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Treatment of Ulcerative Colitis based on Cohosh-atractylodes

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Abstract: *Ulcerative colitis (UC), also known as chronic nonspecific ulcerative colitis, is a chronic inflammatory bowel disease of unknown etiology. The disease is characterized by frequent diarrhea, tenesmus, crampy abdominal pain, mucus, pus, and bloody stools [1]. According to the existing statistics in China, the prevalence and incidence of ulcerative colitis are increasing year by year, and it has become a common and frequent disease in China, and the treatment methods of modern medicine are limited, and the combination of traditional Chinese and Western medicine in the treatment of ulcerative colitis will have better efficacy and development. In the theoretical system of traditional chinese medicine, ulcerative colitis also belongs to the category of spleen and stomach diseases. In the history of traditional chinese medicine, Li Dongyuan, a physician who created the "spleen and stomach theory" of traditional chinese medicine, has a unique theoretical system and prescription system for the treatment of spleen and stomach diseases. Li Dongyuan is a clinical master of traditional chinese medicine, known as one of the "Four Masters of Jin Yuan" and "Replenishing Soil". His works "On the Spleen and Stomach" and "On the Distinction of Internal and External Injuries" laid an important foundation for the development of the "Theory of the Spleen and Stomach". After researching these works, the author found that Li Dongyuan's prescription medicine is mostly cold and hot drugs, among which cohosh-atractylodes is one of Li Dongyuan's commonly used drug pairs. After clinical and modern research, this pair of drugs has a good therapeutic and regulatory effect on ulcerative colitis. However, in clinical practice, these two drugs have not been widely used, and further discussion and research are needed.*

Keywords: *Cohosh-Atractylodes; ulcerative colitis; LI Dongyuan; IL-6; IL-8*

1. Introduction

Ulcerative colitis (Figure 1) is now one of the common diseases in china, and the western medicine treatment mainly to relieve symptoms, regulating immunity, promoting mucosal healing, reducing complications, etc [1]. Aminosalicylic acid, glucocorticoids, immunomodulators, antibiotics and other drugs are used for treatment, and in severe cases, surgery can be used. But the recurrence rate remains high after treatment. The treatment of TCM for ulcerative colitis follows syndrome differentiation and multi-target treatment. Comparatively speaking, TCM has unique advantages in the treatment of UC, especially in the field of anti-recurrence.

Traditional Chinese medicine believes that ulcerative colitis will manifest as a syndrome type of mixed cold and heat, virtual and real, which is more difficult to treat, and the prescription should also be used in combination with cold and heat, and cold and heat are in the same tone. The author looks for treatment ideas from classic works such as "Treatise on the Spleen and Stomach", "The Secret Collection of the Orchid Room", and "The Theory of Distinguishing Internal and External Injuries" by Li Dongyuan, the founder of the "School Of Invigorating The Earth", which found that Li Dongyuan in the treatment of gastrointestinal diseases, Such as “The decoction of nourishing qi”, “The decoction of lifting yang and nourishing stomach”, “The decoction of nourishing spleen and stomach”and so on. Then, these prescriptions showed that most of the prescriptions which all includes "cohosh-atractylodes" [2]. Modern doctors also often use Li Dongyuan's classic prescription to treat gastrointestinal diseases, and cohosh-atractylodes also occurs at a higher frequency.

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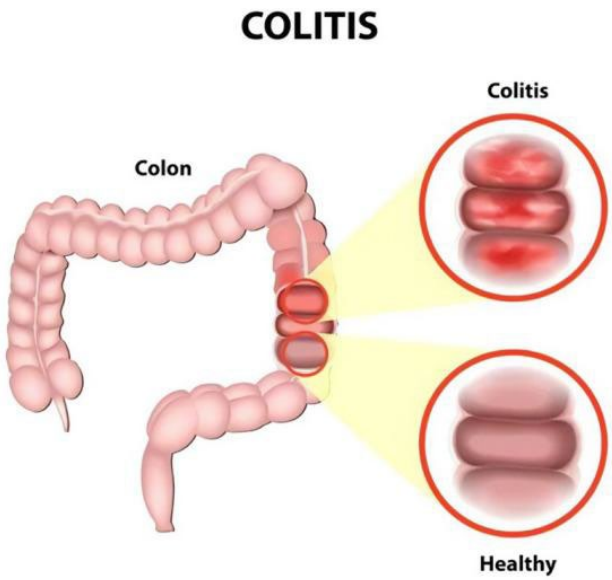

