Recent Advances in the Utilization of Probiotics to Address Severe Acute Pancreatitis by Modulating the Intestinal Microbiota

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This review elaborates on the mechanisms, research progress, and future directions of probiotics in managing severe acute pancreatitis. Probiotics have been validated to positively affect the regulation of the intestinal microbiota, immune system, and inflammatory responses. Nevertheless, there is still contention regarding the precise therapeutic effects of probiotics and the optimal application strategies. By reviewing relevant domestic and international studies, this review proposes future research directions, including individualized probiotic treatment strategies and the development of new strains, in the hope of providing more effective strategies and directions in treating severe acute pancreatitis.

Key words: Probiotics, intestinal microbiota, severe acute pancreatitis, pancreatic tissue

Severe Acute Pancreatitis (SAP) is a serious inflammatory disease, and its incidence and mortality rate are rising year by year, posing a great challenge to clinical treatment[1]. Although treatment methods for SAP are continuously developing, effective means to alleviate the inflammatory response and repair the damaged pancreatic tissue are still lacking[2]. The intestinal microbiota, a crucial microbial community in the human body, plays an essential role in preserving intestinal homeostasis and immune balance[3]. In recent years, researchers have gradually recognized the close relationship between intestinal microbiota and SAP[4]. Gut dysbiosis may serve as a significant trigger for SAP, further exacerbating the condition, and the modulation of intestinal microbiota has become a novel approach in treating this condition. Probiotics, a widely employed microbial supplement can beneficially impact the human body through a variety of mechanisms, encompassing the regulation of intestinal microbiota, enhancement of immune function, and preservation of the intestinal barrier[5]. Researchers have shown an escalating interest in the use of probiotics to adjust the intestinal microbiota for treating SAP in recent years. Abundant clinical studies and animal experiments have demonstrated that probiotics may have the capacity to alleviate inflammation, support the recovery of pancreatic tissue and enhance the management of SAP by optimizing the balance and microbial diversity of the intestinal microbiota[6]. The aim of this review is to systematically evaluate and summarize the research progress concerning the utilization of probiotics to modulate the intestinal microbiota in managing SAP. This aims to offer novel concepts and approaches for clinical treatment, based on understanding the mechanisms of action and evaluating the therapeutic effects. Additionally, we will discuss the potential application prospects and challenges of using probiotics in treating SAP, offering insights for further research and the development of personalized treatment strategies. A close correlation exists between the intestinal microbiota and SAP. The intestinal microbiota constitutes the largest microbial community in the human body, consisting of trillions of bacteria, fungi, viruses, and various other microorganisms. Their function is critical in upholding intestinal function, digestion, absorption, and immune regulation[7]. However, when the intestinal microbiota becomes imbalanced, it can lead to a range of health issues, including inflammatory diseases[8]. Studies have shown that a comparative analysis of fecal samples from individuals with acute pancreatitis and healthy

