhea caused by *E. coli* infection on weaned piglets; affects the mucosal transcriptome profile	Luise et al. (2019)
L. plantarum ZLP001	5.0×10^{9} CFU/g	30 d	Inhibits the increase of intestinal permeability induced by *E. coli*; reduces the expression of *IL-6*, *IL-8*, and *TNF-α*; prevents the increase of tight-junction protein	Wang et al. (2018)

AST = aspartate transaminase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; TNF = tumor necrosis factor; IL = interleukin; IFN = interferon.

absorption of protein affect the physiological and metabolic properties of the host (Jahan-Mihan et al., 2011).

Intestinal microbes produce short-chain fatty acids by fermentation of CHO and proteins, which can serve as an important mediator linking nutrition, intestinal flora, intestinal physiology, and pathology (Ríos-Covián et al., 2016). Moreover, the small peptides produced by protein decomposition in the intestine can be digested by brush-edge peptidase on the surface of IEC, and then produce free amino acids or oligo amino acids, which may be absorbed by the body and participate in important physiological processes (Jelen, 2006; Shimizu, 2004). The increase of digestive enzymes such as metalloprotease, cellulase, α-amylase, and protease activity in pig intestines after feeding probiotics may be caused by the stimulation of probiotics themselves or may be produced by changes in the intestinal microbial system (Lee et al., 2016; Sharma Bajagai et al., 2016).

4.2. The improvement of gut health effected by probiotics via participation in intestinal morphology and immune response

The integrity of the intestinal morphology is extremely important for maintaining intestinal health. For example, changes in the intestinal morphology caused by inflammation will destroy the digestion and absorption of nutrients and the immune function of the intestinal mucosa (Willing and Van Kessel, 2009). The intestinal-morphology results of *Salmonella infantis* challenge after intragastric administration with *Lactobacillus johnsonii* L531 for a week showed that *L. johnsonii* L531 reduced the damage of *S. infantis* to intestinal villi and the endoplasmic reticulum of piglets (Yang et al., 2020). The evidence suggested that adding 100 mg/kg *Clostridium butyricum* CGMCC 9386 (5×10^{10} CFU/g) to 21-d weaned piglets for 28 d could improve growth performance, intestinal morphology, and colonic microflora (Cao et al., 2019). In poultry, the combination of 2 g/kg organic acids and probiotics (containing more than bacillus 5×10^{11} CFU/kg) improved the digestibility of crude fiber, increased the height of villi, and reduced the number of *Escherichia coli* (Rodjan et al., 2018). Moreover, butyrate, a major end-product of intestinal-microbial fermentation, is an important energy source for IEC, which affects various functions of colonic mucosa, such as inhibiting inflammation and cancer, enhancing the colonic defense barrier, and reducing oxidative stress (Guo et al., 2020; Hamer et al., 2008; Tang et al., 2020). The study showed that sodium butyrate (supplement at 2 g/kg) alleviated diarrhea and reduced intestinal permeability but had no effect on the early growth of piglets. In addition, sodium butyrate promotes Claudin-3 expression in the colon in a GPR109A-dependent manner through the Akt-signaling pathway (Feng et al., 2018).

Intestinal immunity is an indispensable barrier protecting the body from foreign antigens or pathogens, and this barrier is composed of GALT and a mass of dispersed innate and adaptive effector cells that can tolerate symbiotic bacteria and dietary antigens (Mowat and Agace, 2014). The population of antigen-presenting cells in the gut administrates the balance between tolerance and immunity that may trigger inflammation in the gut. The well-regulated tolerance mechanism of GALT can avoid or eliminate the occurrence of intestinal inflammation (Artis, 2008). GALT contain immune cells capable of antigen presentation such as M-cells, T-cells, B-cells, dendritic cells, and macrophages (Spahn and Kucharzik, 2004). There is considerable evidence that probiotics regulate the intestinal immune response. Dietary supplementation with *Bacillus amyloliquefaciens* SC06 decreased the expression of nuclear factor (*NF*)-*κB-P50* and Toll-like receptor (TLR) 6 and reduced the gene expression of tumor necrosis factor (*TNF*) and *IL-1α* in the intestinal mucosa, but the levels of IL-6 and IL-8 were increased; moreover, the levels of IL-4, interferon (IFN)α, and IL-1β in serum were decreased. All of this indicated that *B. amyloliquefaciens* SC06 could enhance the immune function of IEC by activating the TLR-signaling pathway (Du et al., 2018). The study demonstrated that dietary supplementation of *Lactobacillus acidophilus* improved the immune response of laying hens via enhancing T- and B-lymphocyte proliferation, the antibody titer against sheep red blood cells, and the phytohemagglutinin-wattle swelling test, while the ratio of heterophils to lymphocytes was decreased (Alaqil et al., 2020; Wang et al., 2019b). Furthermore, the study demonstrated that *Lactobacillus plantarum* 16 and *Paenibacillus polymyxa* 10 are beneficial to cell apoptosis and proliferation while enhancing the gene expression of *IFN-γ*, *IL-6*, and *IL-10* in the jejunum, reducing the levels of alkaline phosphatase and creatine kinase, which indicates that *L. plantarum* 16 and *P. polymyxa* 10 protect the health of broilers by reducing apoptosis and enhancing intestinal immunity (Wu et al., 2019).

