

Effects of probiotics on the improvement and regulation of intestinal barrier dysfunction and immune imbalance in intra-abdominal infections (Review)

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Abstract. Intra-abdominal infections (IAIs) are one of the most common critical diseases in clinical practice, with high morbidity and mortality rates. A variety of abdominal diseases can lead to abdominal infection, such as acute appendicitis, acute cholecystitis, various causes of gastrointestinal perforation, post-operative complications and trauma. It has been demonstrated that probiotics are of utmost significance in improving the treatment and prognosis of patients with IAIs. Probiotics play a beneficial role in the host's metabolism, immunity and nervous system by interacting with the host microorganisms, preventing the colonization of pathogens, improving intestinal barrier function, regulating immune function and producing related metabolites. The aim of the present review article was to discuss and summarize the regulatory effect of probiotics on intestinal barrier dysfunction and immunological imbalance in IAIs, in order to provide a foundation for the development of novel therapeutic approaches and disease prevention measures.

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1. Introduction

As one of the most common and severe acute abdomen diseases, intra-abdominal infections (IAIs) have become the main factor for the high mortality rate in diverse and complicated refractory disease (1). IAIs are mainly associated with abdominal traumatic surgery in the form of post-operative complications (2). The mortality rate from complicated intra-abdominal infections (CIAIs) varies between different countries and regions and ranges from 3–42% (3). In addition, the associated morbidity also exhibits an increasing trend. A previous multinational observational cohort study demonstrated that secondary peritonitis accounted for the vast majority of cases (68.4%), followed by biliary tract infection (12.2%), intra-abdominal abscess (6.9%) and pancreatic infection (6.3%) (4). IAI is a risk prognostic factor for complications of these diseases, and despite advances in treatment over the last few decades, the morbidity and mortality remain at high levels.

The definition of IAI is a general term for a class of diseases and represents a wide array of pathological conditions, including cholecystitis, pancreatitis, appendicitis, diverticulitis, and abdominal abscess and sepsis (5). Classified by its severity, IAI can be divided into two categories as follows: i) Uncomplicated intra-abdominal infection, which emerges in a single organ and is accompanied by mild symptoms; this can be treated using antibiotics therapy; and ii) CIAI, which not only affects the hollow organs, but also penetrates the pathological organs to reach the peritoneum (6), resulting in secondary peritonitis and even in severe abdominal abscess. Of note, peritonitis is typical of CIAI, and is mainly divided into primary and secondary peritonitis (Fig. 1). Moreover, CIAI can be further categorized into two types: Community CIAI that may be severe and occurring in the community, and hospital CIAI, which is also termed healthcare-acquired

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CIAI, usually occurring in patients who were hospitalized or who were admitted to other medical care institutions; the latter type is more common than the former (7), particularly as regards post-operative infections. IAI is a severe post-operative complication, which can lead to systemic inflammatory response syndrome, sepsis and even in multiple organ dysfunction syndrome. It induces pseudoaneurysm, sepsis and septic shock, which not only exacerbate patient suffering, but also lengthen hospital duration and increase medical costs; in addition, IAIs decreases the quality of life of patients and may even result in mortality (8).

Probiotics are live bacteria that, when consumed, modify the gut microbial flora and provide the host with health benefits (9). The use of probiotics has been examined in inflammatory bowel disease, irritable bowel syndrome and antibiotic-associated diarrhea (10-12). In the present review article, the current literature on the use of probiotic therapy in the treatment of IAIs is summarized.

2. Literature search strategy

The following electronic databases were used to search potentially relevant studies: PubMed (1995 to October, 2021), China National Knowledge Infrastructure (1995 to October, 2021) and Wan Fang Data (1995 to October, 2021).

The key words used included probiotics, intra-abdominal infections, intestinal barrier dysfunction (IBD), immune imbalance, mechanism, source control, antibiotics, bacterial translocation and intestinal mucosal permeability.

3. Mechanisms of action of probiotics

As is already known, there is a collection of microorganisms in nature. For the most part, this collection of microorganisms and bacteria has a negative impact on the daily life of humans. However, decades of research have revealed that bacteria, which is a subset of microorganisms that also includes viruses, fungi and other protists, plays a critical and useful role in the human body. All these microbes combine to form a chemical that some researchers have termed the microbiota. The microbiota can be found in a variety of tissues, including the mouth cavity, gastrointestinal tract, nasal cavity, and others. In particular, ~80% of the normal microbiota is concentrate in the gut (13). It has been reported that almost 1,014 bacteria are present in adult intestinal cells, which is 10-fold larger than the amount present in normal cells in the human body (14). Consequently, some researchers have even indicated that the intestinal microbiota is one of the organs in the human body (15).

