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Research Progress on the Mechanism of Huanji Zhixie Decoction in Improving Diarrhea - Predominant Irritable Bowel Syndrome of Liver Depression and Spleen Deficiency Pattern via Mediating the TP53-PI3K-AKT Signaling Pathway

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Abstract: ***Diarrhea-predominant irritable bowel syndrome (IBS-D) is a functional bowel disorder with chronic recurrent diarrhea, abdominal pain and abdominal distension as the core symptoms, accompanied by intestinal motility disorder, visceral hypersensitivity and abnormal intestinal mucosal barrier function. Its pathogenesis involves multiple levels including intestinal mucosal barrier injury, neuro-endocrine-immune (NEI) network imbalance, intestinal flora disorder and abnormal regulation of signaling pathways. In traditional Chinese medicine (TCM), the core pathogenesis of IBS-D is "spleen deficiency and liver hyperactivity, internal retention of dampness and turbidity". Huanji Zhixie Decoction, a self-designed TCM compound prescription by Director Yu Tao for the clinical treatment of IBS-D, has the effects of soothing the liver and invigorating the spleen, relieving depression and eliminating dampness, stopping diarrhea and resolving stagnation. Its clinical efficacy has been initially verified, but the mechanism of action has not been fully clarified. The TP53-PI3K-AKT signaling pathway, as a key pathway regulating cell survival, proliferation, apoptosis and metabolism, plays an important role in the repair of intestinal mucosal barrier, regulation of intestinal motility and maintenance of inflammatory microenvironment homeostasis, and is closely related to the core pathological features of IBS-D. This paper systematically sorts out the modern medical research progress of IBS-D, TCM theoretical understanding and application basis of Huanji Zhixie Decoction, focuses on the mechanism of the TP53-PI3K-AKT signaling pathway in IBS-D and the regulatory effect of TCM compound prescriptions on this pathway, and finally points out the current research gaps and the research ideas of this subject, so as to provide theoretical basis and literature support for the mechanism research of Huanji Zhixie Decoction in the treatment of IBS-D.***

Keywords: Diarrhea-predominant irritable bowel syndrome, Huanji Zhixie Decoction, TP53, PI3K-AKT signaling pathway, Intestinal mucosal barrier, Intestinal motility, Visceral hypersensitivity.

1. Introduction

1.1 Research Background and Clinical Significance

Irritable bowel syndrome (IBS) is a common and frequently - occurring disease with global prevalence. The global incidence rate of IBS is about 11.2%, with differences in prevalence among different countries and regions: the incidence rate is about 8%-23% in European countries, about 10%-19% in African countries, and about 5%-10% in Asian countries. The prevalence of IBS in China ranges from 1.4% to 11.5% [1-3]. According to the Rome IV criteria, IBS is divided into four subtypes according to the main symptoms of diarrhea, constipation, mixed defecation habits, or unclassified type: diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed (IBS-M) and unclassified (IBS-U). IBS-D is the most common subtype in China, and also the most studied subtype at present [4]. At present, the treatment of IBS-D is mainly symptomatic treatment, including antispasmodics, antidiarrheals, probiotics, antidepressants, etc. However, there are problems such as large individual differences in efficacy and high recurrence rate, and there is a lack of radical treatment targeting the etiology [5]. TCM has the unique advantage of "syndrome differentiation and treatment, holistic regulation" in the treatment of IBS-D. Classic compound prescriptions and active components of TCM have shown good efficacy in improving symptoms, regulating intestinal function and reducing recurrence rate. However, due to the "multi-component, multi-target" action characteristics of TCM compound prescriptions, the research on their molecular mechanism is still weak. It is urgent to clarify their action targets and pathways through modern science and technology, so as to provide evidence-based medical evidence for clinical application.