4.3. The improvement of gut health effected by probiotics via alteration of the composition of gut microbes

The final purpose of a probiotic intervention is to confer a positive impact on the health of the targeted population, which involves the regulation of the host in many aspects, such as enhancing the intestinal-epithelial cell barrier, regulating the immune system, or reprogramming the gut-microbial composition (Bai et al., 2019; Sánchez et al., 2017). Intestinal microbes are important factors affecting the development of IEC and the immune system. These microorganisms promote the development of the lymphoid structure, affect the properties of the mucous layer, and balance the production of IgA and AMP (Sommer and Bäckhed, 2013). Evidence from many animal models shows that probiotics can change the composition of the gut microbiota to maintain intestinal health. Supplementation of 2.0 g/kg of *B. amyloliquefaciens* in piglets with intra-uterine growth retardation diets for 28 d increased the level of IL-10 but decreased the level of TNF-α in the small intestine, as well as reduced the abundance of *E. coli* in the jejunum while increasing the content of *Lactobacillus* and *Bifidobacterium* in the ileum, which indicates that *B. amyloliquefaciens* may help to improve the early growth of piglets (Li et al., 2018). The combination of *Yarrowia lipolytica* and *Saccharomyces cerevisiae* reduced the amount of *E. coli* in the gut (Czech et al., 2018). The evidence demonstrated that oral administration of *Lactobacillus delbrueckii* in 21-day-old piglets reduces the level of malondialdehyde in the serum and liver but increases the activity of glutathione and glutathione peroxidase in the liver. Compared with the control group, *L. delbrueckii* increased the levels of IgA and inflammatory cytokines in the intestinal mucosa (Li et al., 2019). In addition, probiotics maintain gut health by fermenting fiber-rich foods to promote the production of beneficial metabolites (Underwood, 2019). The evidence reveals that short-chain fatty acids such as acetic acid, propionic acid, and n-butyric acid produced by microbial fermentation in the large intestine may have a positive effect on the proliferation of porcine-epithelial cells, and also have an improved effect on the secretory pancreas (Suiryanrayna and Ramana, 2015).

5. Probiotics and intestinal diseases of monogastric animals

Although gut microbes have been studied for decades and have been implicated in the development of many diseases, it is not clear whether they are caused by the microbes or the effect of the gut. Scientific evidence shows that probiotics play an important role in the digestive system and influence the development of diseases. This section provides evidence of the beneficial health effects of probiotics and reviews the regulation of probiotics on diarrhea and promoting the colonization of the intestinal tract in piglets with IUGR.

5.1. Diarrhea

Diarrhea is a common disease caused by pathogens. It not only affects human health but also damages the health of livestock and poultry, especially animals in the weaning stage (DuPont, 2016; Heredia and García, 2018). Stressful periods such as weaning may cause digestive disorders. Postweaning diarrhea caused by *E. coli* mainly affects piglets at about two weeks and is characterized by dehydration, diarrhea, and growth retardation of dead and surviving piglets, which causes serious economic losses (Amezcua et al., 2002; Fairbrother et al., 2005). For example, piglets in the weaning stage may experience diarrhea due to enterotoxin-producing *E. coli*, resulting in death (Liao and Nyachoti, 2017). Many studies on *E. coli*-induced diarrhea models of weaned piglets have shown that probiotics can relieve the negative effects of *E. coli* on animals (Krause et al., 2010). Cytokines are a type of low-molecular-weight protein produced by mononuclear phagocytes that constitute the immune system, and they participate in signal transduction between cells and regulate immune responses (Delirezh et al., 2016; Guan et al., 2019). Pro-inflammatory cytokines such as IL-6 and TNF-α are associated with tissue damage (Hernández-Rodríguez et al., 2004). Evidence suggests that the inhibition of pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) supports the protective effect of Jiawei Xianglian Decoction on diarrhea induced by irinotecan (Lu et al., 2020). In the diarrhea piglets model induced by *E. coli*, the results showed that *L. plantarum* ZLP001 could significantly inhibit the increase of intestinal permeability induced by *E. coli*, reduce the expression levels of *IL-6*, *IL-8*, and *TNF-α*, and prevent the increase of tight-junction protein expression (Wang et al., 2018). The evidence showed that *S. cerevisiae* supplied in the diet reduced diarrhea and the duration of diarrhea increased the serum IgA level and inhibited *E. coli* colonization in the intestinal tract (Trckova et al., 2014). Moreover, the study showed that *B. amyloliquefaciens* DSM25841 reduced *E. coli* F4ac infection, reduced the diarrhea caused by *E. coli* infection on weaned piglets, and affected the mucosal—transcriptome profile (Luise et al., 2019). Diarrhea caused by a drug-resistant strain of *Clostridium difficile* is reported to cause 14,000 deaths a year in the United States, and *C. difficile* may also infect the gut of newborn pigs (Gross, 2013; Grześkowiak et al., 2019).