The positive bacterial component is constituted by probiotics. Probiotics are microorganisms that may be of net benefit to humans when consumed. The administration of sufficient doses of probiotics, which are defined as live microorganisms, primarily modifies the balance of the intestinal microflora of the host (16). Probiotics are live microorganisms that can alter the intestinal microbial flora when ingested, and confer beneficial health effects to the host. Their use has been studied in various gastrointestinal conditions, including inflammatory bowel disease, irritable bowel syndrome and antibiotic-associated diarrhea. Metchnikoff, who worked at the Pasteur Institute at the turn of the century, was the first to

bring forth the hypothesis that individuals could benefit from the consumption of fermented milk (17). As a result, the World Health Organization (WHO) and the United Nations Food and Agriculture Organization (FAO) designated it as a food-grade ingredient used in dairy products that would promote the host's health. In one of his articles from 1954, Vergin (18) discussed the mechanisms thorough which antibiotics damage the healthy gut microorganisms. Since then, the general comprehension of probiotics and related applications have become increasingly thorough, and further in-depth research has been conducted.

Probiotics are currently categorized into three groups: *Lactobacilli*, *Bifidobacteria*, and *Gram-positive cocci*, including certain yeasts and enzymes. However, depending on the source and mode of action, they are divided into symbiotic bacteria, native bacteria and fungi (19). *Lactobacilli*, *Bifidobacterium*, butyric acid-producing bacteria, *Escherichia coli* (*E. coli*), *Streptococcus thermophilus* and other bacteria are all considered to be applicable to the human body on a global scale. Currently, the mechanisms of action of probiotics, such as lactic acid bacteria, *Bifidobacteria* and yeast, are relatively well understood, and previous research has been performed in this field. For instance, it has been demonstrated that the combined use of *Lactobacillus rhamnosus* GG (LGG) with conventional antibiotic therapy reduces bacterial translocation, preventing bile duct obstruction (20). *Lactobacillus* strains have also been shown to significantly enhance the phagocytic activity of macrophages (21). In recurrent respiratory tract infections, the abundance of *Bifidobacterium* has been shown to be reduced (21).

Probiotics mainly restore the balance of the flora of the body via a mechanism termed the flora-host interaction (22). A multitude of biological reactions are also involved in this process. Probiotics have been shown to function via a variety of mechanisms. For example, through competitive inhibition, they can limit the ability of pathogens to adhere to and colonize mucous membranes. Some probiotics secrete proteases which aid in the breakdown of toxins. Probiotics have also been shown to alter host immune functions by inhibiting the release of pro-inflammatory cytokines by T-cells, and some probiotic strains have been shown to inhibit mitogen-induced lymphocyte proliferation *in vitro* in a similar manner to dexamethasone (23). In addition, probiotic bacteria exert a potential protective effect against enteropathogens through various mechanisms, including the production of antimicrobial compounds, the reduction of pathogenic bacterial adhesion and the competition for host cell binding sites. The probiotics principle can be characterized by the following mechanisms: Immunoregulation, competitive inhibition, signal transduction and metabolic alterations are all examples of barrier function (24-27). Immunoregulation can be further divided into innate and specific immunity (25). It can also inhibit the adhesion and colonization of pathogens through competitive inhibition (28). The oral administration of probiotics can increase the number of IgA cells in the intestinal lamina propria (29). Moreover, probiotics can also induce IgA circulation and significantly increase the activity of macrophages distal to the gastrointestinal tract (30).

Regulatory effects of probiotics on the disruption of the bacterial flora in IAIs. Similar to the endogenous microbiota,

CLASSIFICATION OF PERITONITIS

Involved scope	Pathogenesis
Diffuse peritonitis	Primary peritonitis (spontaneous peritonitis) ☆ hemolytic streptococcus ☆ Streptococcus pneumoniae ☆ Escherichia coli
Localized peritonitis	
Clinical course	Secondary peritonitis ☆ Escherichia coli (most common) ☆ anaerobic bacteroides, ☆ Proteus ☆ streptococcus (often mixed infection,)
Acute peritonitis	
Chronic peritonitis	

Figure 1. Classification of peritonitis. Peritonitis was classified in terms of the scope, clinical course and pathogenesis.

