

Research Progress of Oral Chinese Medicine in Treating Ulcerative Colitis and Its Pathogenesis

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Abstract: Ulcerative colitis is a common and difficult disease of the digestive system, which has the characteristics of long course of disease and easy to repeat the condition. Studies have shown that with the extension of the course of the disease, patients with ulcerative colitis also have an increased chance of colon cancer. Western medicine still lacks specific and effective treatments for this disease, but traditional Chinese medicine in the treatment of ulcerative colitis in continuous in-depth research and testing, has made a series of progress, and traditional Chinese medicine in the treatment of this disease has the characteristics of high cost performance, fewer adverse reactions, so it is gradually accepted by patients in the clinical treatment. This article intends to summarize the research on oral treatment of ulcerative colitis with traditional Chinese medicine in recent years, and systematically elaborate its related mechanism of action, in order to provide new ideas for the clinical research and diagnosis and treatment of ulcerative colitis in the future.

Keywords: Ulcerative colitis, Chinese medicine, Pathogenesis, Research progress, Review

Ulcerative colitis (UC) is a disease type of inflammatory bowel disease (IBD), and most of the lesions in this disease begin to present with mucosal inflammation from the rectum and then gradually extend to the colon^[1]. UC is a common and difficult disease in gastroenterology, and the common clinical manifestations are diarrhea, abdominal pain, and mucopurulent bloody stools^[2]. There are many causes of this disease, and it is generally accepted that the pathogenesis of UC is affected by genetic susceptibility, environmental factors, immune system disorders, and whether intestinal microorganisms are balanced or not^[3]. The disease can occur at any age, there is no significant difference in the incidence between men and women. With the change of people's dietary structure and the influence of emotional factors, etc., the incidence of this disease has a gradually increasing trend. Western medicine treatment of UC has no obvious specific drug, the purposes of treatment are to control the recurrence of inflammation, promote mucosal healing, prevent complications, etc., commonly used clinical drugs are 5-aminosalicylates, glucocorticoids and immunosuppressive agents^[4]. However, the above drugs have the disadvantages of long medication cycle, easy to produce side effects, and easy to produce drug resistance for a long time. Therefore, it is extremely important to explore a more convenient and effective diagnosis and treatment plan with few side effects. At present, it has been found that traditional Chinese medicine (TCM) can improve the progression of the disease and improve patients' quality of life by regulating the expression of signaling pathways^[5], regulating the level of inflammatory factors^[6], maintaining intestinal bacterial homeostasis^[7], repairing the colonic mucosal barrier^[8] and regulating the activity of the immune system^[9] in the treatment of UC. There are many studies on the treatment and pathogenesis of UC with TCM. The author reviews the research on oral treatment of UC with traditional Chinese medicine and its pathogenesis.

1. Etiology and pathogenesis

There is no disease name of "ulcerative colitis" in the motherland medicine, which is mostly attributed to the categories of "diarrhea", "bowel wind", and "bloody stools" according to clinical manifestations^[10]. The disease is located in the intestine, and the lesions are mostly caused by deficiency of the spleen and stomach, dietary factors, emotional disorders and infestation of exogenous pathogens^[11]. *Su Wen* says: "Fire victory, then the fireworks countryside, cold and heat more. Civil disease injection white teeth, less abdominal pain drowning red, and even bloody stools", this sentence

summarizes the incidence of this disease as damp-heat evil internal accumulation of intestines, qi impassability, intestinal collateral damage, then dysentery pus blood and even bloody stools. Li Ya et al.^[12]summarized Professor Wang Chuijie's experience in the treatment of UC and concluded that this disease is based on deficiency of both spleen and kidney, with dampness-heat toxic stasis as the standard. Cao Kai et al.^[13]summarized Professor Sha Jingtao's experience and concluded that the treatment of UC is based on clearing away heat, dissipating dampness and invigorating spleen, taking qi and blood stasis as the standard, and at the same time, it is accompanied by the method of tonifying the kidney and soothing the liver, and Tongfu stagnation. Although physicians have different views on the etiology of UC, the understanding and research of UC in TCM has a long history, and TCM has obvious advantages in improving this disease.

2. Oral Chinese Medicine Improves the Pathogenesis of UC

2.1 Repair colonic mucosal barrier

The colonic mucosal barrier consists of four layers: mechanical barrier (intestinal mucosal epithelial structure), chemical barrier (mucus, digestive fluid and bacteriostatic substances secreted by intestinal mucosal epithelium), immune barrier (intestinal mucosal lymphoid tissue and intestinal plasma cell secretory antibody) and biological barrier (intestinal normal parasitic flora)^[14]. The intestinal mucosal barrier function is normal, which can effectively resist the invasion of harmful substances. The adverse effects of food and the disorder of intestinal environment lead to the destruction of colonic mucosal barrier and the increase of mucosal permeability, which can not resist the invasion of external pathogens and endotoxin, which can induce UC^[15-16].