Figure 1: Ulcerative colitis (UC)

2. Research status of UC at home and abroad

The domestic research on ulcerative colitis is based on many aspects, the most of which is still based on inflammatory factors. The findings of Weining Wang et al. [3] found that the IL-6 mRNA and protein expression of the diseased colonic mucosa of UC patients were significantly higher compared with the normal group, indicating that the concentration of IL- -6 in the diseased mucosa of active UC patients was higher than the normal value and was positively correlated with the inflammation grade. After treatment, the concentration of IL-6 also decreased with the remission of the disease. The results of Jia Bailing et al. [4] showed that the serum IL-6 level in UC patients was significantly higher, and the serum IL-6 level was significantly reduced after lesion remission, and its level was related to the severity of the disease and the range of lesion involvement, which suggested that IL-6 is involved in the pathological process of UC, indicating that the determination of serum IL-6 level can reflect the condition of UC, and that IL-6 can be used as one of the indicators of efficacy and prognosis. UC is mostly accompanied by the activation of various intestinal immune cells and the occurrence of inflammatory cascade, involving the production of a large number of chemokines. For example, interleukin-8 (IL-8), IL-8, also known as chemokine 8 (CXCL 8), the serum IL-8 level increases in UC patients, which can bind the corresponding receptors such as CXCR 1 / 2 and recruit neutrophils [5]. It can be seen from the above studies that the abnormal immune response of UC is mainly manifested in the abnormal release of cytokines. The serum IL-6 and IL-8 of UC patients are significantly increased. After treatment, IL-6 and IL-6 and IL-8 will gradually decrease with the remission of the disease.

The main purpose of routine treatment of ulcerative colitis abroad is to achieve control and improve symptoms through drug treatment. The use of drugs includes 5-aminosalicylic acid, corticosteroids, immunosuppressants, and biological, preparations, etc [6]. Taking surgical resection if necessary. However, a significant proportion of patients do not respond or lose response to pre-existing underlying therapies, which necessitates the development of new therapeutic strategies, including the development of new drugs.

At present, the prescription of treatment for UC abroad is expanding, and the types of drugs with new targets will increase rapidly in the future, including small molecule transplantation therapy, improvement of intestinal microecology, cell therapy and epitherapy. In the study by Magro Fernando et al. [7] found that UC was prolonged 5 years after onset in 10% to 19% of patients and in 11% to 28% after 10 years of patients in both cohorts. Whereas the disease activity seems to improve with the disease course. Most patients begin to relapse in the first few years of the disease. The cumulative recurrence rates have also increased over the past 10 years. From 1962 to 2004, the proportion of colonic resections tended to decline, demonstrating the continuously efficient treatment of drugs. Most colectomies are performed in patients in the first two years of the disease. Salycilate Is the most consumed drug, followed by systemic

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steroids, immunosuppressants, and anti-TNF, and the intake of the latter two drugs has increased significantly over time.

It is known that ulcerative colitis is a chronic disease with complex etiology. Stakenborg Michelle Study believes that [8] UC is associated with excessive neutrophil infiltration and collateral tissue damage, but its association is not fully understood. Serum HGF was significantly increased in active UC patients and positively correlated with C-reactive protein and neutrophil counts. Flow cytometry analysis also revealed an elevation of colonic MET + neutrophils during DSS colitis. Genetic ablation of neutrophil MET reduces the severity of colitis caused by DSS. Meanwhile, TH 17 cells were reduced, likely due to reduced IL-1βproduction by MET-deficient neutrophils.

