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A brief Analysis of Huang Qin Decoction in Treatise on Cold Damage and Modern Pharmacological Studies

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Abstract: ***Huangqin Decoction is one of the ancient prescriptions in traditional Chinese medicine. It was first recorded in Zhang Zhongjing's Treatise on Cold Damage and Miscellaneous Diseases at the end of the Eastern Han Dynasty. The formula consists of four herbs: Scutellaria baicalensis, white peony root, licorice, and jujube. This simple prescription is potent, with the ability to clear heat, dry dampness, relieve pain, and stop diarrhea. Numerous studies have reported that Huangqin Decoction has anti-inflammatory, antipyretic, analgesic, and antibacterial effects. In modern clinical practice, it is primarily used for treating gastrointestinal diseases associated with damp-heat stagnation. This article aims to summarize and discuss the modern pharmacological research on the complete formula of Huangqin Decoction and its herbal composition, providing a reference for further studies on the specific mechanisms of action of Huangqin Decoction.***

Keywords: Scutellaria baicalensis decoction, Modern pharmacology, Damp-heat stagnation**.**

1. Huang Qin Decoction

Huang Qin Decoction is recorded in the book "Treatise on Cold Damage Diseases" written by Zhang Zhongjing at the end of the Eastern Han Dynasty. In Article 172 of the Treatise on Cold Damage Diseases, it states: "For combined diseases of Taiyang and Shaoyang with self-induced diarrhea, use Huang Qin Decoction; if there is vomiting, use Huang Qin plus Pinellia and ginger decoction as the main treatment." From this, we can understand that Huang Qin Decoction primarily treats self-induced diarrhea caused by combined diseases of Taiyang and Shaoyang. What are combined diseases? The "Six Books of Cold Damage" says, "Combined diseases refer to two or three yang meridians being simultaneously affected, where the disease has not spread. Concurrent diseases refer to one yang meridian being affected first, then another meridian, where the disease has spread." The "Complete Book of Jingyue" states, "I have long been deeply involved in the study of cold damage diseases. Initially, I found the concepts of combined and concurrent diseases unclear, but now I fully understand them. Combined diseases refer to two or three yang meridians being simultaneously affected, where the diseases are combined. Concurrent diseases mean that if Taiyang is first affected and does not resolve, it may also involve Yangming and Shaoyang" [1-2]. Many modern scholars also believe that combined diseases involve simultaneous symptoms of two or three meridians, but the concise and refined text of Huang Qin Decoction has led to varying interpretations throughout history regarding its indications. The "Golden Mirror of Medicine" suggests that the condition should include external symptoms of "Taiyang disease", "For combined diseases of Taiyang and Shaoyang, it means Taiyang fever, aversion to cold, and alternating chills and fever with Shaoyang symptoms" [3]. Later generations, noting the absence of herbs like hemp and cinnamon in Huang Qin Decoction for treating Taiyang disease, believed that Huang Qin Decoction mainly treats Shaoyang diseases. Ran Xiande [4] believed that the pathogenesis of Huang Qin Decoction involves evil invading Shaoyang and gallbladder fire ascending. Wang Xinghua [5] and others believed that although the article mentions combined diseases, the primary pathogenesis of Huang Qin Decoction is "Shaoyang fire stagnation", Shaoyang fire stagnation internally leads to downward pressure on Yangming, causing abnormal bowel function and diarrhea. They also believed that the symptoms described in Article 258 of the Treatise on Cold Damage Diseases, such as bitter taste in the mouth, dry throat, and dizziness, refer to Huang Qin Decoction. Li Zhongyu et al. [6] believe that Huangqin Decoction primarily treats the syndrome of Shaoyang Qi stagnation and heat invading the spleen, with the formula demonstrating the function of consolidating yin and stopping diarrhea. Zhang Zailiang et al. [7] argue that the pathogenesis of Huangqin Decoction is the transformation of Shaoyang Qi stagnation into fire. Although the original text describes a combined condition of Taiyang and Shaoyang, Shaoyang should avoid inducing sweating or resolving exterior symptoms, hence no drugs for resolving exterior symptoms or inducing sweating are included in the formula. Nowadays, most people consider Huangqin Decoction to be part of the treatment for Shaoyang diseases, where the pathogenesis often involves unresolved Shaoyang Qi stagnation and heat, dysfunction of the three burners, and water retention in the large intestine leading to diarrhea. Therefore, the formula uses bitter-cold herbs like Scutellaria as the principal herb to clear and resolve Shaoyang Qi stagnation and heat, while also drying dampness and stopping diarrhea. The sour-cold herb peony root gathers yin and harmonizes the body, and when paired with licorice, it works together to achieve the effects of nourishing blood and softening the liver found in Shaoxian Decoction. Jujube tonifies qi, nourishes blood, strengthens the spleen, and harmonizes all the herbs, preventing the liver and gallbladder from obstructing the spleen, and can also prevent the harm of diarrhea and blood deficiency caused by peony's sour and sweet properties. The entire formula is simple yet potent, with tightly integrated and rigorous drug combinations,

