

Treatment of Functional Dyspepsia with Liver-stomach Disharmony by Chaihu Shugan Power based on the theory of "brain-gut axis"

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Abstract: Functional dyspepsia (FD) is a common digestive disorder. The brain-gut axis (BGA) is a bidirectional regulatory channel between the brain and the gastrointestinal tract. "Brain-gut interaction" is the core of FD pathogenesis, which echoes the theory of liver-spleen. Traditional Chinese medicine has an improve effect on BGA, by regulating the liver qi, strengthening the spleen and stomach, the internal organs and qi are reached. The functional activities of the spleen manifesting in normal transformation and transportation, and Shui Gu subtly can be digested and transmitted. At the same time, the five internal organs are unimpeded, the qi and blood are harmonized, the heart and veins are smooth, and the emotions are also relaxed. Chaihu Shugan Power is an effective prescription for the treatment of FD with liver and stomach disharmony. Based on the BGA theory, this paper summarizes the clinical evidence-based medicine evidence and action targets of Chaihu Shugan Powder in regulating "brain-gut interaction", and provides a scientific basis for its clinical application.

Keywords: Brain-gut axis, Functional dyspepsia, Brain-gut interaction, Liver and stomach disharmony, Chaihu Shugan Power.

1. Introduction

Functional dyspepsia (FD) is a common clinical functional gastrointestinal disorder, a group of clinical syndromes with epigastric pain, epigastric distension, early satiety, belching, loss of appetite, nausea, vomiting and other manifestations in the epigastric region, but its clinical manifestations cannot be explained by organic, systemic or metabolic diseases, etc [1]. The prevalence of FD is high and tends to increase year by year, and the group of patients with dyspeptic symptoms diagnosed with FD after examination is about 79.5 percent [2].

Chinese medicine does not have functional dyspepsia disease name, from the evidence, symptoms point of view analysis, the disease belongs to the "dullness", "plumpness", "noisy", "gastric pain". This disease belongs to the categories of "dullness", "plumpness", "noisy" and "gastric pain". The consensus opinion of FD Chinese medicine diagnosis and treatment points out that FD is located in the stomach, which is closely related to the liver and the spleen, and the basic pathogenesis of FD is a deficiency of the spleen and stagnation of qi, and a loss of harmony in the stomach [3]. According to traditional Chinese medicine, emotions and moods are inseparable from the occurrence of diseases, and emotions and moods are characterized by rebellious qi. The treatment of FD is based on the theory of cerebral-intestinal axis, to explore the target of Chaihu Shugan Power in treating FD of liver-stomach disharmony and to explain its scientific connotation.

2. Concept of the Brain-gut Axis

Brain-gut axis (BGA) was firstly proposed by Prof. Mike Gerson in the United States, which is a two-way pathway connecting the brain and intestine, and its basic components include Central-Nervous System (CNS), Autonomic-Nervous

System (ANS), Hypothalamic-Pituitary-Adrenal Axis (HPA), and Enteric-Nervous System (ENS). Its basic components include the Central-Nervous System (CNS), Autonomic-Nervous System (ANS), Hypothalamic-Pituitary-Adrenal Axis (HPA), and Enteric-Nervous System (ENS), which is a complex neuroendocrine-immune network [4]. These three nervous systems interact with each other, transferring information by way of nerve conduction, endocrine regulation and immune network, forming a two-way and closely linked pathway between the brain and the intestine, i.e., the cerebral-intestinal axis, which is known as the cerebral-intestinal interaction between the central system and the gastrointestinal tract, and is regulated by the cerebral-intestinal axis in both directions [5]. Physiologically, the two maintain a dynamic balance; pathologically, a lesion on one side can affect the other side through signaling, i.e., encephalopathy and intestines, intestinal disease and brain.

Brain gut peptide (BGP) is dually distributed in the gastrointestinal and neurological systems, and is the important material basis of the "two-way contact network" of BGA, with the dual role of hormones and neurotransmitters, and plays the role of bridging and regulating the various links in BGA. There are more than 10 BGPs associated with FD, including vasoactive intestinal peptide (VIP), which enhances gastrointestinal mucus secretion, diastatizes gastrointestinal smooth muscle, and regulates peristalsis in the gastrointestinal tract [6]; Motilin (MTL) promotes strong gastric contractions and small intestinal segmental motility, as well as pepsin secretion, facilitates digestion and accelerates gastric emptying [7]; 5-Hydroxytryptamine (5-HT) is an important neurotransmitter of the brain-gut axis, which has the effect of increasing visceral sensitivity and contracting smooth muscle, and can promote gastrointestinal motility [8]; Calcitonin gene related protein (CGRP) is an endogenous neuropeptide that transmits a variety of physical and chemical stimulus signals from the intestinal lumen or wall and is involved in regulating

