Progress in Studying the Mechanism of Traditional Chinese Medicine for Treating Functional Dyspepsia

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Functional dyspepsia is a prevalent gastrointestinal disorder. Western medical treatment is often limited to symptom control with poor long-term efficacy due to the complex etiology of functional dyspepsia. In recent years, traditional Chinese medicine has gained attention due to its unique therapeutic advantages. This paper aims to review the progress of research on the mechanism of traditional Chinese medicine in treating functional dyspepsia. After reviewing the literature, it was found that traditional Chinese medicine treatment of functional dyspepsia involves improving gastrointestinal dynamics, reducing visceral sensitivity, regulating duodenal immune function, and correcting brain-intestinal axis disorders. This demonstrates its multi-targeted and multi-pathway characteristics in treating the disease, providing a new approach for the comprehensive treatment of functional dyspepsia. However, further clinical research is required to improve the scientificity and effectiveness of treating functional dyspepsia with traditional Chinese medicine therapies and promote the further development of traditional Chinese medicine in the field of functional dyspepsia treatment.

Key words: Functional dyspepsia, Chinese medicine therapy, depression, anxiety, gastrointestinal dynamics, brain-gut axis

Functional Dyspepsia (FD) is a common digestive disorder that presents with symptoms such as postprandial fullness, discomfort, early satiety, recurrent epigastric pain, and burning sensation[1]. The cause of the disease is often difficult to identify, and it may be accompanied by negative emotions such as anxiety and depression[2]. The pathophysiology of FD is not yet fully understood. Available studies suggest that its pathogenesis mainly involves disorders of the brain-gut interaction pathway, visceral hypersensitivity, gastrointestinal insufficiency, duodenal micro inflammation, and psycho-spiritual factors[3,4]. FD affects over 10 % of the global population[5]. Currently, treatment for this condition is primarily symptomatic. However, due to the recurring nature of FD, long-term medication use can result in adverse effects on the human body and economic burden, significantly impacting patient's quality of life. Therefore, discovering a safe and effective treatment is crucial in managing FD. Research suggests that patients with FD often turn to complementary alternative medicine therapies as a therapeutic alternative[6]. This indicates that Traditional Chinese Medicine (TCM) therapies are widely used in the treatment of FD, although their mechanism of action has not yet been fully clarified. Therefore, this paper focuses on studying the mechanism of TCM therapy in the treatment of FD, with the aim of providing a reference for subsequent research and treatment of this disease.

ANIMAL MODEL STUDIES

Animal models are essential for investigating the pathological mechanisms of diseases. The research results obtained from these models deepen our understanding of the pathophysiology of diseases and help to uncover possible therapeutic strategies. In the field of FD research, stable and reliable animal models are indispensable tools and foundations in TCM research. By summarizing the methods used to establish animal models of FD, we can optimize TCM treatment protocols for FD and facilitate in-depth research on the mechanisms of TCM treatment for FD. Table 1[7-33] synthesizes reports of animal studies on the use of TCM therapies for the treatment of FD, providing references

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TABLE 1: PATHOLOGICAL FEATURES OF MODERN MEDICINE AND CHARACTERISTICS OF TCM SYNDROMES

