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# Research progress of treatment of functional dyspepsia with traditional Chinese medicine compound based on cell signal pathway

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Functional dyspepsia (FD) is the most common clinical gastrointestinal disease, with complex and prolonged clinical symptoms. The prevalence of FD is increasing year by year, seriously affecting the quality of life of patients. The main causes of FD are related to abnormal gastrointestinal dynamics, increased visceral sensitivity, *Helicobacter pylori* (HP) infection, intestinal flora disturbance and psychological factors. A review of the relevant literature reveals that the mechanisms of traditional Chinese medicine (TCM) in the treatment of FD mainly involve the following pathways: 5-HT signal pathway, AMPK signal pathway, C-kit signal pathway, CRF signal pathway, PERK signal pathway, NF- $\kappa$ B signal pathway. Based on a holistic concept, TCM promotes gastrointestinal motility, regulates visceral sensitivity and alleviates gastrointestinal inflammation through multiple signal pathways, reflecting the advantages of multi-level, multi-pathway and multi-targeted treatment of FD.

## KEYWORDS

signal pathway, fd, TCM, research progress, treatment

## 1 Introduction

FD is a chronic functional gastrointestinal disorder that presents with a range of symptoms such as postprandial fullness, early satiety, and abdominal pain and cannot be explained by organic, systemic, or metabolic disease. It is defined by Rome IV as a disorder of bowel-brain interaction (DROSSMAN and HASLER, 2016). With reference to the Rome IV diagnostic criteria, FD can be divided into two subtypes, postprandial discomfort syndrome and epigastric pain syndrome, based on the characteristics of the symptoms (DROSSMAN and HASLER, 2016). The pathogenesis of FD is diverse and includes gastrointestinal motility disorders, visceral hypersensitivity, brain-gut axis, gastrointestinal hormone dysregulation, HP infection, genetics and psychosomatic disorders (Douglas, 2016; Tack and Drossman, 2017). At present, most of the clinical treatment is based on HP eradication drugs, gastrointestinal motility drugs, visceral hypersensitivity relief and anti-anxiety and depression drugs, but the efficacy is not

satisfactory. Chinese medicine contains a variety of methods such as herbal compounding, herbal monomers and acupuncture for the treatment of FD, which can act synergistically in multiple ways by promoting gastrointestinal dynamics, reducing visceral sensitivity and regulating intestinal flora, with multi-targeted synergistic effects that have certain advantages over the application of Western medicine alone. FD is a psychosomatic disease with complex etiology and closely related to mental and emotional factors, resulting in no specific medication in Western medicine and easy recurrence. Chinese medicine can improve the body's internal environment, the digestive tract and symptoms of emotional disorders, giving full play to its unique advantages, with few adverse effects and long-term treatment, and is increasingly becoming a research hotspot (Ren et al., 2019; Wang and Pan, 2022). This paper further elaborates the molecular mechanism of Chinese medicine in the treatment of FD based on cell signalling pathways and provides a scientific basis for its exploration of potential therapeutic approaches.

## 2 5-HT signalling pathway

5-HT is a tryptophan-derived neurotransmitter that functions by binding to functionally distinct receptors and is thus involved in many physiological and pathological processes in humans (Jiang et al., 2021). The 5-HT signalling system is widely distributed throughout the body and is responsible for regulating gastrointestinal motility, visceral hypersensitivity, anti-inflammation, regulation of immunity and psychological status. It affects visceral sensitivity by interfering with 5-HT binding to receptors and regulating gastrointestinal secretion and peristalsis (Su et al., et al.). When the gastrointestinal tract is stimulated, intestinal chromophores (EC) release 5-HT and the expression of 5-HT-positive nerve fibres or neurons is enhanced, leading to the activation of multiple neuroactive substances in visceral afferent nerves, causing increased visceral sensitivity and gastrointestinal discomfort (YU et al., 2016). In addition, in the central nervous system, substance *p* (SP) acts as an excitatory transmitter to induce the release of 5-HT, causing visceral hypersensitivity (Teng et al., 2016). 5-HT is a brain-gut neurotransmitter that is found in more than 95% of serum and gastrointestinal tissues. It promotes communication between the brain and the gastrointestinal system, and plays an important role in the brain-gut axis. 5-HT influences gastrointestinal motility by directly affecting smooth muscle and other nerve fibers (Li et al., 2014; Jing et al., 2015). 5-HT concentrations reflect the state of central nervous activity, and reduced function can lead to mood disorders such as anxiety and depression (Duffey et al., 2013). Results of a homozygous study suggest the presence of receptor genes in the chromosomal portion of 5-HT<sub>3</sub>AR and 5-HT<sub>3</sub>BR, which can cause depression and schizophrenia (Wu et al., 2015). The pathogenesis of FD is still unclear, but disorders of brain-gut

interaction are an important pathogenesis. When 5-HT levels in the central system and gastrointestinal tract are too high, excitotoxicity can be triggered, further causing increased visceral sensitivity and gastrointestinal motility disorders (Stasi et al., 2014; Wauters et al., 2020). The 5-HT<sub>1A</sub> receptor (HTR<sub>1A</sub>) can influence neurological activity and mood by regulating dopamine in the brain (Pinna et al., 2021).