the functional activities of the gastrointestinal tract [9]; Leptin (LP) has anxiolytic and depressive effects, and LP expression is decreased in the brains of depressed patients [10]; The main role of gastrin (gastrin, GAS) is to promote gastric acid secretion and to protect the gastric mucosa [11]; Cholecystokinin (CCK) stimulates gastric secretion of gastric acid, excites and promotes gallbladder contraction to eliminate bile and pancreatic secretion, regulates gastric emptying and intestinal motility, and stimulates the hypothalamus to produce a large number of satiety signals [12]. Thus, the material basis, such as neurotransmitters, constitutes the brain-gut axis pathophysiological signaling during brain-gut interaction.

3. FD and BGA

The Rome IV: Functional Gastrointestinal Disorders, published in Rome in 2016, identified FD as an abnormality of bowel-brain interaction [1], symptoms are associated with pathogenic factors such as abnormal gastroduodenal motility, visceral hypersensitivity, *Helicobacter pylori* infection, psychological factors and dietary disorders [13,14]. BGA is the core of the pathogenesis of FD, BGP can link the emotional and cognitive centers of the brain with the peripheral gastrointestinal tract function, abnormal psychophysiological factors through the CNS-gastrointestinal nerve pathway, affecting the frequency of gastric contraction as well as slowing down the conduction velocity, inhibiting gastric motility, causing gastrointestinal motility disorders, dyspepsia, abdominal pain and other symptoms [15]. Modern treatment of FD usually involves general therapy, including education about the disease and guidance to improve the patient's lifestyle; Pharmacological treatments include: *Helicobacter pylori* eradication drugs, acid suppressants, gastrointestinal prokinetic agents, gastric mucosal protectors, anti-anxiety and depression drugs, digestive enzymes and micro-ecological agents, etc. However, current treatments are prone to recurrence or are associated with serious adverse effects [16,17]. Its recurring condition seriously affects patients' quality of life and causes a great burden on medical resources [18].

FD is an advantageous type of Chinese medicine [3], which not only effectively improves the symptoms of abdominal pain and belching, but also solves the related psychological disorders and other problems, with the advantages of high safety and clear therapeutic effects [19]. Basic research found that *Hovenia kuanzhong* capsule improved gastric 5-HT₃ system activity and increased 5-HT₄ distribution in lower 5-HT, and improved FD-associated gastric hypersensitivity and motor dysfunction [20]. Given a small dose of *Hovenia glutinosa* to mice in the FD model group, body weight, gastric emptying rate and intestinal propulsion were significantly elevated, LP, VIP, and CGRP expression were decreased, and MTL, GAS, gastric starvation hormone, and CCK expression were elevated, suggesting that a small dose of *Hovenia glutinosa* can increase gastrointestinal peristalsis and gastrointestinal hormone levels [21]. Acupuncture treatment was also effective in FD. Electroacupuncture stimulation of the Zusanli point acupoints in FD rats effectively regulated the cerebral-gastrointestinal axis, increased the rate of intestinal propulsion and gastric emptying, and reduced the damage to the hypothalamus-gastrointestinal tract. The

gastrointestinal function was significantly improved after treatment, indicating that electroacupuncture stimulation of the Zusanli point acupoints is a safe and effective method for treating FD [22].

4. TCM and BGA's Knowledge of FD

4.1 Theory of Chinese Medicine and BGA

Although the concept of BGA has not been explicitly mentioned in Chinese medicine, the theory of Chinese medicine is that the heart is the master of God and has the function of dominating the mental activities of the human body. "The heart is the official of the sovereign, and the gods come out of it" says Suwen Lingnan Mysteries, pointing out that the physiological functions of the body's internal organs and tissues depend on the mastery of the mind and spirit. "The heart in its will is joy, the liver in its will is anger, the spleen in its will is thought, the lungs in its will is sadness, and the kidneys in its will is fear", says the Su Wen - The Great Theory of Yin and Yang. The Spiritual Pivot Jing-Ben Shen and put forward" so any object is called the heart, the heart has a memory is called the intention of the..... because of the consideration of the object is called wisdom", fully explains the heart for the psychological activities of the center and the master, on a variety of psychological activities play a role in regulating the whole. The functions of the "heart" in Chinese medicine include some of the functions of the "brain" in modern medicine. Zhang Xichun in the "medical Zhongzhong Senxi Lu" in the proposed: "human shenming, the original in the heart and brain in two places", "cover the body of shenming hidden in the brain, shenming of the use of hair in the heart, " that the spirit of the brain in the brain, knowledge of the spirit in the heart, the heart and the brain are closely linked, and the master of the shenming. The Secret Book of the Brocade recorded: "The brain is the house of the gods, presiding over the five gods to regulate the yin and yang of the internal organs, the use of the limbs and bones," indicating that the five viscera are attributed to the brain, the spleen, stomach and intestines of the physiological function of the heart, brain of the gods depend on the presidency of the heart.