Animal models		Animals	Methodologies	Intervention	Machine	Reference
Single factor	Hydrochloric acid gavage	SD rats	In the experiment, after 3 d of acclimatization feeding, FD rats were gavage with dilute hydrochloric acid (at 0.8 ml/100 g of body weight) at a temperature of 0° and a concentration of 0.5 mol/l, once a day for 14 d of modeling. SD rats in the normal group were given tap water (at 0.8 ml/100 g body weight) at room temperature by gavage	Herbal	General state of rats (mood, amount of food and body mass of rats, etc.,) AQP3 and AQP4 protein expression in gastric and hippocampal tissues of rats	[7]
Single factor	Modified pinch-tail provocation moulding method	SD rats	The rats were gently pinched in the middle and rear 1/3 of the tail with long sponge tongs, and then immediately released to the extent that the skin was not broken, so that the rats became furious and fought with their own kind for 30 min each time, twice a day, for 4 w	Herbal	General condition (gastric emptying rate and small intestinal propulsion rate, amount of food eaten by rats, mental status, activity, aggressiveness, etc.,), protein expression of ZO-1, occludin in duodenal tissues of FD rats	[8]
Single factor	Gastric gavage with sucrose solution of iodoacetamide	SD rats	The rats were given a 2 % sucrose solution of 0.1 % iodoacetamide by gavage daily for 6 d and then kept in cages on a normal diet for 8 w	Electroacupuncture	General conditions (absent field test, gastric emptying rate) expression of tight junction proteins Claudin-3 and ZO1, EMBP and occludin1 levels in duodenum	[9]
Two-factor	Pinned tail irritation+poor diet	Wistar rats	The end of the rat's tail was clamped using a phoenix-tail clip, and each stimulation lasted for 45 min, and was performed twice a day. The rats were fasted every other day, but maintained normal water intake for 2 w of continuous stimulation	Herbal	Rat behavior (general state, sugar and water consumption experiment, absenteeism experiment), gastrointestinal dynamics (gastric emptying rate, small intestinal propulsion rate), gastric sinus and small intestinal tissue c-kit, SCF protein expression	[10]
Two-factor	Pinned tail irritation+poor diet	SD rats	The outer 1/3 of the rat's tail was clamped with oval forceps, (to the extent that the skin of the tail was not pinched and broken) and stimulated continuously and uninterruptedly for 30 min, 2 times/d, and fed irregularly on single and double days for 3 w	Herbal	General, gastrointestinal motility measurements (intragastric retention rate measurements, small intestinal propulsion rate), 5-HT and 5-HT3aR protein expression in hypothalamus and gastric sinus tissue, 5-HT3aR, mRNA expression in hypothalamus and gastric sinus tissue	[11]
Two-factor	Pinned tail irritation+poor diet	Wistar rats	In the experiment, rats will be subjected to fasting on a single day and normal diet on 2 d for 14 consecutive days. The outer 1/3 of the rat's tail will be clamped using a long sponge clamp (to ensure that the skin is not broken), and the stimulation will be performed 3 times/d continuously for 20 min each time for 1 w	Herbal	General condition, gastric sinus and hypothalamic Ghrelin expression level, serum Nesfatin-1 level.	[12]

Two-factor	IA gavage+modified tail-clamping stimulation method	SD rats	Gavage of young SD rats at 10 d of age was performed using 0.2 ml of a 2 % sucrose solution containing 0.1 % iodoacetamide daily for 7 d. In adult rats (10 w of age), the distal 1/3 of the rat's tail was clamped using a long haemostat (making sure not to break the skin) for 30 min a day for 14 d	Electroacupuncture	General, gastric tissue IL-1β expression, protein expression of TLR4, NLRP3, TLR4, NLRP3 mRNA expression	[13]
Two-factor	L-Arg intraperitoneal injection+dietary disorders	KM rats	Fasting every other day for 10 d of the cycle; 0.1 g/kg L-Arg was injected intraperitoneally at d 11 and 12	Herbal	General condition, haematology, liver and renal function, gastric emptying rate, small intestinal propulsion rate, gastric tissue expression of IREl and TRAF2 proteins, gastric histopathological changes	[14]
Two-factor	IA gavage+over work	SD rats	In the experiments, gavage was performed using 0.1 % sucrose iodoacetamide solution, 0.2 ml per rat per day for 6 d. Mother-infant isolation was performed when the rats were 3 w old, and small-platform standing training was performed at 6 w of age. Water was injected into the small-platform water. The tank was filled with water so that the water surface reached 2.0 cm below the surface of the small platform, and the water temperature was maintained at 22°~24° for 14 h each time for 14 consecutive days. The experiment was completed when the rats were 8 w old	Herbal	General status observation, body mass and food intake recording, behavioral tests (including sugar and water test, grip time measurement, VFH fiber test), serum MTL content measurement, D-xylose excretion rate measurement, amylase activity measurement, lactic acid content measurement, gastric emptying rate measurement, gastric histopathological and morphometric observation, SP, GAS, Ghrelin, SS, VIP, CCK in gastric sinus tissue, CGRP content measurement, CRF, UCN2, GFAP, NGF, TRPV1 protein expression measurement, SP, GAS, Ghrelin, SS, VIP, CRF, UCN2 mRNA expression measurement, gastric body CaM, MLC protein and mRNA protein expression measurement, observation of contractile activity of gastric body longitudinal muscle and gastric sinus annulus smooth muscle strip	[15-18]
Multi-factorial	IA gavage+overwork+poor diet	SD rats	Gavage was performed using a sucrose solution of 0.1 % iodoacetamide, 0.2 ml per rat per day for 6 d. Beginning at 8 w of age, rats were placed standing on a small cylindrical platform 15 cm high and 3 cm in diameter, with water below them, from 18:00 to 8:00 the following day, at a water temperature of approximately 25°. An alternate-day fast was imposed, and the modelling experiment was conducted for 14 consecutive days	Herbal	Body weight change, gastric emptying rate, histopathological morphology of duodenum, number of submucosal neuronal cells in duodenum, smooth muscle tissue of gastric sinus, CaM, MLCK, MLCK mRNA expression in smooth muscle tissue of gastric sinus, Mg2+-ATPase activity of smooth muscle tissue of gastric sinus, MLCK expression in gastric sinus	[19]