5.2. Intrauterine growth retardation

Intrauterine growth retardation is a phenomenon in which newborn piglets are underdeveloped due to placental insufficiency, leading to a low birth weight, which further leads to higher mortality and morbidity in piglets before weaning (Oksbjerg et al., 2013; Tao et al., 2019). In the middle and later stages of pregnancy, nutrients are mainly delivered from the mother to the pig embryo through uterine-placental circulation and the umbilical-cord vein (Kiserud and Acharya, 2004). However, due to the decrease in blood flow, the composition and content of nutrients obtained by the fetus have changed (Kim et al., 2013; Reynolds et al., 2006). Proteomic analysis of IUGR pig embryos in the middle and third trimester of gestation, namely at d 60, 90, and 110 of gestation, showed impaired cell metabolism, decreased ATP, and increased oxidative stress and apoptosis in IUGR embryos. IUGR is characterized by sacrificing the internal organs of the small intestine to maintain the substrate supply of other important organs (Salam et al., 2014). Particularly, this defect hinders the natural immune-maturation trajectory and damages the secreted products and components of the intestinal-epithelial surface (Attig et al., 2013; Zhang et al., 2020).

Verification by western blotting showed that, compared with normal developing embryos, the expression of hypoxia-inducible factor-1 (*HIF-1*) in IUGR embryos increased, while the expression of glyceraldehyde 3-phosphate dehydrogenase (*GADPH*), vascular endothelial growth factor (*VEGF*), and vascular endothelial growth factor receptor (*VEGFR*) decreased (Chen et al., 2015). The intestines of IUGR piglets show a decrease in goblet cells and more adhesion and translocation of pathogenic microorganisms that may lead to the damage of the mucosal barrier, which may lead to intestinal-tract inflammation and infection of IUGR piglets, and then lead to growth retardation and weakness in piglets (Zhang et al., 2019). Generally, in the intestines of piglets a few days after birth, *Lactobacilli*, *E. coli,* and *Streptococci* begin to increase rapidly, and then the colonization of *Bacteroides*, *Enterobacteria*, and *Clostridia* occurs in sequence (Bauer et al., 2006; Moughan et al., 1992). With the intake of a solid diet, the number and species of anaerobes in the intestinal tract increases until a stable micro-ecosystem has formed (Inoue et al., 2005; Konstantinov et al., 2006; Pieper et al., 2008). Clinical studies have shown that the incidence and severity of necrotizing enterocolitis were reduced in IUGR newborns (Kliegman, 2005). Animal-model studies have shown that probiotics added to the diet of sows could promote the colonization of beneficial bacteria in neonatal piglets (Herfel et al., 2013; Yan et al., 2017). Compared with normal-developing piglets, IUGR leads to a decrease in piglet-growth performance and villus height, a decrease in the number of goblet cells, and an imbalance in the expression of pro-inflammatory and anti-inflammatory cytokines. Compared with the IUGR piglet, BA increased the daily-average weight gain and feed utilization of piglets with IUGR, improved jejunum morphology, increased ileal-goblet cell density, and increased IL-10 levels, but reduced the level of TNF-α. In addition, BA reduced the content of *E. coli* in the jejunum, while it increased *Lactobacillus* and *Bifidobacterium* in the ileum (Yan et al., 2017). Another study demonstrated that IUGR reduced the levels of IgA and IL-1 in plasma, decreased the activity of maltase, and decreased the mRNA level of *TLR 9* and the expression of Toll-interacting proteins in the ileum. *Bacillus subtilis* PB6 increased the expression of zonula occludens 1 and claudin-1 in the ileum of piglets with IUGR and increased the number of *Bacillus* in the colon via adding *B. subtilis* PB6 to formula milk for piglets with IUGR (Hu et al., 2017a). Although probiotics have shown many benefits for the health regulation of piglets with IUGR, their possible potential effects and mechanisms need to be further explored.

6. Conclusion

The probiotic “family” has expanded as research evidence has been added, and it has been found that the family has benefits in a wider range of areas, with broad prospects in animal nutrition and animal health. Studies have demonstrated that probiotics actively participate in the digestion and absorption of intestinal nutrients, participate in animal immune regulation through themselves and their metabolites, and actively participate in intestinal micro-ecological balance, to maintain animal health, reduce manpower, and bring considerable economic benefits. The interaction between probiotics and the gut microbiota of an animal may lead to multiple changes in multiple systems, which may involve the balance of other “regions”. At the same time, the use of probiotics will not make the intestinal microbe produce drug resistance, which brings a broader choice of antibiotic substitutions.

Author contributions

Sujuan Ding: Conceptualization, Writing-Original draft preparation. Wenxin Yan: Investigation, Writing-Reviewing. Yong Ma: Investigation, Writing-Reviewing. Jun Fang: Supervision, Writing-Reviewing and Editing.

Conflict of interest

We declare that we have no financial or personal relationships with other people or organizations that might inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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