Advances in Research of Effect of Huanglian Wendan Decoction on Intestinal Barrier Function of Ulcerative Colitis

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Abstract This study systematically reviews the pharmacological mechanisms of Huanglian Wendan Decoction in improving intestinal barrier function in ulcerative colitis (UC), including the regulation of intestinal chemical barrier, the regulation of intestinal immune barrier, and the improvement of intestinal biological barrier, in order to provide theoretical basis and new ideas for the clinical treatment of UC.

Key words Huanglian Wendan Decoction, Ulcerative colitis (UC), Intestinal barrier function, Pharmacological mechanism, Traditional Chinese medicine compound

1 Introduction

Ulcerative Colitis (UC) is a chronic non-specific inflammatory bowel disease primarily affecting the colonic mucosa and submucosa, with clinical manifestations including diarrhea, mucopurulent stool, and abdominal pain. Its pathogenesis involves complex interactions among genetic susceptibility, environmental triggers, dysregulated immune responses, and gut microbiota dysbiosis[1]. Recent studies indicate that intestinal barrier dysfunction serves as a pivotal mechanism in UC progression, encompassing mechanical barrier impairment (*e. g.*, tight junction protein disruption), chemical barrier degradation (*e. g.*, diminished mucus layer), immune barrier dysregulation (*e. g.*, innate immune cell dysfunction), and biological barrier compromise (*e. g.*, microbial dysbiosis). These collective disruptions increase intestinal permeability, promote bacterial translocation, and sustain chronic inflammation[2].

Huanglian Wendan Decoction originates from Systematic Differentiation of the Six Pathogenic Factors. It comprises Coptidis Rhizoma, Pinelliae Rhizoma, Citri Reticulatae Pericarpium, and Bambusae Caulis In Taenias, exerting effects of clearing heat, drying dampness, resolving phlegm, and harmonizing the stomach. Traditionally used for treating digestive system disorders[3]. Modern pharmacological studies reveal that Huanglian Wendan Decoction and its active components, such as berberine and baicalin, can regulate UC intestinal barrier function through multiple targets and pathways. For example, berberine alleviates inflammatory responses by inhibiting the NF-κB signaling pathway and repairs expression of tight junction proteins, such as ZO-1, and occludin[4]; baicalin improves the intestinal mucosal immune barrier by modulating Th17/Treg immune balance[5]. Additionally, Huanglian Wendan Decoction enhances biological barrier function by restructuring the gut microbiota, for example, increasing short-chain fatty acid-producing bacteria)[6].

At present, although some progress has been made in the research on the improvement of intestinal barrier function in UC by Huanglian Wendan Decoction, the specific molecular mechanism and the synergistic effect of drug formula still need to be further explored. Systematically combing its pharmacological mechanism will not only help to clarify the scientific connotation of traditional Chinese medicine, but also provide a theoretical basis for the development of new treatment strategies for UC. Future research can combine network pharmacology, intestinal organoid model and other technologies to further reveal the multi-dimensional regulatory network of Huanglian Wendan Decoction and promote its clinical transformation and application.

2 Composition and traditional efficacy

2.1 Drug composition and compatibility characteristics Huanglian Wendan Decoction is a classic formula in Traditional Chinese Medicine, primarily composed of Coptidis Rhizoma, Pinelliae Rhizoma, Citri Reticulatae Pericarpium, Poria, Glycyrrhizae Radix Et Rhizoma, Bambusae Caulis In Taenias, Aurantii Fructus Immaturus, and Zingiberis Rhizoma Recens. In this formula, Coptidis Rhizoma serves as the monarch drug, leveraging its bitter-cold properties to clear heat; Pinelliae Rhizoma and Citri Reticulatae Pericarpium act as minister drugs, functioning to dry dampness, resolve phlegm, regulate qi, and harmonize the stomach; Poria and Glycyrrhizae Radix Et Rhizoma serve as assistant drugs, fortifying the spleen, percolating dampness, and harmonizing the various medicinal components; Bambusae Caulis In Taenias and Aurantii Fructus Immaturus act as Envoy drugs, clearing heat, resolving phlegm, moving qi, and dissipating fullness[7]. The precise compatibility of ingredients in the formula embodies the TCM therapeutic principle of "clearing heat, resolving phlegm, harmonizing the stomach, and descending counterflow." The combination of Coptidis Rhizoma and Pinelliae Rhizoma forms the core of the formula: Coptidis Rhizoma clears heat with its bitter-cold nature, while Pinelliae Rhizoma resolves phlegm with its

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acrid-warm properties. Their combined cold and warm natures synergize, preventing Coptidis Rhizoma from excessively injuring the stomach with bitter-cold and counteracting Pinelliae Rhizoma's potential to generate heat through excessive warmth. The pairing of Citri Reticulatae Pericarpium and Poria demonstrates the cooperative action of regulating qi and percolating dampness, jointly harmonizing spleen-stomach function. This multi-layered, multi-targeted medicinal compatibility endows Huanglian Wendan Decoction with unique advantages in treating digestive and neurological disorders.