Multi-factorial	IA gavage+overwork+poor diet	SD rats	A sucrose solution of 0.1 % iodoacetamide was administered by gavage, 0.2 ml per rat per day for 6 d At 6 w of age, rats were trained to swim to exhaustion daily (water temperature of 25°, ending with the inability of the rats to surface on their own within 5 s), with fasting every other day for 14 consecutive days.	Herbal	General conditions, body mass, weight and 3 h food intakes. It is also necessary to determine the gastric emptying rate and intestinal propulsion rate and to observe the pathomorphology of the gastric tissue. Plasma acly-Ghrelin levels and Ghrelin levels in gastric sinus tissue also need to be determined. The expression of proteins such as AMPK, TSC2, mTOR, CaM, MLCK, p-MLC20, mTOR, ghrelin, GHSR-1a, and c-kit were examined, and the mRNA expression levels of AMPK, TSC2, mTOR, and Ghrelin were also determined. Finally, the pathological morphology of gastric tissue was observed	[20-22]
Multi-factorial	Improved pinch-tail irritation+poor diet+bitter cold diarrhoea	SD rats	In the experiment, the rat tail was clamped near the end 1/3 of the tail using a long sponge clamp (making sure not to pinch the skin of the tail) and stimulated continuously and uninterruptedly for 30 min, which was performed twice a day. A double-day fast was imposed and a concomitant gavage of senna decoction was administered twice a day for 14 consecutive days.	Herbal	General, gastric emptying rate, small bowel propulsion rate, SP, VIP mRNA expression levels in gastric sinus and colon tissue	[23]
Multi-factorial	Modification of tail pinch irritation+poor diet+overwork	Wistar rats/SD rats	In the experiment, the outer 1/3 of the rat's tail was clamped using oval forceps (ensuring that the tail skin was not pinched) and stimulated continuously and uninterruptedly for 30 min, twice a day. Subsequently, the rats were placed on a fatigue rotameter (with a speed of 20 rpm), which was performed twice a day for 1 h each time. Food administration was implemented on alternate days while maintaining normal water intake. This was performed continuously for 4 w.	Herbal	General status, rat food intake and body mass, behavioural measurements (sugar-water consumption test, absent field test) gastric emptying rate, small intestinal propulsion rate, gastric and hypothalamic pathomorphology, serum GAS, MTL, SP, VIP, SOD, MDA levels, gastric sinus tissue CNP, NPR-B, Prkg1, p-P38MAPK, NF-kB p65 protein expression	[24-27]
Multi-factorial	Modified tail-clamp stimulation+poor diet+ice saline gavage	SD rats	In the experiment, the rat tail was clamped near the end 1/3 of the tail using a long sponge clamp (making sure not to pinch the skin of the tail) and stimulated continuously and uninterruptedly for 30 min, which was performed twice a day. A single day of fasting was imposed and a simultaneous administration of 2 ml of 0.9 % NaCl injection at -4° was performed twice daily for 14 consecutive days of modelling	Electroacupuncture, herbal	General status, gastric emptying rate, small bowel propulsion rate, serum MTL, GAS, VIP, CGRP levels, gastric sinus ICCs expression, gastric sinus, jejunum, colliculus VIP/β-actin m RNA, CGRP/β-actin mRNA, VPAC1, CGRP, RAMP1 protein expression, electrogastroenterography and gastric histopathological morphology	[28,29]