Occludin and claudin-1 are important connexin components of intestinal epithelial structure. The increase of their expression level can effectively reduce the damage of intestinal epithelium and the occurrence of inflammatory reaction^[17]. By comparing the expression levels of occludin and Claudin-1 in the colonic mucosa of the two groups, Yu Yuan^[18] and others confirmed that Tongxie Yaofang oral administration can up regulate the expression levels of occludin and Claudin-1 in the intestinal mucosa of patients and improve the barrier function of intestinal mucosa. Zhao Wenjuan^[19]and others randomly divided 60 patients with UC into treatment group and control group. The treatment group was treated with Shenling Baizhu powder combined with mesalazine orally, and the control group was only treated with mesalazine orally. After 4 weeks of intervention, the results showed that the total effective rate of the treatment group was 90.00%, 13.33% higher than that of the control group, The difference was statistically significant ($P < 0.05$), and the mucosal condition under colonoscopy was significantly better than that before treatment. Ding Honghui^[20]randomly divided 76 patients with UC into two groups. The control group was treated with mesalazine, and the observation group was treated with modified formula of oral Shaoyao Decoction on the basis of the control group. Both groups were used continuously for 2 weeks. The results showed that the total effective rate of the observation group was 94.7% and that of the control group was 78.9%. The score of intestinal mucosa under enteroscopy was significantly lower than that of the control group, and the difference was statistically significant ($P < 0.05$). Zhang Jinzhong^[21]randomly divided 116 patients with spleen kidney yang deficiency UC into two groups. The control group was treated with sulfasalazine, and the observation group was treated with modified Fuzi Lizhong Decoction and sulfasalazine. The observation results showed that the TCM symptom score and colonoscopy score of the observation group were significantly lower than those of the control group, and the total effective rate of the observation group was 93.10%, 13.79% higher than that of the control group, the difference was statistically significant ($P < 0.05$).

In conclusion, it can be seen that oral administration of traditional Chinese medicine has a therapeutic effect on UC, and the clinical symptoms of patients can be improved by repairing intestinal mucosal barrier.

2.2 Regulate inflammatory factor levels

Studies have shown that the occurrence of UC is related to the level of cytokines. The increase of pro-inflammatory factors and the decrease of anti-inflammatory factors will accelerate the occurrence of UC^[22]. Among them, interleukin-1 β (IL-1 β), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), interleukin-4 (IL-4) and interleukin-10 (IL-10) are anti-inflammatory factors. As a proinflammatory factor, the increase in IL-1 β content is positively correlated with the incidence of the disease. It is produced by macrophages, which can weaken the function of intestinal mucosal barrier and accelerate

the intestinal inflammatory response of patients by activating monocytes and neutrophils to secrete a large amount of inflammatory substances^[23-24]. The overexpression of IL-6 will affect the homeostasis of the internal environment, increase the permeability of the body, and lead to the infiltration of neutrophils into the inflammatory area. And TNF- α is secreted by macrophages, T cells and B cells. It can amplify the inflammatory response and accelerate the injury of intestinal mucosa by activating epithelial cells and inducing chemokines^[25]. As anti-inflammatory factors, the decrease of IL-4 and IL-10 will lead to the decline of anti-inflammatory ability. The results show that IL-4 and IL-10 can inhibit the expression of TNF- α , IL-6 and IL-15, can also inhibit the intestinal inflammatory response of UC by reducing vascular endothelial growth factor^[26-27].

Zhang Guangru^[28] randomly divided 98 patients with UC into two groups for clinical observation and research, and the symptom score, serum IL-8 and serum TNF- α levels were observed. The results showed that the total effective rate of the experimental group was 93.88%. However, the reduced level of the experimental group was significantly better than that of the control group ($P < 0.05$). Ye Julin^[29] and others randomly selected 32 patients with large intestine damp heat UC as the treatment group to be treated with oral Pulsatilla Decoction and 28 patients in the control group to be treated with mesalazine for 2 months. The results showed that pulsatilla decoction can reduce the level of pro-inflammatory factors, improve the level of anti-inflammatory factors, improve the hypercoagulable state of blood and reduce the disturbance of intestinal mucosal microcirculation. Zhao Guanggang^[30] randomly selected 34 patients with UC as the study group and took Fuzi Lizhong Decoction orally. The same number as the control group was treated with sulfasalazine and prednisone. After 4 weeks of treatment, the curative effects of the two groups were observed. The results showed that the total effective rate of the study group was 88.2% better than 73.5% of the control group, and the difference was statistically significant ($P < 0.05$). The following conclusions were drawn by analyzing the test data, the difference between the two groups may be related to the inhibitory effect of Fuzi Lizhong Decoction on TNF- α , IL-1 β and other related factors to reduce inflammatory response and protect intestinal mucosa. Wei Hua^[31] randomly divided 76 patients with UC into two groups. The results showed that after treatment, the TCM symptom scores of the two groups decreased and the serum inflammatory factors improved, and the results showed that the improvement level in all aspects of the treatment group was more significant than that of the control group ($P < 0.05$). The above data show that oral administration of traditional Chinese medicine can treat UC by regulating the level of inflammatory factors in patients.