To sum up, it is believed at home and abroad that although UC is a local disease, it involves multiple systems, multiple links and multiple channels, which still needs multiple targets for treatment, and a single treatment is difficult to be effectively controlled. At the same time, treatment plans and therapeutic drugs also need to be constantly updated and developed. Chinese medicine is a representative of multi-target treatment. For the treatment of UC, the combination of Chinese and western medicine will have more space for development.

3. Traditional Chinese medicine understanding of cimicifuga-atractylodes medicine in the treatment of ulcerative colitis

In traditional chinese medicine, ulcerative colitis belongs to the category of "long leakage", "long dysentery", "blood in stool" and "bowel". Its disease location is in the large intestine, related to liver, spleen, kidney and other viscera. Traditional chinese medicine believes that ulcerative colitis has a long delay, then cold and heat are mixed with false and real, which belongs to the category of jue and Yin disease from the perspective of the six symptoms. Its etiology is complex, including heredity, affection, unclean diet, excessive fatigue or exogenous disease evil caused. Its basic pathogenesis mainly causes the deficiency of healthy qi, spleen deficiency, weak rise, ineffective water and valley, and diarrhea [9]. The user should also be cold and hot, cold and heat modulation, rise and turbidity. In the treatment of ulcerative colitis, traditionalchinese medicine has the characteristics of multi-targets, multi-directional and multi-links, and has the characteristics of improving clinical symptoms, repairing intestinal mucosa, maintaining long-term remission, reducing recurrence rate, and few adverse reactions.

Atractylodes has a pungent, bitter, and warm taste, and returns to the spleen and stomach meridians. The function of Atractylodes is drying dampness and strengthening the spleen, and expelling wind to dispersing cold. It is commonly used in digestive system diseases, mainly used for dampness and coke, abdominal distension and diarrhea, etc. Cimicifuga has a spicy, slightly sweet, slightly cold taste. It has the function of lifting yang qi, clearing heat and detoxifying, and issuing diaphragm, which returns to the lungs, spleen, large intestine, stomach meridian. In diseases of the digestive system, it is mostly used for falling diseases and diseases that manifest falling symptoms, such as colitis, gastritis, etc. Li Min et al. found that cohosh belongs to the "wind medicine" in traditional Chinese medicine. "Wind medicine" has spicy taste, light texture and rising and floating properties. Wind medicine was put forward by Li Dongyuan and expanded its application [10]. Wind medicine has the effect of lifting spleen Yang, promoting hair and spreading stagnation, dredging liver and regulating qi, promoting blood circulation and removing blood stasis, and wind medicine is suitable for the whole process of treatment of ulcerative colitis [11]. Cohosh and atractylodes both are wind drugs, which could lift yang qi, and avoid plague, diarrhea. Both drugs have strong targeting to the digestive system, which is also a commonly used chinese medicine of the treatment of digestive diseases. Cold with hot could strengthen the spleen, dry dampness, lift yang qi, and detoxificate, conforming to the ulcerative colitis of TCM basic pathogenesis, which is one of the important medicine to treat ulcerative colitis.

4. Modern studies of cohosh for UC

4.1. Modern study of cohosh

Cohosh (Figure 2) has a long history of medication, and has the effects of publishing rash, clearing heat and detoxification, lifting yang qi. In clinical chinese medicine, it is often used for cold, measles, mouth sores, sore throat, qi deficiency, gastric ptosis, long diarrhea and anal prolapse and other diseases. Zhang Yuan su, Jin Yuan physician, classified cimicifuga as a "wind lifting" drug, who pointed out that it is "foot Yangming stomach, foot yin spleen meridian medicine". Later, Li Dongyuan inherited his

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academic ideas. In the use of cohosh, paying attention to the spleen and stomach meridian, which playing its economic role. In the clinic, chosh often appears in Li Dongyuan prescriptions such as the decoction of nourishing qi, the decoction of lifting yang and nourishing stomach. Although cohosh is also often used for the treatment of digestive disorders. However, the syndrome of deficient qi and the syndrome of descending qi are used as the main use basis, whereas in ulcerative colitis, the frequency of use is still low. Based on the modern pharmacological studies, more efficacy of cohosh can be further explored in the case of ulcerative colitis, whih can also be used by more basis.