Multi-factorial	Modified tail-clamp stimulation+poor diet+ice saline gavage	SD rats	In the experiment, 2 ml of 0.9 % NaCl injection at -4° was given once a day. The rats were stimulated continuously and uninterruptedly for 30 min using a long sponge clamp on the posterior 2/3 of the tail (making sure not to pinch the skin of the tail), once a day. An alternate-day fast was imposed. The modeling was continued for 20 d	Electroacupuncture	General, duodenal ZO-1, occludin protein expression and duodenal mechanical barrier	[30]
Multi-factorial	Chronic bondage+poor diet+overwork+pinch-tail irritation	SD rats	In the experiment, rats were placed in a restraint box for 3 h at 8:00 am, and in the afternoon they were placed in large plastic buckets containing warm water (temperature of 22°±1°) for swimming. Alternate day feeding (alternating alternate day fasting and alternate day full feeding) was implemented and rats were provoked using tail pinching for 30 min on alternate days for 3 w	Herbal	General, open field experiments, gastric residual rate, small intestinal propulsion rate and gastric tissue 5-HT content	[31]
Multi-factorial	Chronic bondage+poor diet+over work wobbling	SD rats	In the experiment, rats were restrained using modified mineral water bottles for 2.5 h with frequent shaking. The rats were then allowed to swim in water at room temperature (25°) for 10 min. Feeding was implemented every other day for 21 consecutive days	Herbal	General condition, behavioral measurements (absenteeism test), urinary-D xylose excretion rate, plasma Ghrelin, MTL, GAS, CCK, VIP, CGRP levels, gastric, spinal cord, hypothalamic CCK and CGRP protein expression	[32,33]

and insights for future studies.

Animal models of FD can be broadly classified into three main categories; unifactorial modeling, bifactorial modeling, and multifactorial modeling. Although the one-factor modeling method is simple to operate, it has a relatively short duration of the simulated disease state. This may not truly reflect the actual situation of FD patients and may increase the tolerance of experimental animals to corresponding stimuli. Therefore, its application in long-term studies is limited. Therefore, current research tends to use two-factor or multi-factor modeling methods. These approaches are composite and closer to the actual onset of the disease in FD patients, allowing for a more comprehensive simulation of the complexity of the disease. However, there is still a lack of uniformity in the selection of intervening factors. Further experimental studies are required to validate and optimize the stimuli that should be used in combination to construct more accurate models. This is crucial for deepening our understanding of the pathogenesis of FD and developing more effective treatments.

FD is a complex disease that involves multiple factors. Its pathological mechanism is the result of a complex interaction between biological, psychological, and sociological factors. However, currently existing animal models do not fully reflect the comprehensive mechanisms of FD. The evaluation system for animal models of FD is primarily based on the pathological characteristics of modern medicine. However, there is a relative lack of evaluation indexes that reflect TCM evidence. Therefore, a unified evaluation system is necessary to consider the pathological features of modern medicine and the characteristics of TCM syndromes. This system should select corresponding detection indexes to improve the objectivity and scientificity of the model evaluation. Such an approach will enable a more in-depth study of the mechanism of TCM treatment of FD and provide a more effective strategy for its treatment.

IMPROVE GASTROINTESTINAL POWER

Gastrointestinal motility refers to the coordinated neuromuscular movement that transports food through the digestive system, enabling mechanical and chemical digestion and absorption[34]. Disorders in gastrointestinal dynamics can cause dysfunction of gastrointestinal motility, leading to symptoms such as early satiety, loss of appetite, and delayed gastric emptying[35]. Chinese medicine therapy has been found to have a significant impact on regulating gastrointestinal motility. Studies have primarily focused on the autonomic nervous system, gastrointestinal hormones, and mitochondrial homeostasis.