2.3 Regulation of signal pathway expression

In recent years, researchers have studied the pathogenesis of UC more and more widely. Many studies have confirmed that the occurrence of UC is significantly related to the abnormal function of signal pathway. NF KB (K-light chain enhancement of nuclear factor activated B cells) is a multifunctional nuclear transcription factor, which can affect the pathological changes of inflammatory and immune diseases by participating in the regulation of gene transcription. Literature evidence showed that abnormal NF KB pathway plays an essential role in the pathogenic development of UC^[32]. MAPK signaling pathway can activate and promote transcription factors into the nucleus to regulate TNF- α , the degree of IL-2 and other inflammatory factors in vivo further accelerates the process of intestinal mucosal inflammatory response^[33]. P13K / Akt / mTOR (phosphatidylinositol 3-kinase / protein kinase B / mammalian rapamycin target protein) signal pathway can promote the continuous proliferation of colonic mucosal epithelial cells, accelerate the occurrence and development of UC, and even induce the formation of carcinogenesis^[34].

Hu Yue^[35] adopted the method of randomized controlled trial. 30 patients with UC were selected as the control group and treated with mesalazine, and 30 patients as the experimental group were treated with Jijian Tongxie Yaofang formula combined with western medicine. The results showed that the total effective rate of the experimental group was 96.67%, which was 23.34% higher than that of the control group ($P < 0.05$). It was found through network pharmacology and bioinformatics analysis, Jijian Tongxie Yaofang can act on 16 different signal pathways such as NF KB, P13K / Akt and MAPK to regulate the occurrence and development of UC. Song houpan^[36] and others found that the mechanism of Pulsatilla Decoction in the treatment of UC is mainly related to its regulation of P13K / Akt signal pathway, MAPK signal pathway and TNF signal pathway.

2.4 Regulation of intestinal bacterial homeostasis

In general, the intestinal parasitic flora in healthy individuals is in a state of balance. Intestinal

microbial imbalance promotes the occurrence and development of UC, inhibits the growth of intestinal pathogens during treatment, prevents the reduction of beneficial bacteria, and restores intestinal bacterial homeostasis to promote the healing of colonic mucosa in UC patients^[37-38]. Among them, probiotics can improve intestinal mucosal barrier function and immune system function, promote the secretion of anti-inflammatory factors, further inhibit the growth of harmful bacteria in the intestine, and inhibit the occurrence of inflammatory reactions^[39]. Studies have shown that targeted removal of harmful bacteria from the intestine can prevent, reduce or even reverse the development process of the disease^[40].

Li Keya et al.^[41] randomly divided 71 patients with UC into treatment group and control group. The control group was treated with mesalazine, and the treatment group was treated with oral Wumei Pill on the basis of the treatment of the control group for 1 month. The observation results showed that the levels of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* in the treatment group were higher than those in the control group, while the levels of pathogenic bacteria such as *Fusobacterium* and *Salmonella* were significantly lower than those in the control group. Yu Yuan et al.^[42] observed the changes of intestinal bacteria count and symptom score in 40 UC patients with liver depression and spleen deficiency, and demonstrated that *Tongxieyaofang* increased the number of beneficial bacteria in the intestinal tract, improved intestinal flora imbalance, and improved the quality of life of patients. Lu Benyin^[43] clinically observed 120 patients with UC, and the results suggested that the overall response rate of the *Fuzi Lizhong Decoction* combined with mesalazine group was 96.55% higher than that of the mesalazine group (84.21%), while its improvement of intestinal hypoxia and regulation of intestinal microbial balance level were superior to those of the western medicine alone group, and the differences were statistically significant ($P < 0.05$). The above suggests that maintaining a stable intestinal environment has a promoting effect on disease improvement in UC patients.

