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Research Progress in Integrated Traditional Chinese and Western Medicine for Intestinal Barrier Injury in Acute Pancreatitis

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Abstract: ***Intestinal mucosal barrier dysfunction occurs in the early stage of acute pancreatitis (AP), especially severe acute pancreatitis (SAP). It is a key link inducing enterogenic infection, systemic inflammatory response syndrome and even multiple organ dysfunction. Modern medicine has limited interventions for intestinal barrier injury, while traditional Chinese medicine (TCM), with its holistic regulatory advantages of multi-target and multi-pathway effects, has shown unique value in this field. This paper systematically reviews the theoretical basis and experimental evidence of TCM treatment for intestinal barrier injury in AP in recent years, sorts out its mechanism of action from four dimensions: mechanical barrier, immune barrier, biological barrier and chemical barrier, and integrates the latest progress in network pharmacology and molecular biology research, so as to provide references for clinical practice and basic research.***

Keywords: Acute pancreatitis, Integrated traditional Chinese and western medicine, Intestinal barrier, Therapeutic progress, Traditional Chinese medicine, Intestinal microecology**.**

1. Introduction

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Acute pancreatitis is a disease with high incidence and high medical resource consumption worldwide. Its pathological core is the abnormal activation of pancreatic enzymes in acinar cells, leading to pancreatic autodigestion and local inflammation, which can rapidly cascade into uncontrolled systemic inflammatory response. Although most cases of AP are mild and self-limiting, approximately 20%–30% of patients progress to SAP with persistent organ failure, and the case fatality rate can reach 20%–40% [1]. Intestinal microecological imbalance and intestinal mucosal barrier dysfunction appear in the early stage of SAP, and this pathological link is regarded as the hub triggering the "second hit" — intestinal bacteria and endotoxin translocate into the blood circulation, inducing enterogenic infection and systemic inflammatory response syndrome (SIRS), and ultimately leading to multiple organ dysfunction syndrome (MODS). Therefore, protecting the integrity and function of the intestinal mucosal barrier has become one of the core strategies for the treatment of SAP [2,3].

Modern medical interventions for intestinal barrier injury mainly include fluid resuscitation, antibiotic application, nutritional support and probiotic supplementation, but their effects are controversial. Some studies even suggest that single use of probiotics may increase the risk of complications [4]. With "purging fu-organs to relieve interior excess" as the main therapeutic principle, combined with methods of clearing heat and detoxifying, activating blood circulation and removing blood stasis, TCM has shown unique advantages in repairing the intestinal barrier. In recent years, studies have gradually revealed the mechanism of action of TCM compounds and active ingredients at the organ, cellular and molecular levels [5]. This paper systematically reviews the research status of TCM treatment for intestinal barrier injury in AP from four aspects: pathophysiological basis, TCM theoretical understanding, experimental research evidence and mechanism progress.

2. Pathophysiological Basis of Intestinal Barrier Injury in Acute Pancreatitis

The intestinal mucosal barrier is composed of mechanical barrier, immune barrier, biological barrier and chemical barrier. Under the pathological state of SAP, all four barriers are damaged:

Mechanical barrier injury is the core link. The mechanical barrier is mainly composed of intestinal epithelial cells and tight junctions (TJ) between intestinal epithelial cells. It has been confirmed that a variety of proteins are involved in the formation of TJ, including Claudin proteins, Occludin proteins and ZO structural proteins. Their normal expression plays a decisive role in maintaining the structural function of TJ and intestinal permeability. In addition, the intact intestinal mucosal mechanical barrier has low permeability and does not allow macromolecules such as pathogens and endotoxin to pass through, thus maintaining the stability of the internal environment. However, when the intestinal mucosal mechanical barrier is damaged and intestinal homeostasis is broken, microorganisms and endotoxin in the intestine break through the intestinal mucosal barrier, enter the blood and cause bacterial and endotoxin translocation, promoting the occurrence of enterogenic infection, and even developing into systemic inflammatory response syndrome or multiple organ failure [6].

The immune barrier consists of gut-associated lymphoid

tissue, dispersed immune cells and various immune molecules such as secretory immunoglobulin A (sIgA), transforming growth factor-β (TGF-β) and intestinal trefoil factor (ITF/TFF3). It maintains the stability of the intestinal immune environment by activating humoral and cellular immunity, and prevents pathogens from damaging the body [7].