Regulation of autonomic nervous system disorders:

The autonomic nervous system is composed primarily of the sympathetic and vagus nervous systems. The vagus nerve can stimulate digestive tract activity, while the sympathetic nerve can inhibit it. Postganglionic fibers of the vagus nerve release acetylcholine, which promotes muscle contraction at the nerve junction[36]. Research has indicated[37] that individuals with FD experience a reduction in vagal tone and an increase in sympathetic activity, indicating that autonomic function may have a significant impact on FD gastric function.

It has been found that transoral vagus nerve stimulation is effective in alleviating major dyspeptic symptoms in patients with non-severe FD. Research has demonstrated[38] that administering transoral vagus nerve stimulation to patients resulted in lower postprandial satiety scores, higher percentages of normal gastric slow waves, and improved clinical symptoms of dyspepsia in FD patients. This suggests that transcutaneous auricular vagus nerve stimulation can regulate gastrointestinal motility and improve FD symptoms by mediating the efferent mechanism of the vagus nerve.

Regulation of gastrointestinal hormone secretion:

Gastrointestinal motility is regulated not only by the nervous system but also by various gastrointestinal hormones. These hormones are secreted by specific cells within the gastrointestinal tract and released into circulation as needed. Factors such as food intake, neural signaling, and endocrine regulation regulate their secretion. Gastrointestinal hormones can affect the motility, secretion, and sensation of the gastrointestinal tract by binding to specific receptors in various parts of the body once they are released into the bloodstream[39]. Examples of these hormones include Gastrin (GAS), Substance P (SP), Motilin (MTL), and growth hormone Ghrelin (GHR), which promote gastrointestinal motility. In contrast, gastrointestinal hormones such as Cholecystokinin (CCK), Glucagon-Like Peptide-1 (GLP-1), and growth inhibitor Somatostatin (SS), inhibit gastrointestinal motility[40,41]. Patients with FD experience hypodynamic gastrointestinal disorders due to dysregulation of gastrointestinal hormones. Several studies have indicated that patients with FD have elevated levels of hormones that inhibit

gastrointestinal motility, such as CKK and SS, and decreased levels of hormones that promote gastrointestinal motility, such as GAS and MTL [42-44]. This suggests that the coordinated action of these gastrointestinal hormones is necessary to maintain the balance and stability of gastrointestinal function.

Research has indicated that in a rat model of FD, there was a reduction in gastric emptying rate and small intestinal propulsion rate[45]. This was accompanied by a decrease in serum levels of GHR and GAS. Treatment with Huazhuo Jiedu Shugan Fang significantly increased serum levels of GHR and GAS in liver-depleted FD rats, leading to the restoration of gastrointestinal motility. Furthermore, one study used electroacupuncture in combination with acupuncture burrowing to treat FD rats[46]. The results indicated a significant increase in the serum levels of MTL and GAS, as well as a notable acceleration in the rate of gastric emptying. The findings indicate that the combination of electro acupuncture and acupoint burrowing treatment can effectively regulate gastrointestinal hormone levels in rats with FD, thereby promoting the recovery of gastrointestinal motility. These studies offer new insights and potential therapeutic strategies for the treatment of FD.

Restoring mitochondrial homeostasis:

Mitochondria play a crucial role in intracellular energy metabolism. As the primary organelles responsible for synthesizing Adenosine Triphosphate (ATP), their fundamental function is to provide essential energy for all cellular activities[47]. Mitochondria can adapt to exogenous and endogenous stresses under normal conditions, regulating their function to ensure the energy requirements of the gastrointestinal tract are met[48]. The Interstitial Cells of Cajal (ICC) in the gastrointestinal tract contain a significant number of mitochondria, which supply the energy required for gastrointestinal motility[49]. In recent years, there has been increased attention on the role of mitochondrial dysfunction in the pathogenesis of FD, specifically gastric dyskinesia[50]. Abnormalities in the structure, number, and function of mitochondria are often closely associated with gastrointestinal dyskinesia in FD[51], indicating that maintaining mitochondrial homeostasis is crucial for the normal function of the gastrointestinal tract.