Modern studies have found that cohosh has the functions of anti-inflammation, analgesia, spasmolysis, immune regulation and regulation of gastrointestinal motility. Sun Huijuan et al. found that the aqueous extract of cohosh can effectively inhibit the production of inflammatory cytokine IL-6 by vascular endothelial cells. Liang Yu et al. [12] found that nosh can inhibit the expression of interleukin (interleukin, IL) -4, IL-9, IL-13 in local tissues induced by fluorescein isothiocyanate, thus inhibiting inflammatory cell infiltration, congestion, edema and other pathological changes, and play an anti-inflammatory and anti-allergic effect. The study findings of Liu Yinze et al. [13] indicated that when using cohosh to treat ulcerative colitis caused by inflammation, adding cohosh to the treatment with basic drugs can effectively improve the treatment effect and delay the occurrence and development of the disease to a certain extent. Its mechanism of action may be due to the inflammatory factor interferon-γand interleukin (Interleukin, IL) -6 secreted components [14]. Although ulcerative colitis is a complex systemic disease, chronic inflammation is still one of the main factors, and cohosh has an obvious effect of inhibiting inflammatory factors, which is consistent with the "elimination" of all drugs recorded in ancient books of traditional Chinese medicine. Chen Liyi et al. also found that cohosh could inhibit the release of inflammatory mediators, regulating the expression of inflammation-related mediators, and regulate neutrophils [14]. It can be seen that cohosh is indeed the dominant drug in the treatment of inflammation.

Zhu Jing et al. [15] found that cimicifuga has a good function of regulating the gastrointestinal tract by studying mice with weak gastrointestinal function, and its mechanism is mainly related to the regulation of gastrointestinal motility and the regulation of gastrointestinal hormone disorders Zhang Jianying et al. found that cohots can effectively inhibit diarrhea [16], Liang Yu et al. also believed that the function of cohosh in lifting yang qi can be reflected on the basis of its regulation of gastrointestinal motility [17].

In conclusion, cohosh has the effects of anti-inflammatory, antibacterial, immune regulation and gastrointestinal motility, which is more consistent with the etiology of ulcerative colitis.

Figure 2: Cohosh

4.2. Modern studies of atractylodes

Modern studies have found that ketone has the function of protecting intestinal mucosa, inhibiting inflammation and enhancing immunity, volatile oil has gastrointestinal regulation function, and ketone has anti-allergic inflammatory reaction. The findings of Zhuang Dan et al. [18] showed that the regulation of serum interleukin-6 (IL-6), serum interleukin-8 (IL-8). For example, the only crude extract can reduce the secretion of IL-6 and IL-8. Sorracolide also has anti-inflammatory effects, it can regulate the secretion of IL-6. Crackeone has an antiviral effect. The volatile oil was able to improve colonic histopathological damage in ulcerative colitis, reducing the content of IL-6, IL-8 in the colonic tissue. Xiaolan Liu et al. found that the mechanism may be related to the upregulation of Beclin1, P62 mRNA expression and the amount of LC3 / I protein. IL-6 is an important inflammatory factor mediating ulcerative colitis and is

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important by by regulation. IL-6 is mainly secreted by macrophages and Th 2 cells, which can promote the proliferation and differentiation of various cells, such as the secretion of plasma cells, B cells, T cells and other immune cells, and stimulate the trauma of the immune response, thus leading to inflammation. In addition, it can also induce the generation of acute phase response protein in hepatocytes and promote cytotoxic T cell (CTL) function. IL-6 is one of the core members of cytokines. Excessive secretion of IL-6 can lead to abnormal differentiation of B cells, produce a large number of antibodies, causing a series of autoimmune responses, thus aggravating the intestinal inflammatory damage, and ulcerative colitis is a typical autoimmune disease.