Biological barrier: Intestinal microecology in the narrow sense only includes bacteria, while in the broad sense, it takes bacteria as the main component and includes non-indigenous microorganisms such as viruses and fungi. Intestinal flora can be divided into symbiotic bacteria, pathogenic bacteria and opportunistic pathogenic bacteria according to physiological functions. The main flora constituting the biological barrier are Lactobacillus and Bifidobacterium, which maintain the intestinal anaerobic internal environment and limit the colonization of aerobic bacteria [8].

The chemical barrier: Crypt tissues under the intestinal mucosal villi can secrete mucus, enzymes and other substances, which can inhibit pathogen invasion and play an important immune defense function in the host. Glycoproteins secreted by goblet cells are the main components of the intestinal mucus layer. Glycoproteins contain different types of polysaccharide core structures, providing nutrition and attachment sites for intestinal microorganisms, and can also secrete antibodies against specific pathogenic microbial antigens [9]. When pathogens invade, glycoproteins transmit signals to dendritic cells and trigger intestinal mucosal immune response [10]. In addition, digestive juices such as gastric acid and bile in the intestine can kill some foreign pathogenic microorganisms. Meanwhile, bacteria adhering to the submucosa can also produce anti-adhesion molecules through their own metabolism to inhibit the growth of pathogenic microorganisms [11].

The destruction of the above four barriers is interrelated, forming a vicious circle, which ultimately leads to bacterial/endotoxin translocation and triggers a systemic inflammatory cascade reaction.

3. Understanding of Acute Pancreatitis in Traditional Chinese Medicine

There is no specific name for “pancreas” in ancient TCM literature, so the attribution of the pancreas in the five zang-organs and six fu-organs has long been controversial. Based on the core concepts of “holism” and “syndrome differentiation and treatment”, most discussions hold that the pancreas belongs to the “spleen”. AP is classified into the categories of “abdominal pain”, “spleen heart pain” and “pancreatic jaundice” in TCM. Its core pathogenesis is “obstruction of fu-qi, intermingled dampness-heat, stasis and toxin”, and therapeutic methods represented by “purging fu-organs to relieve excess, clearing heat and detoxifying, activating blood circulation and removing blood stasis” have been established [12].

TCM treatment of AP is not simply “one prescription for one disease”, but is based on a rigorous syndrome differentiation and treatment system, and its efficacy is being explained by modern scientific methods.

Mechanism of TCM prescriptions

Studies have shown that prescriptions such as Dachengqi Decoction, Qingyi Decoction and Chaishao Chengqi Decoction and their analogous prescriptions can improve gastrointestinal function, protect the intestinal mucosal barrier, regulate immune inflammatory response, and help initiate early enteral nutrition in the treatment of AP [13-15]. For example, Chaishao Chengqi Decoction has shown good efficacy in clinical application, and its mechanism of action has also been deeply studied [16].

Modern studies have also confirmed from the perspective of microcirculation disorder that single TCM herbs such as rhubarb, Salvia miltiorrhiza and mirabilite, as well as Chinese patent medicines such as Salvia miltiorrhiza injection, can improve microcirculation disorder and reduce the body’s inflammatory response [17]. Studies have also gone deep into the level of signaling pathways. For example, it has been found that active ingredients of TCM can disrupt the inflammatory cascade by regulating the MAPKs signaling pathway, and protect pancreatic and extra-pancreatic tissues [18].

Dachengqi Decoction and the method of purging fu-organs to relieve interior excess

This is the representative prescription for the syndrome of excess heat in fu-organs in AP. Studies have shown that Dachengqi Decoction can not only stimulate intestinal peristalsis to promote defecation, but also down-regulate the levels of serum inflammatory factors (TNF-α, IL-6), protect the intestinal mucosal barrier, reduce bacterial/endotoxin translocation, and improve pancreatic microcirculation. Its mechanism of action is closely related to the inhibition of classic inflammatory signaling pathways such as NF-κB and MAPKs [19].