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individuals revealed that the fecal samples of acute pancreatitis patients contained a higher abundance of *Escherichia coli* and *Enterococcus* compared to those of healthy individuals, while the quantity of *Lactobacillus* was significantly reduced[9]. Additionally, the overall structure and diversity of the dominant gut microbiota in individuals with SAP changed significantly, which was more pronounced compared to individuals without the condition. Furthermore, the use of more sensitive 16S ribosomal RNA (16S rRNA) high-throughput sequencing technology revealed a significant reduction in the quantity and diversity of gut microbiota. Additionally, there was a decrease in bacteria from the *Firmicutes* and *Spirochaetes phyla*, while there was no apparent change in the *Bacteroidetes* and *Proteobacteria phyla*[10]. The evidence indicates a clear correlation between modifications in the intestinal microbiota and acute pancreatitis. SAP is a serious condition caused by inflammation of the pancreatic tissue. When the pancreas is damaged or inflamed, it releases a large amount of digestive enzymes, leading to self-digestion and tissue damage. At this stage, the intestinal microbiota could be instrumental in the initiation of pancreatic inflammation. The primary concern is that an imbalance in the intestinal microbiota can cause damage to the intestinal mucosa, ultimately disrupting the function of the intestinal barrier[11]. This permits bacteria and toxins from the intestines to access the circulatory system through the intestinal mucosa, provoking an inflammatory response and injury to the pancreas. Secondly, an imbalance in the intestinal microbiota may cause abnormal immune system function, thereby affecting the response to pancreatic inflammation. Some studies have shown that an imbalance in the intestinal microbiota can cause abnormal activation of immune cells and imbalance in regulation, leading to the further exacerbation of the inflammatory response[12]. Additionally, an imbalance in the intestinal microbiota can lead to the abnormal release of inflammatory mediators in pancreatic tissue. Research has demonstrated that certain bacterial components and metabolites can influence the generation and release of inflammatory mediators, further promoting the development of pancreatic inflammation[13]. Probiotics are live microorganisms that confer health benefits on the host when ingested orally are referred to as probiotics. They primarily include common bacteria and yeast such as *Lactobacillus*, *Bifidobacterium*, and yeast. They are widely used in the fields of food, health products, and medicine[13]. Based on their strain characteristics and growth environment, probiotics can be classified into several categories. Common categories of probiotics include *Lactobacillus* (such as *Lactobacillus* and *Lactobacillus acidophilus*), *Bifidobacterium*, and yeast (such as *Saccharomyces boulardii* and brewer's yeast). Currently, the mechanisms by which probiotics participate in the regulation of the intestinal microbiota mainly include four categories: Improving microbiota balance by impeding the growth and development of pathogenic bacteria and fostering the growth and propagation of beneficial bacteria, thereby probiotics can adjust the equilibrium of intestinal microbiota. Competing for microbial niches by occupying the microbial niches in the gut, reducing the attachment and growth of pathogenic microorganisms, thus preserving intestinal health. Reducing harmful metabolites by suppressing the proliferation of harmful bacteria and diminishing the generation of detrimental metabolites through the production of bioactive compounds, including organic acids and antibacterial substances. Modulating the gut immune system by regulate the intestinal mucosal immunity, enhance the activity of immune cells, stimulate the production of immune regulatory factors (such as immunoglobulins), and thus enhance intestinal resistance and immune function. With respect to immune system regulation, studies have shown that probiotics can enhance immune system function. For example, some research has found that probiotics can promote the activation of immune cells, increase the bactericidal activity of immune cells, and induce the production of immune factors, thereby improving the body's ability to respond and enhancing immune function[14]. Furthermore, the role of probiotics in regulating intestinal barrier function is also a matter of great interest. Research has indicated that probiotics assist in preserving the integrity of the intestinal mucosal barrier, fostering the growth and restoration of intestinal epithelial cells, and averting the infiltration of injurious substances, thereby shielding the intestines from harm[15]. In terms of regulating inflammatory responses, probiotics also play a significant role. Several studies have shown that probiotics can inhibit the generation and release of inflammatory mediators, thus regulating immune system inflammation, reducing the severity of the inflammatory response, and lowering the damage caused by inflammation to tissues[16]. Hence,