Liu Fen et al. found that the volatile oil of atractylodes can enhance the gene expression of gastrointestinal mucosa, improving the defense mechanism of the body and the gastric mucosa, repairing the ultrastructure of gastric mucosa tissue cells, improving the pathological damage of gastric mucosa, and then promote the recovery of gastrointestinal diseases [19].

Experimental studies have found that sortylohas a good immunomodulatory effect, and its decoction can improve immunoglobulin titer, interferon (Interferon, IFN), IL-5 and jack bean lectin A (Concanavalin A, ConA) and other indicators [20]. Atractylodes is also an important drug for the treatment of gastrointestinal diseases in clinical practice. Traditional chinese medicine believed that it can dry dampness and strengthen the spleen, and ascend lucidity and descend turbidity. Modern medicine believed that it has good gastrointestinal regulation function, studies found that it can inhibit dopamine D2 receptor (Dopamine Receptor D2, DRD 2) and 5-serotonergic receptor (5-Hydroxytryptamine, 5-HT) to inhibit gastric emptying or small bowel movement [21]. The regulation of gastrointestinal function by volatile oil is mainly achieved by the activation of the vagal pathway, which also participates in the release of gastrointestinal hormones such as gastrin (motilin, MTL), hormone (gastrin, GAS), and SS [22]. This mechanism may also be the mechanism of the spleen transport and spleen.

To sum up, atractylodes (Figure 3) can not only be treated from the aspect of inflammation, but also can be regulated from the aspects of immune regulation, gastrointestinal tract movement etc. With strong targets and multiple points, especially in the gastrointestinal system, the pharmacological effects of atractylodes and its active ingredients in the digestive system mainly include anti-gastric ulcer, promote gastric emptying, regulate gastrointestinal propulsion, anti-diarrhea, choleretic and hepatoprotective, and improve digestion and absorption functions [23], which is an indispensable advantage in the treatment of ulcerative colitis medicine.

Figure 3: Atractylodes

4.3. Summary

Cohosh has anti-inflammatory, anti-virus, antiviral, gastrointestinal, regulating immunity, anti-allergy and anti-cancer, corresponding to the effects of lifting yang qi, clearing heat and detoxification. Atractylodes has anti-inflammatory, antibacterial, immune and gastrointestinal regulation, related to the effects of dry dampness, warm stomach and spleen. The combination of two drugs has a synergistic effect and has a more efficient regulatory effect on ulcerative colitis.

5. Discussion

To sum up, cohosh and atractylodes can be applied to the treatment of ulcerative colitis both from the theory of traditional chinese medicine and from modern research, and have a good curative effect. The two drugs are all "wind medicine" [24], those have the functions of lifting yang qi, promoting stagnation,

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dredging liver and regulating qi, promoting blood circulation and removing blood stasis. Through modern research, it also found that both drugs have the functions of anti-inflammatory and antibacterial, regulating immunity, regulating intestinal function, and protecting the intestinal mucosa [25]. In addition, the two drugs have a regulatory effect on the significant increase of many inflammatory factors, such as IL-6 and IL-8, and have a better regulating effect on human immunity. It can be seen that "wind medicine" treatment of ulcerative colitis can have more development prospects and research needs in the future, we can choose more targeted drugs, such as"cohosh-atractylode", "bupleurum-cohosh, "astragalus-wind", "cohote-wind" [26], etc.

In the clinical practice of traditional chinese medicine, we can choose to add this drug pair to the prescription, or add or subtract the prescription basis of these drugs. While following the etiology and pathogenesis of TCM, syndrome differentiation and treatment, we can refer to more modern medical research and clinical observation of drug use to improve the curative effect.

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