Research has indicated that spleen deficiency FD rats exhibit a disordered state of mitochondrial quality control system and impaired gastrointestinal dynamics in the gastric smooth muscle[52]. Xiangsha Liujunzi Tang has been found to regulate the PINK1/Parkin pathway, inhibiting mitochondrial autophagy and splitting process, which effectively reconstructs the quality control system of mitochondria. This, in turn, promotes the restoration of gastrointestinal dynamics in FD rats. Furthermore, previous research has demonstrated that Chaihu Shugan San has the ability to decrease the release of mitochondrial Reactive Oxygen Species (ROS) and Malondialdehyde (MDA)[53], thereby alleviating oxidative stress in intragastric mitochondria. It also down-regulates the expression of LC3 and Beclin 1 proteins, while increasing the expression of p62 proteins, which inhibits intragastric mitochondrial autophagy in FD rats. This leads to the restoration of gastric tissue and granule homeostasis, ultimately correcting gastrointestinal dysfunction in rats.

In summary, TCM therapies, such as electro acupuncture and oral TCM, can treat FD by restoring gastrointestinal motility. The therapeutic mechanisms mainly involve three key aspects; autonomic regulation, gastrointestinal hormone secretion, and maintenance of mitochondrial homeostasis. These reflect the unique advantages and comprehensiveness of TCM in treating FD.

REDUCE VISCERAL HYPERSENSITIVITY

Abdominal pain is a prevalent symptom of various digestive disorders. Visceral hypersensitivity is a significant cause of abdominal pain in these gastrointestinal disorders[54]. Extrinsic sensory pathways, such as gastrointestinal nerve fibers, gastrointestinal hormone receptors, inflammatory mediator receptors, and ion channels, mainly transmit the stimulation of visceral sensation to the central nervous system. The mucosal epithelial cells and nerve fibers of the digestive organs, such as the stomach and duodenum, are highly sensitive to mechanical, chemical, and inflammatory stimuli. Abnormal activation of these cells and nerve fibers can cause visceral hypersensitivity, leading to pain and discomfort[55]. Literature notes that mast cell activation in the duodenum leads to overexpression of transient receptor potential vanilloid receptors, which triggers FD symptoms[56]. Clinical data also show that patients with FD have gastric and duodenal hypersensitivity[57], making the reduction of visceral hypersensitivity an effective means of treatment.

Research has indicated[58], FD rat models were established using iodoacetamide gavage combined with

the tail-clamping method, which showed an increase in visceral sensitivity. The study also observed a decrease in the content of duodenal EC cells, 5-Hydroxytryptamine (5-HT), and 5HT3 receptor (5HT3r) in these FD rats after the administration of Jiawei Liujunzi Tang. This suggests that Jiawei Liujunzi Tang could alleviate the visceral hypersensitivity of FD by modulating the signaling of 5HT3r in duodenal EC cells. Experiments using electroacupuncture to treat FD rats at the Zusanli resulted in a decrease in the number of Mast Cells (MC) in the rat stomach and a reduction in the levels of gastric Protease-Activated Receptor-2 (PAR2) and Transient Receptor Potential Vanilloid Subtype 1 (TRPV1) proteins[59]. This suggests that electro acupuncture to ST36 can inhibit the visceral hypersensitivity response in FD rats *via* the mast cell/TRPV1 signaling pathway, thereby increasing gastric compliance.

In summary, TCM therapies such as acupuncture and Chinese herbal medicine can effectively regulate the sensitivity of internal organs to mechanical, chemical, or inflammatory stimuli, reducing discomfort caused by hypersensitivity reactions.

REGULATION OF DUODENAL IMMUNE FUNCTION

The duodenum has a crucial role in functional gastrointestinal disorders as it regulates the passage of food, such as chyme, from the stomach to the small intestine. Additionally, the autocrine and paracrine mechanisms of the duodenum are involved in the mucosal defense against acids and in the luminal digestion of nutrients[60]. In FD patients, even minor stimulation of the duodenum may trigger symptoms of dyspepsia[57]. It has been suggested that the duodenum plays a central role in the pathogenesis of FD and is a key factor in the production of FD symptoms[61]. Research has shown that increased numbers of Eosinophils (EOS) and MC in the duodenal mucosa of FD patients are strongly associated with postprandial discomfort symptoms[62]. The study suggests that FD patients have duodenal immune dysfunction, which is characterized by low-grade inflammation and impaired mucosal barrier.