2.2 Traditional efficacy and modern pharmacological effects According to traditional Chinese medicine, Huanglian Wendan Decoction possesses the effects of clearing heat, resolving phlegm, harmonizing the stomach, and calming the spirit. It is primarily used to treat symptoms such as insomnia, palpitations, nausea, vomiting, and epigastric/distension caused by internal disturbance of phlegm-heat. From a modern medical perspective, research has revealed multifaceted pharmacological actions of this formula: Berberine can reduce inflammatory responses by inhibiting the release of inflammatory factors, demonstrating therapeutic effects on intestinal inflammation[8]. Active components in Pinelliae Rhizoma exhibit antitussive, expectorant, and antiemetic properties while regulating gastrointestinal function. Bambusae Caulis In Taenias contains multiple bioactive compounds with antipyretic, sedative, and anti-inflammatory pharmacological activities. Aurantii Fructus Immaturus enhances gastrointestinal smooth muscle tension, promotes peristalsis, and improves digestive function. Volatile oils and hesperidin in Citri Reticulatae Pericarpium contribute to regulating qi, fortifying the spleen, aiding digestion, and reducing inflammation. Poria modulates immune function, enhances bodily resistance, and exerts diuretic effects. Components such as glycyrrhizin and glycyrrhetinic acid in Glycyrrhizae Radix Et Rhizoma demonstrate diverse pharmacological actions including anti-inflammatory, anti-allergic, and immunomodulatory activities. These modern pharmacological mechanisms provide scientific evidence supporting Huanglian Wendan Decoction's efficacy in treating related disorders.

3 Protective effect on intestinal mechanical barrier

3.1 Inhibition of intestinal epithelial cell apoptosis/apoptosis Abnormal increase in intestinal epithelial cell apoptosis/pyroptosis compromises the integrity of the intestinal mechanical barrier. Studies indicate that multiple factors can induce intestinal epithelial cell apoptosis/pyroptosis, while Huanglian Wendan Decoction and its active components may inhibit this process through multiple pathways. Berberine from Coptidis Rhizoma in the formula downregulates pro-apoptotic protein Bax expression while upregulating anti-apoptotic protein Bcl-2 levels, thereby inhibiting apoptosis via the mitochondrial pathway[9]. Research demonstrates that baicalin in this formula blocks the caspase-3 activation pathway, mitigating lipopolysaccharide-induced intestinal epithelial pyroptosis[10]. Hesperidin in Citri Reticulatae Pericarpium inhibits NLRP3 inflammasome assembly, reducing gasdermin D-mediated pore formation in cell membranes to maintain intestinal epithelial integrity[11]. This multi-target regulatory mechanism provides cellular-level protection against intestinal barrier dysfunction. Furthermore, for inflammation-induced intestinal epithelial pyroptosis, Huanglian Wendan Decoction may suppress inflammasome activation, reduce cleavage of pyroptosis-related proteins like GSDMD, consequently inhibiting pyroptosis, preserving intestinal epithelial integrity, and protecting the intestinal mechanical barrier.

3.2 Promotion of tight junction protein expression Tight junction proteins are crucial components of the intestinal mechanical barrier, whose expression levels directly influence intestinal barrier function. Studies demonstrate that Huanglian Wendan Decoction and its active components can promote the expression of tight junction proteins. In *in vitro* cell models, treatment with Huanglian Wendan Decoction significantly increased the expression of tight junction proteins such as occludin, claudin-1, and ZO-1, as detected by Western blot and immunofluorescence techniques. Concurrently, elevated transepithelial electrical resistance values indicated enhanced intercellular tight junctions and improved barrier function[12]. In animal experiments, administration of Huanglian Wendan Decoction to intestinal inflammation models upregulated both mRNA and protein expression of tight junction proteins in intestinal tissues, while reducing intestinal permeability to macromolecules. This further confirms its role in promoting tight junction protein expression and strengthening intestinal mechanical barrier function[12]. The underlying mechanism may involve regulation of relevant signaling pathways, such as activating the PI3K/Akt pathway to facilitate the synthesis and assembly of tight junction proteins, thereby reinforcing intercellular connections among intestinal epithelial cells and enhancing intestinal mechanical barrier function.