The current mechanism research of IBS-D has focused on the regulatory network of "signaling pathway-pathological phenotype". Among them, the TP53-PI3K-AKT signaling pathway, as a key hub connecting upstream regulatory molecules and downstream functional phenotypes, its role in IBS-D has not been fully clarified. As a clinically effective TCM compound prescription, whether Huanji Zhixie Decoction can target regulate the PI3K-AKT signaling pathway through mediating TP53 (or other upstream molecules), thereby improving the core pathological phenotypes of IBS-D such as intestinal mucosal barrier injury, intestinal motility disorder and visceral hypersensitivity, still lacks systematic experimental verification. Therefore, based on the existing literature, this paper reviews the two core issues of "the role of TP53-PI3K-AKT pathway in IBS-D" and "the potential regulatory mechanism of Huanji Zhixie Decoction", so as to provide a theoretical basis for the subject research.

2. Research Progress of Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D)

2.1 Modern Medical Understanding of the Pathogenesis of IBS-D

IBS is caused by a variety of factors, and its pathogenesis has not been fully clarified. It is mainly related to visceral hypersensitivity, gastrointestinal motility abnormality, brain-gut axis dysfunction, gastrointestinal permeability abnormality, intestinal mucosal barrier injury, intestinal low-grade inflammatory response, intestinal flora imbalance and other factors [6]. The research status of common core pathogenesis is described in detail below.

2.1.1 Brain-Gut Axis Dysfunction

The occurrence of IBS is closely related to the disorder of central nervous system and enteric nervous system, namely the imbalance of brain-gut axis function, which is an important research direction of the disease at present. The brain-gut axis is a two-way mutual regulation system, composed of the central nervous system (CNS), autonomic nervous system (ANS) and enteric nervous system (ENS). The intestine produces abnormal response signals to endogenous stimuli (inflammation, improper diet or flora imbalance) [7]. Gastrointestinal secretory cells secrete brain-gut peptides, which transmit signals to the CNS in the form of neurotransmitters, and directly affect the effect of the intestinal system.

The ANS is the link between the CNS and ENS. The CNS receives and integrates internal and external stimuli (such as mental and physical stress or pain), induces abnormal signals in the relevant areas of the cerebral cortex, and then stimulates the hypothalamic-pituitary-adrenal (HPA) axis to control gastrointestinal function through the vagus/sympathetic nerve, leading to the occurrence of IBS-D [8].

2.1.2 Visceral Hypersensitivity

Visceral hypersensitivity refers to an excessive pain or abnormal sensory response of the body to external stimuli, mostly characterized by unfixed location and multi-site pain, which is closely related to the occurrence of IBS-D [9]. Studies have suggested that chronic low-grade inflammatory response in the intestine and activated immune cells (such as increased TNF-α, IL-6, mast cells, etc.) can cause excessive excitation of the nervous system and increase visceral hypersensitivity [10].

Excessive activation of inflammatory factors and immune cells not only acts on the intestinal autonomic nervous system, but also affects the central nervous system through the brain-gut axis, leading to a vicious circle of visceral hypersensitivity. For example, after activation, mast cells release a large number of inflammatory mediators, which directly stimulate intestinal nerve endings and increase pain-causing signals. At the same time, the release of inflammatory mediators into the blood circulation due to the imbalance of intestinal barrier function and increased mucosal permeability can also cause systemic neuroendocrine changes. Therefore, the formation of visceral hypersensitivity requires the joint participation of multiple factors and links, which is the final result of the interaction between the nervous, immune and endocrine systems, leading to hyperalgesia symptoms in patients with IBS-D, which occur repeatedly or persistently.

2.1.3 Gastrointestinal Motility Abnormality

IBS-D is closely related to intestinal motility disorder [11]. Patients with IBS-D have hyperactive intestinal peristalsis with increased frequency and amplitude, as well as rapid peristalsis of the jejunum and small intestine. The food moves faster in the intestinal tract and shortens the retention time in the intestine, resulting in too fast movement of feces and diarrhea. At the same time, literature reports that excessive bile acids can not only enhance the visceral sensitivity of patients, but also increase the permeability of colonic mucosa. Excessive bile acids in the intestinal lumen increase colonic transport activity by activating G protein-coupled receptor 5 (TGR5), which aggravates the clinical symptoms of patients with IBS-D [12].