collectively

2. Modern Pharmacological Studies on Scutellaria Baicalensis Decoction

Due to the primary function of Huangqin Decoction in clearing heat and drying dampness, it has been mainly used in clinical treatment for ulcerative colitis with damp-heat stagnation in the middle burner, bacterial dysentery, acute gastroenteritis, and other digestive diseases in recent years. Moreover, as medical practitioners deepen their understanding of Huangqin Decoction, its application areas have further expanded. For example, Professor Huang Huang [8] combined his clinical experience and believed that Huangqin Decoction can be used to treat gynecological conditions such as threatened miscarriage and uterine fibroids, as well as certain inflammatory joint diseases. Cao Min [9] et al. also experimentally demonstrated that Huangqin Decoction has a certain therapeutic effect on diabetes. A large number of modern studies have shown that Huangqin Decoction has mechanisms such as regulating inflammatory factors, controlling related signaling pathways, protecting the intestinal mucosal barrier, and improving gut microbiota imbalance. Zhu Lin [10] found through experiments with DSS-induced colitis-associated colorectal cancer (CAC) mice that Huangqin Decoction could significantly reduce levels of inflammatory factors such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α). Additionally, Huangqin Decoction can treat CAC by reducing the content of tumor markers (CA199). In the study of Huangqin Decoction for treating CAC, Ma Xuran et al. [11] found that Huangqin Decoction can intervene in the migration and invasion of colon cancer cells HT-29 under inflammatory conditions, regulate abnormal mRNA transcription caused by the Wnt signaling pathway, increase the expression of connective proteins in intestinal epithelial cells, prevent abnormal proliferation of intestinal epithelial cells, and also downregulate β-catenin levels in the Wnt signaling pathway, reduce the expression of CDK4 and cyclin D1 proteins, inhibit the growth and proliferation of colon cancer cells, and lower the incidence of CAC. Other studies have shown that Huangqin Decoction can regulate the balance between T lymphocytes Th1/Th2 and Th17/Treg cells, effectively inhibit the MDP-NOD2 inflammatory signaling pathway, and decrease the expression of IFN-γ, ETS, and other proteins, alleviating apoptosis in colon cells, preventing increased permeability of the intestinal epithelium, restoring intestinal mucosal integrity, and reducing intestinal inflammation [12-14]. Wu Yuzhu et al. [15] believe that Huangqin Decoction can enhance the expression of water channel proteins AOP1, AQP3, and AQP8, preventing electrolyte disturbances to achieve antidiarrheal effects. In terms of gut microbiota, in experiments with DSS-induced ulcerative colitis (US) mice, the abundance of beneficial bacteria such as Bacteroides and Prevotella significantly increased after intervention with Huangqin Decoction, while the abundance of pathogenic bacteria such as Escherichia coli and Shigella significantly decreased. The expression of hallmark proteins of the intestinal mucosal barrier and anti-inflammatory factors was also significantly upregulated, further proving that Huangqin Decoction can indirectly adjust the gut microbiota to treat ulcerative colitis [16, 17]. Huang Li [18] verified that Huangqin decoction had a significant inhibitory effect on the tonic intestinal contraction induced by acetylcholine through animal experiments, and could also prolong the pain threshold reaction time of the tail-shaking test in mice, thus verifying that Huangqin decoction also had the effect of relieving pain.