Qingyi Decoction

As a model prescription for integrated traditional Chinese and western medicine treatment of AP, it is composed of Bupleurum chinense, Scutellaria baicalensis, Picrorhiza scrophulariiflora, Aucklandia lappa, Corydalis yanhusuo, etc., which fits the pathogenesis of “combined disease of Shaoyang and Yangming” in AP. A network pharmacology study systematically revealed the multi-component and multi-target characteristics of Qingyi Decoction. Through active ingredients such as baicalin and emodin, it can act on multiple pathways such as inflammation, apoptosis and oxidative stress at the same time, exerting a synergistic therapeutic effect [20].

Xuebijing Injection

It is composed of Carthamus tinctorius, Paeonia lactiflora, Ligusticum chuanxiong, Salvia miltiorrhiza and Angelica sinensis, and is good at activating blood circulation and removing blood stasis. A large number of clinical Meta-analyses have confirmed that adding Xuebijing on the basis of standard western medicine treatment can significantly reduce the APACHE II score of SAP patients, improve the oxygenation index, and shorten the recovery time of organ

function [21]. Basic studies have revealed that it can inhibit the activation of NLRP3 inflammasome and regulate macrophage polarization, thereby curbing the "inflammatory storm" [22].

4. Mechanism of TCM Treatment for Intestinal Barrier Injury in Acute Pancreatitis

4.1 Protecting the Mechanical Barrier: Reducing Injury and Promoting Repair

The integrity of the mechanical barrier depends on the tight junction structure between intestinal epithelial cells and the survival state of epithelial cells. A number of experimental studies have confirmed that TCM compounds can effectively reduce intestinal mucosal pathological injury in SAP models.

In the SAP rat model intervened by Qingjie Chengqi Formula, the Chiu score of intestinal tissue in the treatment group was significantly reduced, and the levels of serum endotoxin (ET), TNF-α and IL-6 decreased simultaneously, suggesting that this formula protects the intestinal mucosal barrier by down-regulating the expression of inflammatory mediators [23]. Clinical studies of Tongfu Mixture on SAP patients with excess heat in fu-organs syndrome also observed that the intestinal barrier function indexes (such as serum diamine oxidase and D-lactic acid) were improved and the levels of inflammatory factors were reduced in the treatment group [24].

At the molecular mechanism level, caffeic acid (a water-soluble component of Salvia miltiorrhiza) reduces intestinal epithelial cell death by inhibiting the GSDMD-mediated pyroptosis pathway and down-regulating the expression of pyroptosis-related proteins such as Pyrin, NLRP3 and Caspase-1, thereby protecting the integrity of the intestinal barrier [3]. Chaihuang Qingyi Huoxue Granule can reduce the inflammatory cascade and improve intestinal mucosal injury by inhibiting the HMGB1/TLR4/NF-κB signaling pathway [25].

4.2 Regulating the Immune Barrier: Balancing Inflammation and Immunity

As the largest immune organ of the body, the immune function state of the intestine directly affects the prognosis of SAP. The regulation of TCM on the intestinal immune barrier is mainly reflected in two aspects: one is to inhibit excessive inflammatory response, and the other is to restore local immune function.

Network pharmacology studies suggest that Qingyi Decoction may exert therapeutic effects by regulating immune cell infiltration — IGFBP3 is negatively correlated with the infiltration of macrophages (M0) and neutrophils, while SHH is positively correlated with both, suggesting that this prescription may regulate the intestinal immune microenvironment through multiple targets [5]. The NLRP3 inflammasome is a key molecule connecting innate immunity and inflammation. Studies have confirmed that a variety of TCM herbs and their active ingredients target the NLRP3/Caspase-1/GSDMD pathway to inhibit IL-1β maturation and cell pyroptosis, thereby reducing inflammatory injury of the pancreas and intestine [26].

4.3 Remodeling the Biological Barrier: Regulating Intestinal Microecology

The "intestinal flora-host" interaction is a current research hotspot. Intestinal microecological imbalance occurs in the early stage of SAP, manifested as decreased flora diversity and increased opportunistic pathogenic bacteria. TCM has shown unique advantages in regulating intestinal flora and has become a potential method for the treatment of intestinal microecological imbalance in SAP [2].