2.1.4 Intestinal Flora Imbalance

Intestinal flora is a symbiotic flora composed of a variety of complex microorganisms parasitic in the human body, with the highest density in the intestinal tract. It mainly includes more than 400 kinds of microorganisms, with the number reaching 40 trillion, and the total number of genes reaching 150 times that of the human body's own genes [13]. In a healthy state, the resident beneficial bacteria in the intestine mainly include Bifidobacterium, Lactobacillus and Streptococcus, accounting for more than 98% of the total. The remaining proportion includes a part of conditional pathogenic bacteria and pathogenic bacteria. The balance between beneficial bacteria and pathogenic bacteria is an essential key to the structural balance of intestinal microecology. However, under the influence of various factors, intestinal microecological imbalance can be caused, resulting in disorder of the composition and quantity of intestinal flora, leading to intestinal dysfunction and clinical manifestations of the body [14]. Studies [15] have found that patients with IBS-D have abnormal intestinal microecological structure. For example, studies have shown that the beneficial bacteria such as Lactobacillus and Bifidobacterium in the feces of IBS-D are decreased, the pathogenic bacteria such as Enterobacter are increased, and the intestinal colonization resistance (B/E value) is lower than that of normal people. Another study [16] showed that intestinal flora usually has a dynamic balance with the host and the environment. The destruction of this balance can lead to inflammatory response, immune function disorder, intestinal barrier damage, increased fermentation and gas production in the intestine, visceral hypersensitivity and other phenomena, which in turn lead to the occurrence of IBS-D. Therefore, intestinal flora disorder is regarded as one of the causes of IBS-D, which participates in the disease process from multiple links and the whole process by affecting the host's metabolism, immunity and defense system.

2.1.5 Psychosocial Factors

Relevant studies have confirmed that psychosocial factors are

an important inducement for the onset of IBS. The incidence of IBS is higher in people with negative emotions such as anxiety and depression. Patients with IBS-D often show autonomic nervous system dysfunction, mainly manifested as abnormal nerve function, often combined with visceral hypersensitivity and parasympathetic nerve abnormality [17]. Various stressful events in life, mental trauma or bad interpersonal relationships can significantly increase the incidence of IBS [18]. Adverse life events are an important risk factor for pure depressive symptoms in patients with IBS. External pressure factors stimulate the cerebral cortex, activate the HPA axis, and the paraventricular nucleus of the hypothalamus releases excessive corticotropin-releasing factor (CRF), which affects gastrointestinal motility and the secretion of gastrointestinal hormones, leading to accelerated intestinal peristalsis, increased visceral sensation and autonomic nervous system dysfunction [19]. Data show that the prevalence rates of anxiety and depression in patients with IBS are 44% and 36% respectively. Negative emotions and psychological factors can significantly increase the severity of IBS symptoms, and are closely related to treatment [20-22].

2.1.6 Key Regulatory Pathways and Molecular Mechanisms

Studies [23] have shown that the pathogenesis of IBS-D involves a complex process of multi-gene, multi-signaling pathway regulation and multi-stage interaction. The Phosphatidylinositol 3-Kinase/Protein Kinase B (PI3K-AKT) signaling pathway is a compensatory mechanism that activates pro-inflammatory factors. Targeted inhibition of the activation of this signaling pathway can reduce the inflammatory response of brain microvascular endothelial cell injury in rats. In addition, relevant signaling pathways include: Toll-like receptor/nuclear factor κB (TLR4/NF-κB), 5-hydroxytryptamine (5-HT), stem cell factor/KiT ligand (SCF/c-Kit), corticotropin-releasing factor (CRF), adenosine monophosphate-activated protein kinase (AMPK), mitogen-activated protein kinase (MAPK), short-chain fatty acids (SCFAs), cyclic adenosine monophosphate (cAMP), etc [24].