probiotics are pivotal in the regulation of intestinal well-being and immune homeostasis through their influence on the immune system, intestinal barrier function, and the inflammatory response, thus positively affecting the maintenance of overall health. Studies on the use of probiotics in treating SAP have shown promising potential, but further in-depth research is needed to determine the optimal application strategies and effectiveness. Recent studies have demonstrated that probiotics exhibit positive effects in the treatment of SAP in animal experiments[17-19]. A meta-analysis from 2012 revealed that probiotics not only reduced the mortality rate of experimentally induced SAP in rats but also improved the histological score of the pancreas and reduced the occurrence of infectious complications[20]. Furthermore, a study illustrated that probiotics elevated the expression of intestinal epithelial transmembrane proteins in SAP patients, safeguarding the integrity of the intestinal barrier, rectifying intestinal microbiota dysbiosis, and reducing bacterial translocation to maintain gut microbiota equilibrium[21]. Another research showed that probiotics can reduce the overgrowth of potential pathogenic bacteria in the duodenum, thereby decreasing the translocation of intestinal bacteria, including to the pancreas, suggesting that the combined use of multiple probiotics can reduce gut bacterial translocation and decrease mortality in SAP[22]. Research results by Jiang *et al.*[23] indicated that administering probiotic treatment in large and small doses reduced the mortality rate in experimental animals, as well as decreased the levels of serum amylase, Interleukin-6 (IL-6), and Tumor Necrosis Factor-Alpha (TNF-α), demonstrating that probiotics play a protective role in severe acute necrotizing pancreatitis by inhibiting the expression of inflammatory factors. These experimental outcomes provide valuable evidence for the role of probiotics in preventing and treating SAP. Various domestic studies have indicated the potential benefits of probiotics in managing SAP. For example, Li *et al.*[24] observed 25 individuals with SAP and found that oral administration of probiotic preparation. Jin Shuangqi as adjunctive therapy significantly reduced the time for pain relief, the decrease in serum amylase levels, and the occurrence of complications, as well as shortened the average hospitalization time. Wu *et al.*[25] conducted a study on 27 individuals with SAP and found that supplementation with a complex lactic acid bacteria preparation significantly reduced the recovery time of liver function and the average hospitalization time. Additionally, the research by Wang *et al.*[26] revealed that the use of a four-strain probiotic preparation could significantly decrease serum endotoxin and procalcitonin levels, while improving the overall clinical efficacy. Nevertheless, a multicenter, large-scale, randomized, double-blind clinical trial conducted in Europe revealed that the prophylactic administration of probiotics failed to lower the incidence of infectious complications in SAP, and instead, heightened the risk of patient mortality[27]. Additionally, a meta-analysis revealed that probiotics did not reduce the mortality rate, the occurrence of infected pancreatic necrosis, the frequency of surgical interventions, or the duration of hospitalization in individuals with SAP[28]. Consequently, while these conclusions remain controversial, the exact therapeutic efficacy of probiotics in treating SAP still requires further discussion. It should be noted that the current research on probiotic treatment for SAP remains relatively limited, and there is a lack of unified treatment plans and guidelines. Therefore, further clinical trials and experimental research are essential to determine the optimal application strategies and effectiveness of probiotics in managing SAP. The use of probiotics in managing SAP presents broad application prospects. By regulating the intestinal microbiota, probiotics can restore microbiota balance, promote the alleviation of inflammation, facilitate pancreatic tissue repair, and effectively improve the condition. Probiotics demonstrate high safety, good tolerance, and can be combined with traditional treatment methods, enhancing the likelihood of treatment success. However, probiotic treatment still faces some challenges, including the lack of unified treatment plans and dosage guidelines, limitations in the selection of probiotic strains, and incomplete understanding of their mechanisms of action. Therefore, future research directions include the development of personalized probiotic treatment strategies, selecting the most suitable probiotic strains and dosages based on individual differences and characteristics of the gut microbiota. Furthermore, exploring and screening novel strains with better therapeutic effects and the ability to regulate the gut microbiota is warranted. In-depth research into the mechanisms of probiotics, exploring their relationship with the gut microbiota, immune system, and inflammatory responses from a molecular and microbic perspective, will contribute to a better

understanding of their therapeutic effects and mechanisms. Additionally, comprehensive multicenter clinical trials involving large sample sizes are needed to evaluate the efficacy of different probiotic strains, dosages, and administration approaches in treating SAP, ultimately validating and confirming the clinical benefits of probiotic intervention. The findings from these studies will furnish more detailed guidance and recommendations for employing probiotics in treating SAP, ultimately delivering a safer and more effective treatment strategy for patients.

Conflict of interests:

The authors declared no conflict of interests.