3.3 Regulation of cell migration and repair Huanglian Wendan Decoction accelerates the repair of intestinal epithelium through a dual mechanism: on the one hand, the active components of Bambusae Caulis In Taenias can activate the Wnt/β-catenin pathway and promote the proliferation and differentiation of crypt stem cells; on the other hand, glycyrrhizic acid enhances cell migration by upregulating EGF receptor expression[13]. *In vitro* wound healing experiments showed that the prescription could increase the migration rate of intestinal epithelial cells by 40% – 60%, and significantly increase the expression of repair-related genes (TFF3, MUC2)[14]. This pro-repair effect is related to the regulation of intestinal immune microenvironment, which creates favorable conditions for epithelial regeneration by reducing the level of pro-inflammatory factors such as TNF-α.

4 Regulation of intestinal chemical barrier

4.1 Promoting mucus protein secretion Huanglian Wendan Decoction can significantly promote the secretion of mucin

(MUC2) by intestinal goblet cells through its active ingredients (such as Berberine, baicalin, *etc.*), thereby enhancing the chemical barrier function of the intestine. Studies have shown that Berberine can up-regulate the expression of MUC2 gene in goblet cells and promote the synthesis and secretion of mucin by activating AMPK/mTOR signaling pathway[15]. In addition, wogonoside can indirectly protect the integrity of mucus layer by inhibiting NF-κB signaling pathway to reduce inflammatory response[16]. The synergistic effect of these active components enables Huanglian Wendan Decoction to effectively maintain the thickness and continuity of intestinal mucus layer and provide physical and chemical protective barriers for intestinal epithelium.

4.2 Alleviating oxidative stress injury Multiple active components in Huanglian Wendan Decoction (*e. g.*, berberine, geniposide) exhibit significant antioxidant effects. These constituents alleviate oxidative stress-induced damage to the intestinal chemical barrier by scavenging free radicals (*e. g.*, ROS), upregulating antioxidant enzyme activity, such as SOD abd GSH-Px, and inhibiting lipid peroxidation. Specifically, berberine activates the Nrf2/ARE signaling pathway, promoting the expression of multiple antioxidant proteins, thereby enhancing intestinal epithelial cells' resistance to oxidative stress[17]. Furthermore, Huanglian Wendan Decoction reduces oxidative stress at its source by modulating gut microbiota balance and decreasing the abundance of pathogenic bacteria that produce reactive oxygen species.

4.3 Alleviating endoplasmic reticulum (ER) stress Huanglian Wendan Decoction can alleviate the damage of intestinal chemical barrier caused by ER Stress by regulating endoplasmic reticulum stress-related pathways, such as PERK/eIF2α, IRE1α/XBP1 and ATF6 pathways. Studies have shown that Berberine can inhibit the excessive activation of PERK/eIF2α pathway and reduce the apoptosis caused by unfolded protein response (UPR)[18]. Meanwhile, baicalin can alleviate ER stress-induced intestinal epithelial cell injury by down-regulating CHOP expression[19]. The synergistic effect of these active components enables Huanglian Wendan Decoction to effectively maintain the homeostasis of endoplasmic reticulum and protect the normal function of intestinal epithelial cells, thus maintaining the integrity of intestinal chemical barrier.

5 Regulation of intestinal immune barrier

5.1 Regulating the level of inflammatory mediators Huanglian Wendan Decoction, as a classic traditional Chinese medicine compound, contains multiple active components such as berberine and baicalin in its formulation ingredients including Coptidis Rhizoma, Pinelliae Rhizoma, and Citri Reticulatae Pericarpium. These components demonstrate significant effects in regulating intestinal inflammatory mediators. Research indicates that Huanglian Wendan Decoction can markedly suppress the expression of pro-inflammatory factors TNF-α and IL-6 while upregulating the level of anti-inflammatory factor IL-10, thereby alleviating intestinal inflammatory responses. TNF-α and IL-6 are key mediators of intestinal inflammation, whose overexpression can impair intestinal epithelial barrier function, whereas IL-10 exhibits anti-inflammatory and immunomodulatory properties[20]. By inhibiting the activation of the NF-κB signaling pathway, Huanglian Wendan Decoction reduces the release of pro-inflammatory factors while promoting the production of anti-inflammatory factors, thus maintaining intestinal immune homeostasis. Furthermore, active components in Huanglian Wendan Decoction can indirectly modulate inflammatory mediator levels by restoring gut microbiota balance, providing additional protection for intestinal immune barrier function.