probiotics can improve mucosal barrier function, limiting the ability of viral particles to cross the barrier, thus maintaining this physical barrier during viral disease (31). The adhesion of viruses to the mucosal surface is the first step in infection. Extracellular polysaccharides produced by lactic acid bacteria have been shown to interfere effectively with this step, as for example adenoviruses (32). However, the most effective anti-viral effect of probiotics is the regulation of the immune system. Selected probiotics have been reported to increase natural killer cell activity and cytotoxic activity (33). In addition, responses to antiviral cytokines, such as interferon γ (IFN- γ), interleukin (IL)-2, IL-12 and IL-18, as well as improved antibody responses have been reported with the use of probiotics (34). It is thus possible that several of these mechanisms and others operate in parallel and/or consecutively.

The incidence of IAIs, CIAs in particular, is one of the most common reasons for the increased health costs observed \$25,000 per case in the USA (35). The treatment regimen for CIAs, according to the most recent World Society of Emergency Surgery (WSES) management guideline (3), is simply a combination of various antibiotics. It is also for this reason that, as a result of the overuse of antibiotics, resistance to medication is becoming a major concern for all clinicians and patients (36). Thus, it is necessary to search for a promising prevention and treatment strategy for CIAs with limited side-effects. Probiotics appear to meet this requirement. As previously indicated by a clinical questionnaire in 2011, a number of gastroenterologists and surgeons in the UK have recommend the daily oral use of probiotics to their patients; in some cases probiotics have been directly prescribed (37). In a previous systematic review and meta-analysis of randomized controlled trials, 1,354 patients were administered probiotics in the treatment group, while 1,369 patients were administered the placebo in the control group. The outcome manifested that the use of probiotics decreased the risk of developing IAIs and related complications post-operatively (38). Additionally, it has been demonstrated that probiotics can reduce the levels of pro-inflammatory cytokines in rodents with post-infectious irritable bowel syndrome (39). As already aforementioned, IAIs

are associated with the emergence of bacterial translocation. However, bacterial translocation is caused by IBD. The intestinal tract serves as a repository for bacteria and endotoxins, and the colonic mucosal epithelium is tightly connected to this tract, which provides a strong barrier function, so that bacteria (or endotoxins) cannot easily transfer to other normal sterile tissues through the barrier (40). Probiotics can boost the expression of transmembrane binding protein (occludin) and IgA, allowing the barrier function to be improved and bacterial translocation to be reduced (41). Probiotics perform a similar coordinating function by exerting immunomodulatory effects. In animal models, oral *Lactobacillus* strains have been shown to activate the mucosal immune system and to affect the distal intestinal mucosa (42). A previous study discussed the role of probiotics in the prevention and treatment of intestinal infections (25).

Intestinal mucosal barrier (IMB) function of probiotics in IAIs. Intestinal barrier function (IBF) is one of the most essential barriers of the human body. Intestinal epithelial cells (IECs) separate the inner and outer intestinal cavity so that bacteria, endotoxins or other related pathogens, which may cause a variety of infections, are unable to move across the IMB to other tissues outside the intestinal lumen, preventing the body from invasion by endogenous microorganisms and their toxins (43). IBD can accelerate endotoxin and bacterial translocation. IBD is caused by a number of factors, such as inflammation, stress, trauma, hypovolemia and ischemia-reperfusion injury. In particular, infection, which is caused by the invasion of a pathogen into the body, plays a major role in IBD. Infection can lead to the activation and release of inflammatory factors in human organs, and neutrophil aggregation and adhesion result in damage to the intestinal mucosa. This can subsequently reduce intestinal mucosa permeability, thus lead to a series of pathological processes (44). Thus, the intestinal tract is not only the initiator of infection, but also the 'victim' of infection, and both play a causal role. Similarly, the occurrence of abdominal infection aggravates IBD, and the further aggravation of IBD further increases the occurrence of abdominal infections, forming a vicious cycle. The core of

Table I. Studies evaluating the efficacy of probiotics in intra-abdominal infections.