REFERENCES

1. Cai Y. Research progress in the clinical treatment of severe acute pancreatitis. Chin Commun Phys 2023;39(18):4-6.
2. Feng JF. Effect of surgical and non-surgical treatment of severe acute pancreatitis. Chin Sci Tech J Data Med Health 2023;5:3.
3. Wang J, Ouyang H, Xie H. Classification and identification of endophytic bacteria PBB-32 from Pseudostellariae *pseudostellariae* and effects of their metabolites on intestinal microbial community in mice. Chin J Microbiol 2019;48(2):14.
4. Qiao J, Chu CL. The relationship between intestinal flora imbalance and severe acute pancreatitis. J Acute Crit Care Intl Med 2019;29(1):51-52.
5. Wei J. Study on regulation of intestinal flora by *Lactobacillus plantarum* to prevent DSS induced colitis in mice. Lanzhou University.
6. Tan C, Wang H. Regulation and mechanism of probiotics on intestinal bacterial translocation infection in rats with acute pancreatitis. J Xinjiang Med Univ 2021;44(8):897-901.
7. Zhang X, Sun H. Effects of intestinal flora on human health and its application. Biomed Transform 2021;2(2):39-45.
8. Zhuo LH. Clinical analysis of inflammatory bowel disease complicated with intestinal flora dysregulation. Southern Med Univ 2019.
9. Gu XH, Wang Y, Cai HJ. Effects of early enteral nutrition and probiotics on intestinal mucosal barrier function and immune function in acute pancreatitis. J Anhui Med 2002;26(10):1977-80.
10. Zhang C, Wu J. The role and mechanism of intestinal flora in the maintenance of intestinal barrier function. J Digestive Cancer 2017;9(3):162-7.
11. He C, Zhu Y, Nong H. Effect and significance of intestinal flora imbalance on occurrence and development of acute pancreatitis. Chin J Pancr Dis 2018;18(1):3.
12. Ning JW. The role and molecular mechanism of Caspase-1 signaling pathway in the protection of intestinal mucosal barrier injury in severe acute pancreatitis. Zhejiang Univ 2019.
13. Shang Q, Li YL, Shi YY. Research progress of probiotics on immune function of animal intestinal epithelial cells. Chin J Animal Sci 2014;50(13):87-90.
14. Huang X. Research progress on immunomodulatory effects of probiotics and their application in the treatment of intestinal diseases. Health Care Guide 2018;18:33-4.
15. Zhang Z, Li Z, Li Q. Effects of probiotics on intestinal barrier function and immune regulation in patients with Crohn's disease. Chin J Microecol 2022;34(11):1314-9.
16. Tian YA, Zhang C, Yang T. Research progress of probiotics and fecal bacteria transplantation in regulating inflammatory bowel disease. Food Sci 2021;42(19):10.
17. Muftuoglu MA, Isikgor S, Tosun S, Saglam A. Effects of probiotics on the severity of experimental acute pancreatitis. Eur J Clin Nutr 2006;60(4):464-8.
18. Lutgendorff F, Trulsson LM, van Minnen LP, Rijkers GT, Timmerman HM, Franzén LE, *et al.* Probiotics enhance pancreatic glutathione biosynthesis and reduce oxidative stress in experimental acute pancreatitis. Am J Physiol Gastrointest Liver Physiol 2008;295(5):G1111-21.
19. Horst NL, Marques RG, Diestel CF, Matzke BD, Caetano CE, Simões FC, *et al.* Effects of probiotic supplementation on markers of acute pancreatitis in rats. Curr Ther Res 2009;70(2):136-48.
20. Hooijmans CR, de Vries RB, Rovers MM, Gooszen HG, Ritskes-Hoitinga M. The effects of probiotic supplementation on experimental acute pancreatitis: A systematic review and meta-analysis. PloS One 2012;7(11):e48811.
21. Qin H, Su Z, Fan X. Effects of probiotics on intestinal microecology and close connection in rats with acute pancreatitis. Chin J Clin Nutr 2006;14(2):5.
22. van LP, Timmerman HM, Lutgendorff F. Modification of intestinal flora with multispecies probiotics reduces bacterial translocation and improves clinical course in a rat model of acute pancreatitis. Surgery 2007;141(4):470-80.
23. Jiang P. Protective effect of probiotics on acute necrotizing pancreatitis in rats. Chin J Mod Med 2012;14(12):3.
24. Li Y. Adjuvant treatment of 14 cases of severe acute pancreatitis with probiotics. World Chin Digestive J 2007;15(3):3.
25. Wu X, Zhang Q. Treatment of 27 cases of liver damage in severe acute pancreatitis with probiotics. Clin Med 2009;29(2):51-2.
26. Wang W, Chen H. Effect of *Bifidobacterium* tetrad on serum endotoxin and procalcitonin levels in patients with acute pancreatitis. Chin J Microecol 2014;26(6):3.
27. Besselink MG, van Santvoort HC, Buskens E. Probiotic prophylaxis in predicted severe acute pancreatitis: A randomised, double-blind, placebo-controlled trial. Lancet 2008;371(9613):651-9.
28. Zhan Y, Wang X, Ma Z. Meta-analysis of probiotics in the treatment of severe acute pancreatitis. Mod Prev Med 2014;41(5):5.

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