Su Wen - Six Sections of Hidden Elephant Theory said: "The five flavors are imported, hidden in the stomach and intestines, the taste has been hidden, in order to nourish the five gases, the gas and the birth of the fluids and fluids, God is born. The Spiritual Pivot: Ping Ren Jue Gu said: "Deity, the essence of water and grain also. "It means that the spleen and stomach receive the water and grain transportation for the essence, water and grain essence is the material basis of the overall performance of God, the two have a close relationship, the normal operation of the spleen and stomach, the water and grain essence has to be upwardly mobile moistening the heart and brain, and vice versa, the spleen and stomach is deficient, can not be up to fill the brain orifices, the God has no reliance on the emergence of depression, anger, sadness, thoughts, and other symptoms of emotional and mental disorders.

From the meridian point of view, the meridian is an important part of the human body, the human body's qi and blood operation, viscera and organs functional activities and its inseparable. Hand Shao Yin Heart Meridian and Hand Sun Small Intestine Meridian are mutually affiliated, constituting

the relationship between the two meridians, the two meridians communicate with each other, promoting the mutual coordination and cooperation between the heart and the small intestine in the physiological function, and interacting with each other in the pathology. Physiologically, the heart yang warm, heart blood nourishing, conducive to small intestinal material; disease, heart fire hyper-sheng downward shift of the small intestine, so that the small intestinal urinary other turbid dysfunction, dyspepsia and other symptoms can occur. In addition, the "Spiritual Pivot - Meridian Vessels" says: "Foot Yangming's special... up to the head and neck, combined with the qi of the meridians", and "the foot Yangming's special... up to the head and neck, combined with the qi of the meridians". The Foot Yangming Stomach Meridian goes from the head to the feet and passes through the skull, indicating that the meridians belong to the intestines and stomach and the brain, and in the top of the head and the large and small intestines meridians, realizing the unifying effect of the Foot Yangming Stomach Meridian in the meridian circulation to the large and small intestines meridians, and the three of them in the meridian circulation have a close relationship, and the emotional abnormality of the brain can result in the function of the spleen and stomach not functioning properly, and conversely, diseases of the spleen and stomach can also affect the brain along the upward flow of the meridian and lead to emotional disorders.

It can be seen that Chinese medicine attaches great importance to the relationship between the heart and brain and the stomach and intestines, whether from the relationship between internal organs, physiological functions of the root of each other, pathological interactions, or meridian circulation, can show that the heart and brain disorders affecting the spleen and stomach transportation of grains and cereals, the spleen and stomach disorders and there will be emotional anomalies. This coincides with the BGA two-way interaction regulation.

4.2 Liver-spleen Correlation and "brain-gut interaction" are Interlinked

Liver five elements of wood, the nature of its strip, the main drainage, but also the main planning, regulating a qi and spiritual and emotional activities, internal organs and qi and blood harmonization, then the spirit of clarity, emotional and emotional comfort. Liver, heart and brain work together to maintain normal mental and emotional activities, so the function of the liver is most relevant to emotional and emotional activities [23]. Su Wensaid: "all diseases are born in the gas also", if the liver's excretion function is normal, the qi organized, the spleen qi healthy transportation, qi, blood and fluid run smoothly, the meridians fluent; if the liver qi stagnation, cross the spleen and earth, affecting the spleen and stomach transportation, the spleen is not healthy, the stomach is not combined and descends into the liver and stomach disharmony evidence, the epigastric distension and pain, loss of appetite, epigastric distension and fullness, belching frequently and other symptoms. It shows that Chinese medicine has long recognized that the heart, brain and gastrointestinal meridians are connected, and that human mental activity is closely linked to gastrointestinal and digestive functions. Li Dongyuan in the Spleen and Stomach Theory put forward "An Nourish the heart and mind to

regulate the spleen and stomach theory", which has the following statement: "good treatment of the disease, but in the harmonization of the spleen and stomach, so that the heart is not stagnant,..... cover the stomach in the yuan qi to Shu stretch also. "The idea is to regulate the "heart and spirit", to keep the blood of the heart smooth, happy mood, you can achieve a healthy state of stomach qi full and smooth. Therefore, for the treatment of FD, it is not only necessary to pay attention to the symptoms of the digestive tract, but also to grasp the key to the pathogenicity of emotions.