A clinical study of Qihuang Tongmi Soft Capsules combined with probiotics showed that the combined treatment group was superior to the single probiotic or TCM group in reducing inflammatory indicators (CRP, IL-6, TNF-α) and improving intestinal barrier function, suggesting that the strategy of integrated traditional Chinese and western medicine to synergistically regulate intestinal microecology may have a synergistic effect [27]. Its mechanism may be related to TCM promoting probiotic colonization, inhibiting excessive proliferation of pathogenic bacteria, and regulating intestinal metabolites.

4.4 Repairing the Chemical Barrier: Promoting the Recovery of Gastrointestinal Function

The intestinal chemical barrier includes components such as mucus layer, digestive enzymes and bile acids. In SAP, gastrointestinal motility disorder occurs, intestinal contents stagnate, and the chemical barrier function is impaired. TCM herbs for purging fu-organs (such as rhubarb and mirabilite) can promote gastrointestinal peristalsis, shorten the time of intestinal opening, reduce the retention of toxins in the intestine, and indirectly protect the chemical barrier. In addition, some active ingredients of TCM can promote goblet cells to secrete mucus and enhance the barrier function of the mucus layer [4].

5. Research Progress of Compounds and Active Ingredients

5.1 Modern Interpretation of Classic Compounds

Qingyi Decoction is a classic prescription for the treatment of SAP, composed of Bupleurum chinense, Paeonia lactiflora, rhubarb, Scutellaria baicalensis, etc. The latest study integrated network pharmacology, machine learning and molecular docking technology, identified 30 potential therapeutic targets involving signaling pathways such as IL-17, TNF and NF-κB, identified IGFBP3 and SHH as core genes, and found that the p53 signaling pathway plays a key role in the treatment of intestinal barrier injury by Qingyi Decoction [5]. This research provides a methodological reference for revealing the "multi-component-multi-target-multi-pathway" action characteristics of TCM compounds.

A series of studies on Chaihuang Qingyi Huoxue Granule have shown that it protects the intestinal barrier function of SAP model rats through multiple mechanisms such as regulating the HMGB1/TLR4/NF-κB pathway, inhibiting

oxidative stress and improving microcirculation [25]. Compounds with the main efficacy of purging fu-organs, such as Qingjie Chengqi Formula and Tongfu Mixture, have also confirmed their intestinal barrier protective effects in clinical and experimental studies [23-24].

5.2 Mechanism of Active Ingredients

Caffeic acid extracted from Salvia miltiorrhiza protects the intestinal barrier by inhibiting the GSDMD-mediated pyroptosis pathway, providing a new molecular target for the treatment of AP with active ingredients of TCM [3]. This study used transcriptome sequencing combined with gene knockout mouse verification to clarify the key regulatory effect of caffeic acid on the pyroptosis pathway, reflecting the refinement trend of research on effective components of TCM.

The NLRP3 inflammasome has become a popular target for TCM treatment of AP. A review study systematically summarized the evidence that a variety of TCM herbs (such as baicalin, emodin, salvianolic acid, etc.) reduce pancreatic necrosis and intestinal barrier dysfunction by targeting the NLRP3/Caspase-1/GSDMD pathway [26]. Research on TCM targeting the NLRP3 inflammasome has formed systematic evidence. Review studies show that a variety of TCM compounds and active ingredients can reduce pancreatic necrosis, neutrophil infiltration and intestinal barrier dysfunction by inhibiting the activation of NLRP3 inflammasome. For example, Chaihuang Qingfu Pill reduces SAP-induced lung injury by inhibiting NLRP3-mediated macrophage pyroptosis; chlorogenic acid delays the progression of SAP by inhibiting NLRP3 inflammatory activation and activating the Nrf2/HO-1 pathway. These findings provide new molecular annotations for the multi-target regulation of the intestinal barrier by TCM [26].