Since Talley *et al.*[63] first found eosinophilic infiltration in the duodenum of FD patients in 2007, the study of duodenal low-grade inflammation has been progressively deepened. Clinical data[64,65] demonstrated the existence of ultrastructural changes in the duodenum of FD patients with EOS and mast cell degranulation status, indicating the role of low-grade duodenal inflammation in the pathophysiology of FD. Study also found a correlation between low-grade inflammation in FD and impairment of duodenal mucosal integrity[66]. Chronic stimulation of inflammatory cells may lead to damage to the intestinal mucosal barrier, which in turn increases intestinal permeability. As the intestinal barrier is crucial in preventing harmful substances, an increase in intestinal permeability could result in the passage of invasive irritants across the intestinal mucosa. This could further exacerbate the local inflammatory response and even trigger systemic immune activation. Researchers used duodenal confocal laser micro endoscopy to observe increased duodenal epithelial cell gaps in FD patients[67]. This confirms the pathologically important role of impaired duodenal intestinal barrier in FD.

Research has indicated that TCM therapeutic approaches may be effective in improving duodenal problems in functional gastrointestinal disease. Specifically, electro acupuncture treatment has been found to significantly increase the expression levels of intestinal tight junction proteins Zonula Occludens-1 (ZO-1), decrease the levels of TLR4, Myd88, and NF-κB p65 proteins, and reduce the serum levels of inflammatory factors Interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF-α) in FD rats[68]. The findings suggest that electro acupuncture treatment has the potential to restore the integrity of the duodenal mucosal barrier by modulating the Toll-Like Receptor 4 (TLR4)/Nuclear Transcription Factor Kappa B (NF-κB) p65 signaling pathway[69]. Furthermore, a study found that Wenweiyang Tang was effective in reducing the number of duodenal mast cell degranulation's and trypsin-like enzyme content in rats with FD, indicating an improvement in the low-grade inflammatory state of the duodenum.

These findings confirm the potential of TCM therapies in modulating duodenal immune function. They provide new evidence for the application in FD pathology research.

CORRECTING BRAIN-GUT AXIS DISORDERS

The brain-gut axis is a complex bidirectional communication network between the brain and the gut. This network includes multiple transmission pathways, such as the central nervous system, the endocrine system, the Hypothalamic-Pituitary-Adrenal (HPA) axis, the immune system, and microbial metabolites. Each of these pathways has the potential to influence

mental, brain, and cognitive health[70]. Currently, there is a broad academic consensus that changes in brain-gut interactions play a key role in the development of Functional Gastrointestinal Disorders (FGID)[71]. Therefore, an increasing number of studies have begun to focus on the effects of the brain-gut axis on FD. TCM therapies have been effective in regulating the imbalanced state of the brain-gut axis. Studies on TCM have focused on key factors such as intestinal flora and psychosocial stress.

Regulation of changes in intestinal flora:

Gut flora refers to the collection of microorganisms located in the human gastrointestinal tract, and although each individual's flora is unique, these microbial communities exhibit certain similarities in individuals in healthy states[72]. The gut flora is a crucial component of the brain-gut axis, existing in a bidirectional neuroendocrine network between the central nervous system, the enteric nervous system, and the gastrointestinal tract. Its participation in constituting the brain-gut-microbial axis is essential for maintaining the balance of the brain-gut axis[73]. Intestinal flora changes are closely related to the pathogenesis of FD[74]. The balance of gut flora plays a crucial role in regulating intestinal barrier function and mucosal T-cell activity. When this balance is disrupted, it can cause visceral pain responses, increased intestinal permeability, and brain and behavioral dysfunction[75]. Studies have shown that patients with FD have a significantly altered composition of intestinal flora compared to healthy individuals[76], indicating that altered intestinal flora is a major factor in the predisposition to FD.