The pathogenesis of FD is closely related to the BGA theory that, on the one hand, the central nervous system receives signals perceived from gastrointestinal receptors through the BGA and integrates and processes them to feed back to the gut to regulate gastrointestinal function. On the other hand, emotional depression can travel down through the BGA to the gastrointestinal system, leading to abnormalities in gastrointestinal peristaltic function or visceral sensation, such as dyspepsia. BGA from a TCM perspective, The Spiritual Pivot - Pingren Jiegu said, "The God, the essence of water and grain is also." The "Spiritual Pivot Jing - Five Retained Liquids and Fluids" said: "The fluids of the five grains, and combined into a paste, tonifying the brain and marrow," suggesting that the spleen and stomach transported by the essence of the grains and micro-substances, the upward bearing of the brain to play a role in its physiological activities. BGA related theories and traditional Chinese medicine "liver and stomach disharmony" in the pathogenic process and clinical symptoms are similar to the food through the stomach of the acceptance of the stomach, putrefaction into the essence of the material, through the spleen's transportation, ascension and clearing the role of the whole body, moistening the internal organs, the stomach down the spleen rise, the main food digestion, absorption, but the normal operation of the process can not be separated from the liver's "Excretion". In the "Guide to the Problems of Medical Cases", it is said that "if the liver and wood are rampant, the stomach and earth will be injured; if the stomach and earth are injured for a long time, the liver and wood will become more rampant", which is meant to emphasize the relationship of "liver - stomach", and that liver qi stagnation will make the stomach qi not descend, the spleen qi not rise, the qi pivotal function inversion, and that the function of the spleen and stomach is impaired over a long period of time, resulting in the stomach not accepting. As the spleen does not transport and transform, the liver qi stagnation becomes more prevalent, and the cycle repeats itself to the detriment of all the organs. Therefore, the treatment of FD should uphold the holistic view of traditional Chinese medicine, grasp the etiology, mechanism and location of the disease, grasp the relationship between the liver and the spleen and stomach, and understand the impact of regulating qi on the spleen and stomach, such as the "Suwen - Baolingquanxinglian" said: "the earth gets the wood and reaches, " the normal elevation of the spleen and stomach is dependent on the liver's regulation of the liver qi excretion and excretion of the liver in a proper manner, the qi lifting and lowering smooth, in order to make the healthy movement of the spleen and stomach, and only then can we have a good time. The normal elevation of the spleen and stomach depends on the regulation of liver qi.

4.3 Chaihu Shugan Power for Liver-Stomach Disharmony

Type FD

Liver-stomach disharmony is one of the common syndromes of FD. Clinical symptoms include fullness and pain in the epigastrium and abdomen, episodes or aggravation in case of emotional upset, distress, frequent belching, and good sighing. Most of them are triggered by emotional disorders such as depressed mood and excessive worry, which coincides with the BGA theory of modern medicine, i.e., emotional and mental influence on gastrointestinal function. FD episodes and severity are often related to emotions, Ye Tianshi said "wood can dredge the earth and the spleen stagnation to move", so the treatment of this type of FD should be based on regulating qi and relieving depression, harmonizing the stomach and lowering the rebelliousness, so as to achieve the same treatment of the liver and the stomach, so as to make the liver qi regulated, the excretion and the blood flow, then the spleen rises and the stomach descends, and the transportation and transportation of the spleen is in line with each other. Chaihu Shugan Power is one of the representative formulas for treating FD with liver-stomach disharmony [3].

The original formula of Chaihu Shugan Power is from Jingyue Quanshu, which has the efficacy of dispersing the liver, relieving depression, promoting the flow of qi and relieving pain, and is a prescription for the treatment of stagnation of liver qi [24,25]. In this formula, Chai Hu acts as the ruler to relieve liver stagnation. Xiang Fu regulates Qi and dredges the Liver, and Chuan Xiong promotes Qi and activates Blood circulation to relieve pain, together as the subject's herbs, assisting Chai Hu to relieve stagnation of the Liver meridian and increasing its efficacy of promoting Qi circulation and relieving pain. Chenpi and Citrus aurantium regulate Qi and promote stagnation, while Paeonia lactiflora and Glycyrrhiza glabra are used as adjuvants to nourish Blood, soften the Liver and relieve pain. Glycyrrhiza glabra also regulates all medicines and is used as an emollient. The combination of all the herbs works together to relieve the liver and promote circulation of qi, as well as activating blood circulation and relieving pain. It makes the liver qi organized and the blood flow smooth, which in turn strengthens the middle qi, harmonizes the liver and spleen, and enhances the function of the spleen and stomach, relieving symptoms such as distension and pain in the upper abdomen, loss of appetite, belching and sighing.