3. Modern Pharmacological Study on the Composition of Scutellaria Baicalensis Decoction

3.1 Scutellaria Baicalensis

Scutellaria baicalensis, also known as mountain tea root, is a plant of the Lamiaceae family and was first recorded in the Shennong Bencao Jing. It is mainly distributed in northeastern China and Inner Mongolia [19]. Clinically, it is primarily used for treating damp-heat, summer dampness, chest tightness and fullness, diarrhea, jaundice, lung heat cough, high fever with thirst, blood heat causing vomiting and nosebleeds, abscesses and sores, as well as fetal restlessness [20]. Modern pharmacological studies have successfully extracted various chemical components from Scutellaria baicalensis, including flavonoids, phenolic acids, phenylethanol, amino acids, sterols, and essential oils [21]. Among these, flavonoids such as baicalin are the main components and have attracted extensive modern research. Woo K J [22] found that baicalin can affect the expression of the cyclooxygenase COX-2 gene, influence the binding of the transcription factor C/EBPβ to DNA, thereby inhibiting arachidonic acid metabolism and exerting anti-inflammatory effects. Chen Zhiyun [23] concluded from a clinical comparison study of 100 traditional Chinese medicines that Scutellaria baicalensis has a high inhibitory effect on Helicobacter pylori and is of significant reference value for gastrointestinal diseases caused by H. pylori infection. Zhang et al. [24] found that baicalin can significantly reduce the levels of myeloperoxidase (MPO) and nitric oxide (NO) in the colon of mice. Additionally, baicalin can lower the levels of inflammatory factors such as TNF-α, IL-1β, and IL-6 in colon tissue and inhibit the increase in IL-33 and NF-κB protein levels, effectively alleviating clinical symptoms of UC. Other studies have shown that baicalin can reduce the secretion of mucin 5AC (min 5AC, MUC5AC) in the airway epithelium by inhibiting the NF-κB signaling pathway, thereby alleviating respiratory inflammation. Additionally, baicalin can inhibit the proliferation and metastasis of ovarian tumor cells, promote apoptosis, and decrease the levels of albumin (ALB), alkaline phosphatase (ALP), and hyaluronic acid (HA) in serum, as well as reduce the levels of inflammatory factors such as IL-6 and IL-1β, thus improving liver fibrosis. [25-27].

3.2 Peony

Paeonia lactiflora first appeared in the Shennong Bencao Jing, with functions of nourishing blood and regulating menstruation, consolidating yin to stop sweating, soothing liver pain, and calming liver yang [28]. Paeoniflorin is the main compound extracted from red peony and white peony root. Previous studies have found that paeoniflorin has anti-inflammatory, analgesic, sedative, antitumor, and cognitive improvement effects. Therefore, paeoniflorin is widely used in clinical treatments for neurological disorders such as Alzheimer's disease, stroke, depression, and epilepsy [29, 30]. Research indicates that paeoniflorin can significantly