2.5 Modulates immune system activity

The main function of the immune system is to protect against potential infections, and there is excessive immune activation in the intestinal wall of UC patients, with infiltration of a large number of neutrophils, macrophages, and lymphocytes in their lesion mucosa^[44-45]. The systemic inflammatory response leads to an increase in the number of neutrophils and a relative decrease in the number of lymphocytes, and abnormal neutrophil function can lead to disturbances in intestinal bacteria, which will aggravate the intestinal inflammatory response^[46].

The occurrence of UC is also related to the dysfunction of cellular immunity. T cells are an important part of cellular immunity. $CD4^+$ cells and $CD8^+$ cells are two subtypes of T cells. $CD4^+$ cells can be divided into Th1, Th2, Th17 and Treg cells, Th1 can secrete $TNF-\alpha$, IL-2 and other cytokines, and perform cellular immune response to the body; Th2 can secrete IL-10, IL-4 and other cytokines, and perform humoral immune-mediated response to the body; Th17 can secrete IL-17, which has the effect of mediating local infiltration of inflammatory cells and can accelerate mucosal injury; Treg cells, or regulatory T cells, can attenuate cell proliferation *in vitro* and inhibit the activity of autoimmune T cells *in vivo*, thereby avoiding autoimmune diseases, and can also secrete IL-10 to promote wound healing^[44, 47-49]. $CD8^+$ cells are cytotoxic T lymphocytes, which can play an immunoregulatory role by eliminating the antibody response from target cells. The $CD4^+/CD8^+$ ratio indicates the stability of the host immune system, and the imbalance of specific gravity indicates that the body's immune system is unstable, the proportion of T cells is disordered, and cytokines and inflammatory mediators are abnormal, resulting in an inflammatory response in the intestine^[50]. It has been confirmed that the levels of $CD4^+$ cells and $CD4^+/CD8^+$ ratio in UC patients decreased compared with normal subjects, while the levels of $CD8^+$ cells increased compared with normal subjects^[51].

Liang Xiang et al.^[52] took 122 UC patients with spleen deficiency and dampness as the study subjects. The intervention measure of the control group was oral mesalazine, and the treatment group was treated with *Shenling Baizhu powder* on the basis of Western medicine. The changes of IL-17A, $TNF-\alpha$ and IL-17A/IL-10 in the serum of the two groups were observed. The detection results suggested that the improvement level in the treatment group was better than that in the control group, and the improvement of immune imbalance in the treatment group was better. Ma Qianzhang^[53] selected *Pulsatilla decoction* combined with mesalazine oral treatment of 42 patients with heat-toxic flaming UC, the results showed that the effective rate of treatment was 90.47% ($P < 0.05$), the $CD4^+/CD8^+$ ratio in the plasma of patients was higher than that before treatment, and the improvement in the treatment group was more significant than that in the control group. Sun Mengchao^[54] selected *Wumei Pills* combined with western medicine to treat 30 patients with UC. The results showed that the effective rate of the combination was significantly higher than that of the mesalazine group ($P < 0.05$),

the percentage of CD4⁺ cells and CD4⁺/CD8⁺ ratio increased significantly, and the percentage of CD8⁺ cells was lower than that before treatment. Qian Weizhen et al.^[55] randomly divided 62 children with UC into two groups by digital table. The control group was given mesalazine. The intervention measure in the treatment group was synergistic treatment of Shenlingbaizhu Powder and mesalazine. The results showed that after 2 months of treatment, the overall response rate of the two groups was 93.55% and 74.19%, respectively, and the CD8⁺ level in the treatment group was significantly lower than that in the control group, and the CD4⁺ and CD4⁺/CD8⁺ ratio were significantly higher than those in the control group. The difference between the two groups was statistically significant ($P < 0.05$).

3. Conclusions

In summary, with the assistance of the overall concept and syndrome differentiation and treatment, oral Chinese medicine has obvious advantages in relieving clinical symptoms, improving the quality of life, and reducing the incidence of adverse reactions. However, it still has certain disadvantages, such as no uniform standard for TCM syndrome differentiation of UC by physicians, and the lack of multicenter, large-sample data studies in clinical practice. Therefore, for the majority of scholars, it is necessary to establish a standardized diagnosis and treatment system and a multi-center large-sample database. Although the pathogenesis of ulcerative colitis has not been fully clarified, researchers mostly study from the colonic mucosal barrier, intestinal inflammatory factor levels, signaling pathways, intestinal flora and immune system. By reading the literature, the author summarizes the research of the majority of scholars on the pathogenesis of UC on the basis of the literature, in order to provide researchers with experimental research and clinical research ideas.

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