In terms of clinical evidence-based research, Peng Shuling [26] et al. randomly divided 100 cases of FD patients with liver-stomach disharmony into two groups: the control group was treated with oral domperidone, and the treatment group was given Chaihu Shugan Power with flavoring, and the results showed that the total effective rate of the patients in the treatment group was significantly higher than that of the control group, which indicated that the efficacy of Chaihu Shugan Power with flavoring in treating liver-stomach disharmony-type FD was significant. Chaihu Shugan Power plus reduction improves clinical symptoms significantly in patients with liver-stomach-qi stagnation type FD, effectively regulates anxiety and depression status and nucleus pulposus gastric emptying function [27]. A randomized, double-blind, placebo-controlled trial showed that Chaihu Shugan Power was effective in relieving clinical symptoms, promoting gastric motility, and improving gastric emptying rate in

patients with FD, as well as relieving anxiety and depressive states [28]. Yang Keming [29] et al. applied Chaihu Shugan Power to intervene in the model group of rats with poor gastrointestinal dynamics, and their gastric emptying rate and small intestinal propulsion rate were elevated, suggesting that Chaihu Shugan Power has the effect of enhancing gastrointestinal dynamics. Therefore, Chaihu Shugan Power is an effective formula for the treatment of FD.

5. The Scientific Context of Chaihu Shugan Power for FD Treatment

Modern research has shown that Chaihu Shugan Power has a definite antidepressant effect. Chaihu Shugan Power effectively regulates the content of 5-HT, improves the hyperactivity of HPA axis, and achieves antidepressant effect [30]. Chaihu can elevate serum levels of 5-HT in patients with anxiolytic and depressive effects [31,32], it also enhances intestinal muscle contraction and has a hepatoprotective effect [33]. A variety of volatile oils in Fragrant Forsythia have the ability to improve depression, alleviate anxiety, and significantly increase serum levels of MTL and GAS, and have a pro-gastric motivational effect [34]. The active ingredients of Citrus aurantium can significantly improve gastrointestinal motility, which can promote intestinal peristalsis and gastric emptying by regulating the secretion of MTL, GAS, CCK, and modulating the neural pathway, thus regulating gastrointestinal motility and restoring normal gastrointestinal motility to the disordered condition [35]. Chen Pi Extract can regulate GAS and CCK levels, promote gastrointestinal motility, and has a digestive stimulating function [36]. Paeoniflorin contained in white peony has an antispasmodic effect, which can inhibit the spontaneous contraction of the intestinal tube overexcited [37,38]. In addition, Paeonia lactiflora can improve the patient's gastric function, and Paeonia lactiflora combined with licorice has a significant therapeutic effect on chronic gastritis [39]. Intervention of Chaihu Shugan Power in rats with chronic stress-induced depression significantly improved their body mass and food intake, suggesting that Chaihu Shugan Power can effectively regulate the mood and appetite of rats with depression model [40]. In conclusion, Chaihu Shugan Power can regulate the function of plant nerves and gastrointestinal function, with anti-anxiety and depression and enhancement of gastric emptying and small intestinal propulsion.

6. Summary

FD is a psychosomatic gastrointestinal disease caused by a variety of pathogenic factors, the pathogenesis of which is still unclear, and with the proposal and development of the "biopsychosocial" model of medicine, it provides a new way of thinking about the treatment of this type of physical and mental disease. People are an organic whole, the treatment of disease can not only stay in the disease itself, should also consider the psychological, spiritual social and other factors, which coincides with the motherland medicine "holistic view", "form and spirit of unity" thought. Although Chinese medicine and modern medicine are two very different medical systems, they simultaneously recognize that the brain and the stomach and intestines interact with each other, bidirectional regulation, closely related. The BGA theory of modern medicine is a proof of the interoperability between stomach

and intestines and heart and brain in the theory of traditional Chinese medicine, which provides a modern scientific basis for the application of Chaihugan Shugan Power in the treatment of liver-stomach disharmony type of FD with the method of "liver-sparing and stomach-relaxing". In view of the limitations of the current study and the lack of a clearer, more detailed and systematic understanding of the combination of TCM theory and BGA, in the future, in-depth studies are still needed to explore the mechanism of action of TCM in the treatment of FD, to validate the active ingredients and mechanism of TCM involved in the interactive effects of BGA, and to elucidate the scientific connotation of the clinical treatment of FD with TCM.

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