alleviate stress and depression by modulating the HPA axis and the neuroprotective effects of NO/cGMP/cAMP [31]. Wang Liqing et al. [32] established an Alzheimer's disease (AD) rat model and found that paeoniflorin can inhibit the expression of RhoA and ROCK2 proteins, increase the superoxide dismutase (SOD) content in AD rats, reduce reactive oxygen species (ROS) and malondialdehyde (MDA) levels, thereby enhancing antioxidant activity, reducing hippocampal neuronal apoptosis, and improving cognitive function in AD rats. Liping Z [33] also confirmed that paeoniflorin can improve cognitive function in rats, but their experiments were conducted based on the hypothesis that paeoniflorin can lower iron ion content in brain tissue and inhibit neuronal ferroptosis. According to reports [33-36], paeoniflorin can reduce the infiltration of Gram-positive bacteria in the gut, inhibit the MDP-NOD2 pathway, and restore the inhibitory effect of G protein-coupled receptor kinase 2 (GRK2) and β-blocker 2 on ERK1/2-NF-κB to protect the intestinal epithelial barrier. Therefore, paeoniflorin can alleviate various intestinal diseases such as colitis. Other studies have shown that paeoniflorin has the ability to inhibit the STAT3 /PD-L1 and NF-κB signaling pathways, promoting apoptosis of tumor cells and inhibiting their growth and proliferation [37-39]. Regarding its analgesic effects, Wu Li et al. [40] found that paeoniflorin reduces the content of prostaglandin E2 (PGE2), decreases the sensitivity of pain receptors, and increases the levels of β-endorphin (β-EP) in the blood and cerebral cortex, thereby activating endogenous pain mechanisms and reducing pain transmission to produce analgesic effects. Additionally, Hong Jiaqi et al. [41] discovered that paeoniflorin can delay the release of inflammatory factors and the activation of microglia in the spinal cord by inhibiting the Akt/NF-κB signaling pathway, thus alleviating pain symptoms.

3.3 Licorice

Licorice is the dried root and rhizome of Glycyrrhiza uralensis Glycyrrhiza uralensis, Gleditsia sinensis G. inflata, or Glycyrrhiza uralensis G. glabra, which have the effects of tonifying the spleen and invigorating qi, clearing heat and detoxifying, expectorant and antitussive, relieving pain, and harmonizing other herbs [42]. Modern research has found that licorice has anti-inflammatory, antioxidant, antiviral, anticancer, antibacterial, and neuroprotective properties, possibly due to active components such as glycyrrhetin, iso-glycyrrhetin, glycyrrhetinic acid, glycyrrhetin, glycyrrhetin, iso-glycyrrhetin, isoangustone A, and glycyrrhetin [43-44]. Studies have shown that glycyrrhetin can reduce TNF-α, IL-1β, and IL-6 levels in gastric mucosal tissue, thereby protecting the gastric mucosa and preventing damage [45]. Shen Yan et al. [46-47] found that glycyrrhetinic acid can alleviate stress-induced injury and apoptosis in intestinal epithelial cells by interfering with the PERK-eIF2α-NF-κB and caspase-12 apoptotic signaling pathways under endoplasmic reticulum (ERS) stress, preventing increased permeability of the intestinal epithelium, thus exerting a protective effect on the intestinal mucosal barrier. Luo Y et al. [48] demonstrated that glycyrrhetinic acid can lower serum cardiac troponin I and creatine kinase levels, inhibit the activation of the HMGB1 /TLR4/NF-κB signaling pathway induced by coronary microembolism, and provide some protection against myocardial dysfunction. Ya-Jun L [49] found that glycyrrhizin can prevent the translocation of high-mobility group protein (HMGB1) from the nucleus to the cytoplasm in the CA1, CA3, and hilum regions of the hippocampus in rats induced by naringin, thereby improving neuronal damage in these areas and protecting the blood-brain barrier, exerting neuroprotective effects. Other studies have indicated that glycyrrhizin can promote excessive autophagy in HepG2 and MHCC97-H cells, leading to metabolic disorders in hepatocellular carcinoma (HCC) cells. Additionally, Glycyrrhizin and glycyrrhetinic acid can regulate MAPK/Akt/NF-κB and MAPK/STAT3/NF-κB signaling pathways, respectively, inducing apoptosis in liver cancer cells, providing theoretical support for the liver-protective and anti-tumor efficacy of licorice [50-52].