This series of signaling pathways can treat IBS-D by promoting gastrointestinal motility, relieving anxiety, reducing visceral hypersensitivity and improving intestinal micro-inflammation. Among them, the PI3K-AKT pathway, as the core regulatory pathway of cell function, participates in the repair of intestinal mucosal barrier, regulation of intestinal motility and maintenance of inflammatory microenvironment homeostasis in IBS-D by regulating the expression of tight junction proteins, smooth muscle cell contraction, and secretion of inflammatory factors [25]. As the “guardian of the genome”, TP53 not only participates in the regulation of cell apoptosis, but also indirectly affects the activity of the PI3K-AKT pathway by directly binding to the PI3K promoter or regulating the expression of non-coding RNA. The two interact with each other and have a clear relationship [26-27].

2.2 TCM Theoretical Understanding and Treatment Status of IBS-D

2.2.1 Core Pathogenesis and Syndrome Differentiation Classification

In TCM, IBS-D belongs to the categories of “diarrhea” and “abdominal pain”, and its core pathogenesis is “spleen deficiency and liver hyperactivity, internal retention of dampness and turbidity” [28]. Emotional disorder leads to failure of the liver to maintain smooth flow of qi, stagnation of qi activity adversely affects the spleen; improper diet or chronic disease strain leads to deficiency of spleen qi, failure of transportation and transformation, downward flow of dampness and turbidity into the intestine, and failure to separate the clear and turbid, resulting in diarrhea. The disease is mainly located in the intestine, involving the liver and spleen. Some patients may involve the kidney yang, forming the syndrome type of spleen and kidney yang deficiency, which reflects the diagnosis and treatment thinking of “holistic concept”.

On the basis of previous experience, modern physicians still focus on liver qi stagnation and spleen deficiency in the understanding of the etiology and pathogenesis of IBS-D, with slight differences on this basis. Master of Chinese medicine Li Zhenhua [29], Professor Zhang Shengsheng [30] and others all believe that the pathogenesis of chronic diarrhea always belongs to “liver depression and spleen deficiency”, emphasizing that diarrhea is caused by emotion, liver stagnation and qi stagnation, spleen deficiency produces dampness, qi stagnation and dampness obstruction, and the intestine loses conduction, resulting in diarrhea. Master of Chinese medicine Lu Zhizheng [31] believes that “dampness pathogen trapping the spleen” is the key to the persistent and refractory IBS. Dampness is sticky and stagnant, which damages the ascending and descending of the spleen and stomach, resulting in abnormal intestinal conduction.

According to the Expert Consensus on TCM Diagnosis and Treatment of Irritable Bowel Syndrome (2024) [4], IBS-D is divided into 4 main types: liver depression and spleen deficiency pattern, spleen deficiency and excessive dampness pattern, large intestine damp-heat pattern, spleen and kidney yang deficiency pattern. The corresponding TCM prescriptions are Tongxie Yaofang Decoction, Shenling Baizhu Powder, Gegen Qinlian Decoction, and Fuzi Lizhong Pill combined with Sishen Pill, among which the liver depression and spleen deficiency pattern is the most common [32].

2.2.2 Application and Mechanism Research of TCM Compound Prescriptions in the Treatment of IBS-D

Based on the principle of syndrome differentiation and treatment, TCM compound prescriptions realize the holistic regulation of IBS-D through the treatment methods of “invigorating the spleen, soothing the liver, eliminating dampness, stopping diarrhea”. For example, Tongxie Yaofang Decoction, a classic compound prescription for the treatment of IBS-D with liver depression and spleen deficiency pattern, is composed of Atractylodis Macrocephalae Rhizoma, Paeoniae Alba Radix, Citri Reticulatae Pericarpium and Saposhnikoviae Radix. It has been confirmed that it can regulate intestinal motility and improve intestinal mucosal barrier function in patients with IBS-D by soothing the liver, invigorating the spleen and stopping diarrhea [33].