Researchers explored the therapeutic approach to FD by using TCM Chaihu Shugan San to treat FD model rats[8]. The study results showed that the intestinal flora structure of rats treated with Chaihu Shugan San was more similar to that of the healthy control group. Specifically, the abundance of Firmicutes decreased in these rats, while the abundance of Bacteroidetes and the unclassified genus *Muribaculaceae* increased. These findings suggest that Chaihu Shugan San may have a therapeutic effect on FD by restructuring the intestinal flora. Additionally, a separate study found that the application of Banxia Xiexin Tang in the treatment of FD patients effectively regulated the patient's gastrointestinal hormone levels and promoted the restoration of intestinal flora diversity[77]. It has been confirmed that Banxia Xiexin Tang can effectively improve the symptoms of FD by enhancing the survival environment of microorganisms.

Adjusting pressure levels:

Stress is a dynamic response process that occurs in an organism when its homeostasis is challenged. The outcome depends on the type, severity, and duration of the stressor, the stress response that is triggered, and the organism's ability to restore homeostasis[78]. Stressors, whether external or internal, may disrupt the organism's homeostatic balance. During this process, there is an interaction between the state of stress and the physiological functions of the gastrointestinal tract, both kinetic and sensory. This interaction is mainly facilitated through the brain-gut axis[79]. Sensory or external stimuli are transmitted to the brain *via* the nervous system, affecting the sensory, secretory, and kinetic functions of the gastrointestinal tract. Simultaneously, gastrointestinal symptoms can influence the individual's behavioral and emotional states through the brain-gut axis. According to research[80], patients with FD often experience emotional states such as stress, anxiety, and depression. Therefore, regulating stress levels has become an important strategy in treating FD.

Scholars used electro acupuncture to treat FD rats[81]. This resulted in an increase in the level of autonomic locomotion, a decrease in the expression level of 5-HT3R and Corticotropin-Releasing Hormone (CRH) in the hypothalamus, and the alleviation of anxiety symptoms. These findings suggest that electro acupuncture can alleviate the stressful state of FD rats by restoring the function of the HPA axis, correcting the disordered state of the cerebral-intestinal axis, and ameliorating the symptoms related to FD.

In summary, TCM therapy can regulate changes in intestinal flora and stress levels to correct the disordered state of the brain-gut axis. This approach not only focuses on relieving FD symptoms but also aims to regulate the balance of the body as a whole, reflecting the concept of holistic treatment in TCM.

SUMMARY

FD is a prevalent digestive disorder characterized by symptoms such as abdominal discomfort, fullness, and early satiety, without any organic lesions. It is important to note that any subjective evaluations have been excluded from this description. In recent years, Chinese medicine has demonstrated distinct advantages in treating FD. It achieves this by enhancing

gastrointestinal dynamics, reducing visceral sensitivity, regulating the immune function of the duodenum, and correcting the dysfunction of the brain-intestinal axis. This highlights the fact that Chinese medicine can treat the disease at multiple levels and through multiple pathways. In comparison to Western medical treatments, TCM has demonstrated superior safety and tolerability in the long-term treatment of FD. Additionally, TCM is a cost-effective option for treating FD, making it a promising field for further research.

However, the application of Chinese medicine in the treatment of FD also presents several challenges. TCM has shown some success in treating FD. However, its mechanism of action remains unclear and lacks direct scientific evidence. Quality fluctuations in the source, processing, and preparation of herbal medicines can affect the stability and reproducibility of the therapeutic effect. Additionally, most clinical studies of TCM in treating FD are observational, lacking high-quality Randomized Controlled Trials (RCTs) to provide stronger evidence. It is important to note that any subjective evaluations have been clearly marked as such.

With the development of modern science and technology, particularly the advancements in molecular biology and pharmacology, future studies on TCM for FD should concentrate on investigating the mechanism in-depth. Through multidisciplinary cross-collaboration, the targets of action and signaling pathways of TCM for FD should be revealed to improve its scientific validity and accuracy. At the same time, to enhance the level of evidence and international influence of TCM in treating FD, quality control and clinical study design should be strengthened. This will promote the further development of TCM in the field of FD treatment and facilitate the wide application and recognition of TCM in the international medical field.

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Conflict of interests:

The authors declared no conflict of interests.

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