Authors	No. of subjects	Methods	Study duration	Patients	Year	(Refs.)
Poonyam <i>et al</i>	100	Double-blind randomized placebo-controlled	≥4 weeks	Aged ≥18 years (with non-ulcer dyspepsia)	2019	(77)
Çekin <i>et al</i>	159	Randomized placebo-controlled	2 weeks	Patients with <i>H. pylori</i> infection receiving sequential <i>H. pylori</i> eradication therapy	2017	(78)
Shukla <i>et al</i>	46	Prospective randomized controlled trials	12 weeks	Patients were children aged 6-20 years with diagnosed IBD	2016	(26)
Pande <i>et al</i>	110	Double-blind, randomized-controlled trials	6 months	Consecutive patients with cirrhosis	2012	(79)
Diepenhorst <i>et al</i>	30	Prospective randomized controlled trials	4 weeks	Patients scheduled for a PPPD with curative intent for a periampullary or ampullary pancreatic malignancy	2011	(80)

IBD, inflammatory bowel disease; PPPD, pylorus-preserving pancreaticoduodenectomy.

the IBF is IMB, which includes a mechanical barrier, chemical barrier, immune barrier and biological barrier (Fig. 2).

The intestinal barrier can prevent harmful substances in the intestinal cavity, such as pathogens and toxins, from entering other tissues and organs in the body and blood circulation through the intestinal mucosa. It represents a direct physical barrier for the host. Injuries to the intestinal barrier increase intestinal permeability to bacteria and their metabolites (45). The IMB is responsible for the majority of negative effects on IBF. When the IMB is compromised, bacteria and their derivatives in the intestines can break through and enter the bloodstream, causing bacteria or endotoxins to be transferred to other organs, thus promoting the spread of enterogenous illness (46). A number of studies have evaluated the efficacy of probiotics in IAIs (Table I). For example, some lactic acid bacteria and *Bifidobacterium* can upregulate the expression of tight junction proteins, improving intestinal integrity and protecting the IMB (47,48). Miele *et al* (48) demonstrated that damage to the tight junctions of IECs may lead to increased intestinal permeability, leading to the transposition of a large number of bacteria and bacterial endotoxins into the blood circulation. Probiotics can help prevent the invasion of pathogenic bacteria, forming a microbial membrane with intestinal mucosal epithelial cells, and competitively inhibiting the adhesion and colonization of pathogenic bacteria (47).

Immune regulatory mechanisms of probiotics in IAIs. The interaction with IECs and the generation of certain immune regulatory factors to increase the body's immune function and manufacture immunoglobulin to resist harmful microorganisms represent the regulatory effects of the immune system. When activated by antigens, macrophages, B lymphocytes and natural killer cells initiate an immunological response, stimulating the intestinal mucosa to release anti-inflammatory cytokines, increasing intestinal immunological performance and enhancing immunological barrier function (49). Some probiotics can boost phagocytic or natural killer cell activity and interact with dendritic cells directly. Bharwani *et al* treated mice with oral *Lactobacillus rhamnosus* (JB-1) for 28 days, and

the results revealed that treatment with JB-1 increased $IL-10^+$ regulatory T-cells and reduced the activation of stress-related dendritic cells, affecting the regulation of stress on immunity (50). Furthermore, to limit inflammation, *Bifidobacterium* relies on T-cell control, and it can significantly reduce the inflammatory phenotype and histopathology produced by cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies (50).

Regulation of the gut barrier by probiotic metabolites in IAIs. Probiotics lead to the formation of secondary metabolites, such as bacteriocins, extracellular vesicles, short fatty acids chain, indole and extracellular proteins (secreted proteins). Bacteriocins are a class of ribosomally synthesized antimicrobial peptides produced by bacteria (51,52). Bacteriocins can function as colonizing peptides of certain intestinal micro-organisms, promoting these bacteria to obtain a competitive advantage over other strains and to thus occupy established niches in the intestines. Alternatively, bacteriocins can function as 'killing' peptides, since they can interfere with the growth of pathogens (particularly Gram-negative bacteria) by penetrating the inner membrane or disrupting cell wall synthesis (53). Extracellular vesicles are involved in bacteria-host communications and in the maintenance of the gut homeostasis. It has been reported that the oral application of *Akkermansia muciniphila*-derived extracellular vesicles can alleviate dextran sulfate sodium-induced colitis by preventing inflammatory cell infiltration into the colon wall and alterations in colon length (54). Short-chain fatty acids, which comprise mainly butyrate, propionate and acetate, are metabolites secreted by intestinal microbiota from undigested dietary carbohydrates and proteins (55). As butyrate, among all short-chain fatty acids, is the preferred source of energy for colonic epithelial cells, the association between butyrate and the intestinal epithelial barrier has been previously studied (56). Butyrate can promote gut epithelium O_2 consumption, resulting in the stabilization of hypoxia-inducible factor (HIF) and can increase the expression of barrier-protective HIF target genes, connecting microbes and epithelial barriers (57). Indole is usually produced by bacteria that contain tryptophanase and has been reported to function as an intestinal symbiotic bacteria