Shenling Baizhu Powder, by invigorating the spleen and

eliminating dampness to stop diarrhea, can improve the clinical symptoms of patients with IBS-D through multiple targets and multiple ways, such as reducing visceral hypersensitivity, inhibiting intestinal inflammatory response, regulating brain-gut axis and brain-gut peptide levels, improving intestinal flora imbalance and repairing intestinal mucosal barrier, with less adverse reactions [34]. Sishen Pill combined with Tongxie Yaofang Decoction, based on the treatment method of invigorating the spleen and soothing the liver, can improve the autophagy function of patients with intestinal diseases of spleen and kidney yang deficiency combined with liver depression pattern, and down-regulate the level of inflammatory factors by inhibiting the PI3K-AKT-mTOR pathway [35].

Studies by Zhu Mengjuan et al. showed that modified Chaihu Shugan Powder combined with Tongxie Yaofang Decoction plus conventional western medicine treatment can significantly relieve anxiety and depression in patients and improve clinical efficacy [36]. In conclusion, the current research on the mechanism of TCM in the treatment of IBS-D mostly focuses on regulating intestinal flora, improving intestinal barrier function, inhibiting inflammatory response, regulating the balance of signaling pathways and neurotransmitters, and improving visceral hypersensitivity.

3. Mechanism of TP53-PI3K-AKT Signaling Pathway in IBS-D

The TP53-PI3K-AKT signaling pathway is a complex regulatory network composed of upstream regulatory molecules (TP53, miRNAs, transcription factors, etc.), core kinases (PI3K, AKT) and downstream target molecules (mTOR, GSK3β, MLCK, tight junction proteins, etc.) [37]. Among them, the activation of PI3K can promote the phosphorylation of AKT, and the activated AKT participates in a variety of physiological and pathological processes such as cell proliferation, apoptosis, metabolism, barrier function and smooth muscle contraction by regulating downstream target molecules [24]; its abnormal activation or inhibition is closely related to the occurrence and development of a variety of diseases [38].

In the regulation of intestinal physiological function, the PI3K-AKT signaling pathway can maintain the integrity of the intestinal mucosal barrier by regulating the proliferation and apoptosis of intestinal mucosal epithelial cells; at the same time, this pathway can also regulate the activation of immune cells and the secretion of inflammatory factors, and participate in the regulation of intestinal inflammatory response [39,40]. Studies have found that in a mouse model of IBS-D, inhibition of the PI3K/AKT pathway significantly reduced visceral hypersensitivity in IBS-D mice, confirming that excessive activation of the PI3K/AKT pathway is closely related to the pathological mechanism of visceral hypersensitivity in IBS-D [41].

As an important tumor suppressor gene, TP53 not only regulates the cell cycle and apoptosis but also plays a critical role in immune regulation, intestinal flora balance and signaling pathway modulation [42-44]. As a key upstream regulatory molecule, TP53 can indirectly inhibit AKT phosphorylation by transcriptionally inhibiting the expression of PI3K [45], thereby regulating the activity of the pathway, and then leading to the disorder of intestinal mucosal barrier function, increased release of intestinal inflammatory factors and abnormal intestinal motility.

Stress response is the core inducement of IBS-D, and TP53 is a key response molecule of stress signals [46], which can be activated by a variety of stress signals, such as DNA damage, excessive cell proliferation, hypoxia, oxidative stress and ribonucleotide depletion. Pathogenic factors such as restraint stress and intestinal infection can significantly up-regulate the expression of TP53 by activating the NF-κB signaling pathway, which affects intestinal homeostasis by regulating autophagy [47]. In addition, studies have found that oxidative stress can activate the PI3K-AKT pathway, mediate autophagy-related signaling pathways, further promote the activation of oxidative stress, induce cell autophagy, destroy the intestinal mucosal barrier, and lead to the occurrence of IBS syndrome [48]. TP53 mutation can also induce intestinal flora disorder by disturbing sialic acid metabolism, increase the abundance of pathogenic bacteria such as Aeromonas, and further aggravate intestinal inflammation [47].