3.4 Fructus Jujubae

Fructus Jujubae is the dried mature fruit of the jujube plant in the family Juglandaceae; it has a sweet taste, warm nature, and affects the spleen and stomach meridians. Jujubes have the effects of tonifying the middle energizer, invigorating qi, nourishing blood, and calming the mind. Their chemical composition mainly consists of polysaccharides and insoluble dietary fiber, with their pharmacological actions primarily attributed to jujube polysaccharides. Current research indicates that jujube polysaccharides possess anti-depressant, antioxidant, anti-tumor, and immune-enhancing properties [53-54]. Studies have shown that jujube polysaccharides can stimulate the activity of RAW 264.7 immune cells, thereby inhibiting cell proliferation by inducing apoptosis, blocking the G0/G1 phase of the cell cycle, and increasing intracellular ROS in colorectal cancer cells (LoVo) [55]. Jingya R [56] found through experiments on AOM/DSS-induced mice that jujube extract and its lipophilic fraction (mainly triterpenes) significantly reduced mortality, DAI values, tumor burden, and tumor size, demonstrating that jujube triterpenes exert an anti-colorectal cancer (CRC) effect by inhibiting the PI3K/Akt/NF-κB signaling pathway. Ji X et al. [57] discovered that jujube polysaccharides increase the relative abundance of Bacteroides in the intestines of CRC mice while significantly reducing the relative abundance of Firmicutes. In the feces of mice, an increase was observed in Bacteroides and Actinobacteria, while the relative abundances of Firmicutes, Cyanobacteria, Iron bacteria, Spirochetes, and mucosal bacteria decreased significantly, thus proving that jujube polysaccharides also play a therapeutic role in CRC by modulating the gut microbiota. Shiying H et al. [58] demonstrated that jujube polysaccharides can increase serum creatinine (Scr), blood urea nitrogen (BUN), and urinary protein levels, reduce tubular atrophy and interstitial fibrosis of the kidney, thereby improving renal function. They also promote the production of short-chain fatty acids (SCFAs) and erythropoietin (EPO), increasing red blood cells and hemoglobin to improve anemia. According to Chi A's [59] experimental results, when studying chronic fatigue syndrome (CFS) mice, it was found that jujube polysaccharides can enhance cellular immune function. It significantly increases NK cell activity, T cell proliferation, the CD4+/CD8+ ratio, and CD4+ count in CFS rats, as well as SOD and GSH-Px activity, and reduces serum MDA levels, indicating that jujube polysaccharides have certain therapeutic effects on CFS. Additionally, Yuan Y studies [60] showed that jujube polysaccharides can activate AMPK to regulate tight junction

proteins (TJs) between epithelial cells, protecting the intestinal mucosal barrier. This suggests that jujube polysaccharides play a significant role in treating gastrointestinal diseases and maintaining gut health.

4. Summary

Huangqin Decoction is referred to as the "ancestor of treating dysentery for all generations" in Medical Formula Collection and Explanation. In Liu Wansu's Preservation of Life through the Mechanisms of Disease in the Plain Questions from the Jin Dynasty, Shaoyao Decoction was derived by modifying Huangqin Decoction. In recent years, with increased research and discussion, Huangqin Decoction has been widely applied to the diagnosis and treatment of various diseases, achieving certain therapeutic effects. Modern pharmacologists and molecular drug researchers have thoroughly demonstrated that the entire formula and its individual components can reduce TNF-α, IL-1β, and IL-6 inflammatory factors, regulate gut microbiota, inhibit related inflammatory pathways, and protect the intestinal mucosal barrier, thereby exerting anti-inflammatory, antipyretic, and antibacterial effects. However, the mechanisms by which Huangqin Decoction alleviates pain and stops diarrhea still require further exploration. It is believed that as research continues to deepen, the specific pharmacological basis and mechanisms of action of Huangqin Decoction will be gradually elucidated, providing valuable references for the modernization of traditional Chinese medicine.

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