The protective effect of zerumbone on the intestinal mucosal barrier of SAP rats shows a two-way regulatory characteristic. Experimental studies have shown that zerumbone treatment can reduce the infiltration of inflammatory cells in small intestinal tissue, relieve tissue congestion and edema, and reduce the levels of ET, IL-1β, TNF-α, NO, MPO and intestinal vascular permeability. At the mechanism level, on the one hand, zerumbone inhibits the number of NLRP3 and ASC positive cells and the expression of Caspase-1 protein in small intestinal tissue and mesenteric lymph nodes; on the other hand, it significantly up-regulates the expression level of sIgA protein in small intestinal mucosa [28]. This dual regulation mode of "inhibiting excessive inflammation-enhancing local immunity" reflects the fine regulatory characteristics of active ingredients of TCM.

6. Latest Progress in Mechanism Research

6.1 Intestinal Motility Disorder and Gastrointestinal Hormone Regulation

Intestinal motility disorder is not only the result of intestinal barrier injury, but also an important factor aggravating the disease. The mechanism study of Chaihuang Qingyi Huoxue Granule revealed the molecular basis of TCM regulating intestinal motility. The study showed that the small intestinal propulsion rate of SAP model rats was significantly decreased, mucosal damage and inflammatory cell exudation appeared in colon tissue, while the levels of serum tyrosine kinase receptor (c-kit) and motilin (MTL) were decreased, and the levels of substance P (SP) and vasoactive intestinal peptide (VIP) were increased. After intervention with Chaihuang Qingyi Huoxue Granule, the small intestinal propulsion rate increased significantly, colon pathological injury was alleviated, the expression of c-kit and MTL was up-regulated, and the expression of SP and VIP was down-regulated. This indicates that this prescription may indirectly protect the intestinal barrier by regulating the hormone network related to gastrointestinal and pancreatic endocrine system and improving intestinal motility disorder [29].

6.2 Two-way Regulation of the Intestinal Flora-microcirculation Axis

Intestinal flora imbalance and microcirculation disorder interact with each other, forming a vicious circle in the pathological process of SAP. A clinical study of compound Qingyi Decoction provides evidence-based evidence for this. The study included 70 AP patients and randomly divided them into a conventional treatment group and a compound Qingyi Decoction combined treatment group. The results showed that on the 3rd and 7th day of treatment, the white blood cell count, neutrophil count, red blood cell distribution width, interleukin-6, C-reactive protein and lactic acid levels in the combined treatment group were significantly lower than those in the control group, while the number of Bifidobacterium was significantly higher. Correlation analysis showed that the number of Bifidobacterium was negatively correlated with the level of inflammatory factors and positively correlated with platelet count. The researchers believe that compound Qingyi Decoction repairs the intestinal barrier by increasing the number of Bifidobacterium, thereby reducing the level of inflammation and improving microcirculation disorder. Its mechanism involves vascular endothelial injury repair, hemorheology recovery and microthrombus decomposition [30].

7. Summary and Prospect

Research on TCM treatment of intestinal barrier injury in acute pancreatitis has developed from phenomenon description to mechanism discussion, forming a theoretical framework of "taking purging fu-organs to relieve interior excess as the core and protecting four barriers with multiple targets". Existing evidence shows that TCM exerts its effects through the following approaches: (1) Protecting the mechanical barrier — reducing inflammatory injury, inhibiting cell pyroptosis, and maintaining tight junctions; (2) Regulating the immune barrier — regulating NLRP3 inflammasome and balancing immune cell infiltration; (3) Remodeling the biological barrier — regulating intestinal flora structure and improving microecology; (4) Repairing the chemical barrier — promoting gastrointestinal motility and enhancing mucus secretion.

However, current research still has deficiencies: most studies are small-sample clinical observations or animal experiments, lacking multi-center randomized controlled trials; compound components are complex, and the material basis of

pharmacodynamics is not completely clear; the evaluation indexes of intestinal barrier function have not been standardized. Future research should focus on: carrying out high-quality clinical studies to verify the efficacy; integrating omics technology and systems biology methods to deeply reveal the molecular mechanism of "multi-target network regulation" of TCM; exploring the optimized scheme of integrated traditional Chinese and western medicine treatment (such as TCM combined with probiotics); promoting the transformation from the "single-target" research paradigm to the "systemic regulation" research paradigm.

In conclusion, with its characteristics of holistic regulation and multi-target intervention, TCM shows broad prospects in the prevention and treatment of intestinal barrier injury in acute pancreatitis, which is worthy of in-depth research and clinical promotion.

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