In summary, the potential mechanism of the TP53-PI3K-AKT signaling pathway in IBS-D may include: regulating intestinal mucosal barrier, participating in inflammation regulation, affecting intestinal homeostasis, mediating stress adaptation response, regulating visceral hypersensitivity and regulating intestinal motility. Therefore, it is hypothesized that the regulation of PI3K-AKT signaling pathway mediated by TP53 may be one of the key molecular mechanisms of the pathogenesis of IBS-D.

4. Research Basis of Huanji Zhixie Decoction in the Treatment of IBS-D

4.1 Formulation Basis and Conception

Huanji Zhixie Decoction is a self-designed TCM decoction by Director Yu Tao of Shaanxi Provincial Hospital of Traditional Chinese Medicine for the treatment of IBS-D. Through long-term clinical observation, Director Yu Tao found that the pathogenesis of IBS-D with liver depression and spleen deficiency pattern has both the universality of liver depression, spleen deficiency and dampness obstruction, and the particularity of qi stagnation. Therefore, on the basis of invigorating the spleen and stomach, promoting qi circulation to relieve depression, activating qi and resolving dampness can often achieve better clinical efficacy, and this method is summarized as the method of “treating obstruction with dredging”.

Through in-depth excavation of classic TCM prescriptions, Huanji Zhixie Decoction was modified on the basis of Tongxie Yaofang Decoction, Sini Powder and Yigong Powder, with the treatment principles of promoting qi circulation, relieving depression, eliminating dampness and invigorating the spleen based on the method of “treating obstruction with dredging” and syndrome differentiation. The specific composition of the prescription is as follows: Bupleuri Radix (Beichaihu), Codonopsis Radix (Dangshen), Paeoniae Alba Radix (Baishao), fried Aurantii Fructus Immaturus (Chaozhishi), Atractylodis Macrocephalae

Rhizoma (Baizhu), Poria (Fuling), Citri Reticulatae Pericarpium (Chenpi), Saposhnikoviae Radix (Fangfeng), Pogostemonis Herba (Guanghuoxiang), raw Crataegi Fructus (Shengshanzha), fried Hordei Fructus Germinatus (Chaomaiya), charred Massa Medicata Fermentata (Jiaoshenqu), Sepiae Endoconcha (Haipiaoxiao), prepared Polygalae Radix (Zhiyuanzhi), and Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle (Zhigancao).

This prescription has the effects of soothing the liver and invigorating the spleen, relieving depression and eliminating dampness, stopping diarrhea and resolving stagnation, which is consistent with the etiology and pathogenesis of IBS-D. Therefore, it is widely used in the clinical treatment of IBS-D. In long-term clinical practice, Director Yu Tao [49] has diagnosed and treated about 4800 patients with IBS-D, and confirmed that Huanji Zhixie Decoction has the effects of regulating intestinal motility, relieving spasm and pain, anti-inflammatory effect and mucosal immune regulation, has a good effect on abdominal pain, diarrhea, abdominal distension and other symptoms of IBS-D, and can prevent the recurrence of symptoms to a certain extent.