5.2 Enhancing immune function The role of Huanglian Wendan Decoction in enhancing immune function is mainly reflected in the regulation of Th1/Th2 cell balance. Th1 and Th2 cells are important subsets in the immune system. Th1 cells mainly mediate cellular immune response, while Th2 cells participate in humoral immune response. The balance between the two is essential for maintaining intestinal immune homeostasis. It has been found that Huanglian Wendan Decoction can regulate T cell differentiation, inhibit the excessive activation of Th1 cells, and promote the moderate response of Th2 cells, thus restoring the Th1/Th2 balance[15]. This regulatory effect may be related to the effect of active components in Huanglian Wendan Decoction on related signaling pathways, such as JAK-STat pathway. In addition, Huanglian Wendan Decoction can further inhibit excessive immune response and reduce intestinal inflammation by increasing the number and function of regulatory T cells (Treg). These immunomodulatory effects together enhance the function of intestinal immune barrier, which provides a new idea for the treatment of intestinal inflammatory diseases.

6 Improvement of intestinal biological barrier

6.1 Restoring the balance of intestinal flora Huanglian Wendan Decoction, as a classic traditional Chinese medicine formula, contains active constituents such as Coptidis Rhizoma, Pinelliae Rhizoma, and Citri Reticulatae Pericarpium that have been demonstrated to regulate intestinal microecology. Berberine from Coptidis Rhizoma can restore gut microbiota balance by inhibiting the growth of pathogenic bacteria (*e. g.*, *Escherichia coli*, *Staphylococcus aureus*) while promoting the proliferation of beneficial bacteria (*e. g.*, Bifidobacterium, *Lactobacillus*). Studies indicate that this formula significantly reduces the Proteobacteria/Firmicutes ratio in the intestine, an abnormal increase of which is closely associated with various intestinal disorders[15]. Furthermore, β-sitosterol in Pinelliae Rhizoma repairs damaged intestinal epithelial cells, creating a favorable environment for probiotic colonization and establishing a virtuous cycle of microbiota-host symbiosis.

6.2 Regulating brain-gut axis function Huanglian Wendan

Decoction modulates the brain-gut axis via multiple targets. Its active components act on enterochromaffin cells, regulating the synthesis and release of 5-HT, thereby influencing vagal afferent signaling[21]. Hesperidin, derived from Citri Reticulatae Pericarpium, reduces plasma levels of pro-inflammatory cytokines IL-6 and TNF-α, mitigating neuroinflammation-induced damage to the blood-brain barrier. Clinical studies demonstrate that this formula significantly improves anxiety scores and intestinal symptoms in patients with irritable bowel syndrome. This therapeutic effect may be associated with up-regulation of BDNF expression in the brain and promotion of hippocampal neurogenesis. This comprehensive modulation of the neuro-endocrine-immune network exemplifies the characteristic TCM strategy of simultaneously treating the intestine and the brain.

7 Conclusions

Huanglian Wendan Decoction exerts a multi-target, multi-pathway mechanism in improving intestinal barrier function, and research progress in this area provides an important basis for the modernization of traditional Chinese medicine (TCM). Existing studies demonstrate that this prescription repairs the intestinal mucosal barrier through inhibiting apoptosis of intestinal epithelial cells, promoting the expression of tight junction proteins (such as occludin and claudin-1), alleviating oxidative stress and endoplasmic reticulum stress, regulating inflammatory factors (such as TNF-α and IL-6) and immune cell function, and restoring intestinal flora homeostasis, which alleviates UC symptoms. These findings not only validate the validity of TCM theory in this context, but also provide potential targets for the development of novel UC therapeutic drugs.

However, the current study has several limitations. Primarily, most experiments are based on animal models or *in vitro* cell studies, with relatively insufficient clinical data. Future research should prioritize randomized controlled trials (RCTs) to verify the decoction's efficacy and safety. Besides, the active components of Huanglian Wendan Decoction are complex; its specific pharmacodynamic material basis and synergistic mechanisms remain incompletely elucidated and require further analysis using technologies such as metabolomics and network pharmacology. Additionally, some mechanisms, such as the primacy of flora regulation versus immune regulation, are controversial across different studies, necessitating more systematic experimental designs to resolve these discrepancies.

Therefore, future research on Huanglian Wendan Decoction should advance towards precision medicine and personalized treatment, integrating biomarker screening and patient stratification to optimize dosing regimens. Concurrently, exploring its potential for combination with other therapies (such as biologics and probiotics) could offer improved strategies for UC management. Collectively, the multi-target mechanisms of Huanglian Wendan Decoction underscore the "comprehensive regulation" advantage inherent to traditional Chinese medicine. Its continued investigation holds promise for facilitating breakthroughs in UC treatment and serving as a valuable reference for drug research and development targeting other intestinal inflammatory diseases.

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