MECHANISM OF PROBIOTICS IN INTRA-ABDOMINAL INFECTIONS

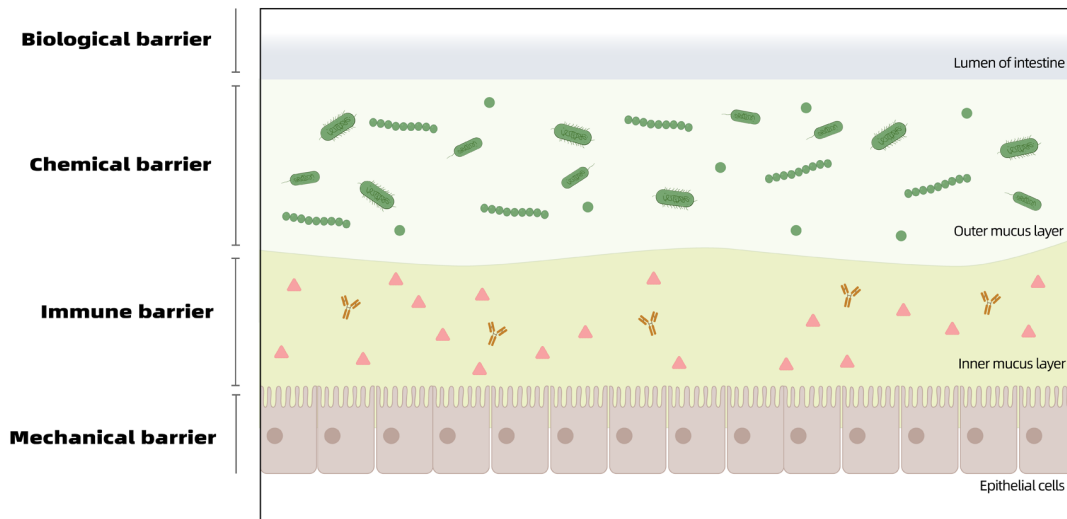
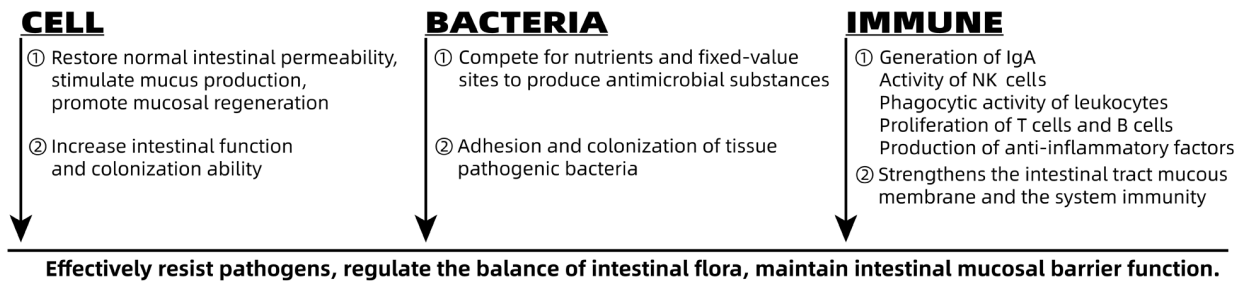


Figure 2. Mechanisms of action of probiotics in intra-abdominal infections. The top panel illustrates the cell-, bacteria- and immune-related mechanisms of probiotics. The bottom panel illustrates the sections of the intestinal mucosal barrier. NK cells, natural killer cells.

signal (58,59). It has been demonstrated that indole produced by symbiotic *E. coli* can inhibit the chemotaxis of pathogenic *E. coli*. *E. coli*-secreted indole can also inhibit the attachment of pathogens to the epithelium by increasing the expression of genes involved in intestinal epithelial function, such as actin cytoskeleton, adhesion junctions and tight junctions (60). The *Lactiplantibacillus plantarum* BMC12 secretes extracellular proteins and considerably reduces the adhesion of microbes or strengthens the gut barrier. It has been shown that two proteins secreted by *p40*, *p75* and *LGG* improve IEC homeostasis. Moreover, *p40* and *p75* maintain gut homeostasis by activating the EGFR/PIK3/Akt signaling pathway. It has been confirmed that probiotic-secreted proteins are involved in the host and symbiotic bacterial association (61).