This prescription is modified from Yigong Powder, Sini Powder and Tongxie Yaofang Decoction. Yigong Powder can invigorate the spleen and replenish qi, while Sini Powder and Tongxie Yaofang Decoction can harmonize the liver and spleen, eliminate dampness and stop diarrhea. In the prescription, Bupleuri Radix soothes the liver and relieves depression, and Codonopsis Radix invigorates the spleen and replenishes qi, which are used as the sovereign drugs. Paeoniae Alba Radix and Aurantii Fructus Immaturus promote qi circulation and soften the liver; Atractylodis Macrocephalae Rhizoma, Poria, Pogostemonis Herba, Citri Reticulatae Pericarpium and Saposhnikoviae Radix invigorate the spleen and resolve dampness, dispel wind and regulate qi; raw Crataegi Fructus, charred Massa Medicata Fermentata and fried Hordei Fructus Germinatus invigorate the spleen and promote digestion, which are used together as minister drugs. Combined with Citri Reticulatae Pericarpium, they strengthen the effect of “simultaneous application of purgation and tonification”. Aurantii Fructus Immaturus promotes qi circulation and removes stagnation according to the method of “treating obstruction with dredging”. Sepiae Endoconcha can astringe and consolidate without hindering the smooth flow of qi. Prepared Polygalae Radix nourishes the heart and calms the spirit as the adjuvant drug. Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle replenishes qi and harmonizes the middle, coordinates the effects of all drugs, and can be used together with Paeoniae Alba Radix to relieve spasm and pain, which is the guide drug.

The combination of all drugs achieves the effect of harmonizing the liver and spleen, invigorating the spleen to stop diarrhea, soothing the liver and regulating qi, and has a clear effect in the clinical treatment of IBS-D. Huanji Zhixie Decoction not only has a basic prescription compatibility consistent with the core pathogenesis, but its modified components are also effective and suitable for various concurrent syndromes, which not only expands its treatment scope, but also further improves the pertinence and clinical efficacy of complex diseases, and takes into account individual physical differences. It may be used as an important material basis and technical support for the research and development of Chinese patent medicine preparations.

4.2 Modern Pharmacological Research

Many Chinese medicines and basic prescriptions in Huanji Zhixie Decoction have been confirmed by modern pharmacological studies to alleviate the symptoms of IBS-D. Modern pharmacological studies have found that Tongxie Yaofang Decoction can regulate the content of 5-HT in serum and colon tissue and the expression of 5-HT receptor protein in IBS-D, thereby reducing visceral hypersensitivity [33,50]. Sini Powder can increase the activity of the hippocampal PI3K/AKT/mTORC1 signaling pathway, inhibit excessive autophagy in the hippocampus, improve the damage of hippocampal neurons, and thus produce an antidepressant effect [51].

Studies [52] have found that TCM for invigorating the spleen and replenishing qi can increase the number of beneficial bacteria such as Bifidobacterium and Lactobacillus, reduce the abundance of conditional pathogenic bacteria such as Escherichia coli, and restore the diversity of intestinal flora. In addition, experiments have proved that a large dose of water decoction of Atractylodis Macrocephalae Rhizoma can promote gastrointestinal propulsion [53]; Paeoniae Alba Radix has the effect of inhibiting parasympathetic nerve excitation to relieve spasm; Citri Reticulatae Pericarpium can antagonize intestinal spasm and anti-allergy; Saposhnikoviae Radix mainly has analgesic, sedative and anti-allergic effects.

Arecae Semen can not only regulate the gastrointestinal function, improve the gastric emptying rate and small intestine propulsion rate of rats with hypomotility, but also regulate M cholinergic receptors to promote gastrointestinal peristalsis, and play a dual regulatory role to normalize gastrointestinal movement [54]. The active component of Saposhnikoviae Radix, Cimifugin, can effectively inhibit gastric emptying and intestinal transport function in experimental animals, and also has analgesic, antibacterial, anti-inflammatory, anti-ulcer and immunity-enhancing effects [55]. Modern pharmacological studies have confirmed that [56] 12 intersection targets including TP53 (p53 tumor suppressor protein) with a correlation score greater than 30 are the key targets of Citri Reticulatae Pericarpium in the treatment of functional gastrointestinal disorders (FGIDs).

An animal experiment results suggested that Atractylodes macrocephala polysaccharide may treat UC mice by down-regulating the expression of Wnt/β-catenin signaling pathway proteins, promoting the repair of damaged intestinal mucosa and improving gastrointestinal function [57]. Studies have confirmed that Astragaloside IV (AS-IV), the main component of Astragali Radix, can exert biological effects by regulating the activity of proteins, thereby inhibiting the excessive activation of immune response in vivo. And AS-IV may reduce the inflammatory response and mucosal barrier injury in DSS mice and Caco-2 cell inflammatory model by inhibiting the phosphorylation level of the PI3K/AKT signaling pathway, thereby alleviating UC [58].

4.3 Reference from Relevant Studies on TCM Compound Prescriptions Regulating TP53-PI3K-AKT Pathway

A large number of studies have confirmed that TCM compound prescriptions and active components can treat digestive system diseases by regulating the TP53-PI3K-AKT pathway. Some examples are listed below to provide reference for the mechanism research of Huanji Zhixie Decoction:

(1) Xia Lixian et al. confirmed that Tongxie Yaofang Decoction can significantly down-regulate the mRNA expression and protein levels of P110 (PI3K catalytic subunit) and AKT in colon tissue of IBS-D model rats, inhibit the excessive activation of PI3K-AKT pathway, increase the number of autophagosomes, and reduce visceral hypersensitivity [59];

(2) Sishen Pill combined with Tongxie Yaofang Decoction, based on the treatment method of invigorating the spleen and soothing the liver, can improve the autophagy function of patients with intestinal diseases of spleen and kidney yang deficiency combined with liver depression pattern, and down-regulate the level of inflammatory factors by inhibiting the PI3K-AKT-mTOR pathway [35];

(3) Shengyang Yiwei Decoction can regulate autophagy balance and improve diarrhea and abdominal pain symptoms in patients with IBS-D by targeting core targets such as PI3K and AKT [60];

(4) Total glucosides of paeony (the main active component of Paeoniae Alba Radix) can reduce chemical liver injury by regulating the PI3K-AKT/mTOR pathway, showing anti-inflammatory and cytoprotective effects [61];

(5) Codonopsis Radix can down-regulate the ratio of p-PI3K/PI3K and p-AKT/AKT in colon tissue of ulcerative colitis model rats, inhibit oxidative stress and inflammatory response, and protect intestinal mucosal function [62];

(6) In the KEGG signaling pathway enrichment analysis by Zhu Cong et al., it was suggested that the effect of Saposhnikoviae Radix may involve the AGE-RAGE signaling pathway, IL-17 signaling pathway, endocrine resistance, and p53 signaling pathway [63].

These studies indicate that TCM compound prescriptions can precisely regulate the PI3K-AKT-mTOR pathway through the synergistic effect of multiple components, restore the normal flux of autophagy, and fundamentally improve the pathological state of IBS-D. These findings suggest that Huanji Zhixie Decoction may target regulate the TP53-PI3K-AKT pathway through the synergistic effect of the active components of its constituent drugs, and play a role in the treatment of IBS-D, and its mechanism of action needs further in-depth study.

5. Conclusion

The pathogenesis of IBS-D is complex, involving multiple pathological links such as intestinal mucosal barrier injury, intestinal motility disorder, visceral hypersensitivity and intestinal flora disorder. The TP53-PI3K-AKT signaling pathway, as a key hub regulating these pathological phenotypes, plays an important role in the occurrence and development of the disease. Huanji Zhixie Decoction, as an effective TCM compound prescription for the clinical treatment of IBS-D, has the effects of soothing the liver and invigorating the spleen, relieving depression and eliminating dampness, stopping diarrhea and resolving stagnation. Existing studies have confirmed that it can improve the core symptoms and related pathological phenotypes of IBS-D, but the mechanism of action has not been clarified.

Based on the analysis of existing literature, Huanji Zhixie Decoction may target the PI3K-AKT signaling pathway by mediating TP53 (or other molecules), thereby repairing the intestinal mucosal barrier, regulating intestinal motility, balancing the inflammatory microenvironment and improving the structure of intestinal flora, and finally achieve the therapeutic effect on IBS-D. The development of this subject will systematically clarify the molecular mechanism of Huanji Zhixie Decoction, provide a scientific basis for its clinical application, and provide a certain technical paradigm for the modernization research of TCM compound prescriptions.

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