These secondary metabolites can protect the gut epithelial barrier, while integrating with certain antimicrobial peptides, instantly enhancing mucus secretion via goblet cells and promoting the tight junction protein expression. They thus participate in the metabolism of human nutrients.

4. Safety of the use of probiotics in intra-abdominal infection

Approximately 230 million surgical procedures are performed worldwide each year. Some can lead to

complications post-surgery, including surgical site infections, urinary tract infections, pneumonia and sepsis. Standard practice is prophylactic antibiotic treatment; however, this is complicated by the increase in antibiotic resistance. A recent network meta-analysis of 2,952 patients undergoing abdominal surgery in 31 studies revealed a beneficial effect of synbiotics on surgical site infection (62). In that meta-analysis, it was found that synbiotics (successful trials focused on *Lactiplantibacillus plantarum*, *Lactocaseibacillus casei* and *Bifidobacterium breve* combined with galacto-oligosaccharides) were the most effective interventions for reducing pneumonia, urinary tract infections, sepsis, hospital duration and antibiotic use, whereas they had no effect on mortality (62). It was concluded that surgeons should consider the use of synbiotics as an adjuvant treatment for the prevention of post-operative complications (54). Another meta-analysis documented similar effects (63), although it was concluded that these observations should be treated with caution due to possible publication bias. In a recent randomized controlled clinical trial, in which 55 patients who underwent liver transplants received four probiotics or polylactic acid-placebo treatments prior to the scheduled transplantation, it was shown that at 90 days following the intervention, the infection rate was significantly lower in the patients receiving the probiotics compared with the control group (5 vs. 48%, $P=0.002$) (64). In

addition, in another randomized controlled clinical trial with 18 patients with head and neck cancer, no symbiotic effects of *Lactocaseibacillus paracase*, *Bifidobacterium lactis*, *Lactobacillus acidophilus* and *Lactobacillus* plus fructooligosaccharides were observed compared with the 18 placebo controls (65). Several clinical trials on human milk oligosaccharides (HMOs) have been registered, and HMOs may well represent a novel trend in prebiotics (66–68). Chemically defined metabolites or cell wall compounds released by probiotics may also become more important in the future (69). Probiotics may affect the gut-brain axis, with implications for patients with irritable bowel syndrome, mood disorders and anxiety (70).

5. Conclusions and future perspectives

In recent years, studies have demonstrated that the intestinal flora of patients with abdominal cavity infections exhibits certain dysfunctions, and the resulting intestinal microecological imbalance and the impaired IMB function may be the starting point of the inflammatory reaction of abdominal cavity infection. When the intestinal flora is unbalanced, the IMB function is impaired, and the impaired IMB function is the most important link for the occurrence of intestinal inflammatory reactions and abdominal infections. As a result, preserving the intestinal microecological balance is crucial in the treatment of abdominal infections (15,42,47,71). It has been shown that H₂O₂, bacteriocin and biosurfactant secreted by *Lactobacillus* can kill pathogenic microorganisms, so as to further control the inflammatory response and enhance the therapeutic effect (47).

The metabolites of probiotics play a crucial role in regulating host-disease interactions. Extracellular polysaccharide (EPSCG11) from *Lactobacillus plantarum* BGCG11 has been shown to alleviate inflammatory pain in rats, reducing the expression of pro-inflammatory factor, and increasing that of anti-inflammatory factors (IL-10 and IL-6), thus exerting potent anti-hyperalgesic and anti-edema effects (72). Therefore, it can be concluded that the application of probiotics for the clinical treatment of abdominal cavity infections may aid in the suppression of the inflammatory response and in relieving associated pain or discomfort.

Despite reports of microbial research in high-impact scientific journals (73–76), a broad definition of probiotics should be avoided. In the case that a probiotic is found to exert a medical effect, it should be noted that this effect is associated with specific strains or specific prebiotics, providing specific health effects in a specific patient or in a specific population. Although this statement is trivial, it is still difficult to distill these positive conclusions from the complex and sometimes contradictory research literature.

In conclusion, probiotics and their metabolites may improve the prognosis of IAIs by regulating IBF, immune regulation and dysbacteriosis. However, further large-sample, multi-center clinical trials are required to further explore the use of probiotics in the treatment of IAIs.

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Authors' contributions

ST and JL conceived the review and drafted the manuscript. CX was responsible for the preparation of the figures and the literature search. DS and HC revised, edited and finalized the manuscript for submission. GZ reviewed the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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