In terms of regulating visceral sensitivity, experimental studies have shown that Pitongshu can reduce 5-HT secretion through regulating the 5-HT synaptic pathway, reducing visceral sensitivity and relieving FD symptoms (Chen et al., 2022a). The combination of acupuncture and traditional Chinese medicine for children with FD reduces 5-HT levels, promotes gastric motility and effectively improves clinical symptoms (Li et al., 2022a). By observing the effect of Shugan Jianpi Qingre recipe on the expression of 5-hydroxytryptamine<sub>1A</sub> (5-HT<sub>1A</sub>) receptor and cyclic phosphatidylinosine effector binding protein (CREB) in the gastric mucosal tissue of FD model rats, we found that it could reduce the expression of 5-HT<sub>1A</sub> receptor content, increase CREB expression in gastric mucosa, regulate visceral sensitivity, and improve body mass and symptoms in FD rats (Lang et al., 2020). On the other hand, 5-HT is closely related to anxiety and depression, and its reduced function can lead to anxiety, depression and other mood disorders, which can affect the function of other systems, fitting the pathogenesis of FD with liver-depression and spleen-deficiency. Weitong Xiaopi Fang can up-regulate the expression of 5-HT mRNA and protein in FD rats with liver stagnation and spleen deficiency, affect the release and activity of neurotransmitters, and accelerate gastric emptying (Fan et al., 2020). The pharmacological analysis of Liang Shu Wan in the treatment of showed that the FD main signaling pathways include the 5-hydroxytryptamine signaling pathway, and experimental studies showed that Liang Shu Wan could upregulate 5-HT expression in FD rats, improve visceral sensitivity and promote gastrointestinal motility (He et al., 2022). In recent years, studies have shown that structural and functional abnormalities such as duodenal mucosal hypersensitivity can cause gastric hypersensitivity, which is an important mechanism for the occurrence and development of FD, and is affected by the reception and conduction of TRPV1 signals (Barbera et al., 1995; Buschmann et al., 2013; Vanheel et al., 2014). Studies have shown that Xiangsha Liujunzi Decoction can alleviate discomfort by down-regulating local duodenal 5-HT and TRPV1 expression, affecting nerve conduction and relieving visceral hypersensitivity (Zhao et al., 2020).

## 3 AMPK signalling pathway

Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) is found mainly in mitochondria and is a key factor in sensing changes in cellular energy (Garcia and

Shaw, 2017). Under physiopathological conditions such as hypoglycemia, hypoxia and local ischemia, AMPK can be phosphorylated by upstream kinases and activated by binding to AMP and ADP. Activated AMPK can regulate various metabolic processes such as cell growth, cell autophagy and apoptosis (Villanueva-Paz et al., 2016; Wang et al., 2016). Autophagy is an important pathway for recycling through lysosomal removal of misfolded proteins, damaged organelles, etc (Bravo-San Pedro et al., 2017). Mitochondrial autophagy is specific macroautophagy that selectively degrades damaged or senescent mitochondria for recycling and is susceptible to the intracellular environment (Bharath et al., 2021; Chen et al., 2022b). In AMPK knockout mouse embryonic fibroblasts, ULK1 is not activated, autophagy is inhibited and damaged mitochondria accumulate. Studies have confirmed that AMPK-induced phosphorylation of ULK1 plays an important role in autophagy (Li and Chen, 2019). Increased levels of AMPK phosphorylation inhibit the activity of phosphorylated target of rapamycin (p-mTOR) proteins, leading to autophagy (Li and Chen, 2019). Gastrointestinal motility disorders are an important part of the pathogenesis of FD, and their main pathogenesis is related to the interstitial cells of Cajal (ICC) or ghrelin (SANGER and PASRICHA, 2017). Ghrelin is a brain-intestinal peptide that promotes gastric acid secretion and accelerates gastric emptying, and mTOR in gastric sinus tissue has been found to ghrelin expression was found to be affected by mTOR in gastric sinus tissue (Kang et al., 2017). Ghrelin was found to enhance phosphorylation of AMPK and its targets in the hypothalamus, suggesting that the promotion of FD gastrointestinal motility by Ghrelin may be related to the AMPK signalling pathway (STEVANOVIC et al., 2012). Slow wave potentials are generated by the ICC and are involved in the signalling of gastrointestinal neurotransmitters. Abnormalities in the number and structure of ICC cause gastrointestinal motility disorders, which may be associated with excessive ICC autophagy (Huang et al., 2017; Sanders, 2019; Zhang et al., 2021). Thus FD pathogenesis may be related to the AMPK-mTOR signalling pathway.

Studies have shown that Pingwei Capsules, based on Pingwei San, regulate gastrointestinal motility disorders in FD with liver depression and spleen deficiency through AMPK signaling pathway-mediated ICC autophagy. (Mao et al., 2021). Tang Lei found that under the same intervention conditions, FD rats showed the same trend of changes in daily behavioural status, gastrointestinal motility and Ghrelin expression, and the opposite trend of changes in mTOR expression, indicating its negative regulatory effect and the negative regulation of mTOR by AMPK. The mechanism of action may be related to the promotion of AMPK phosphorylation, resulting in a decrease in mTOR and an increase in Ghrelin (Tang et al., 2020).

## 4 C-kit signalling pathway

C-kit is a proto-oncogene product and a specific marker of gastrointestinal ICC. Downregulation or loss of the kit signalling pathway results in the transformation of ICCs to smooth muscle-like cells (Tang et al., 2020). It binds to the ligand stem cell factor (SCF) and initiates the SCF/C-kit signalling pathway, which plays an important role in maintaining ICC proliferation and differentiation and is closely related to gastrointestinal motility (Bashamboo et al., 2006; Zhang et al., 2017). Abnormalities in the SCF/C-kit signalling pathway can trigger specific expression of genes that regulate ICC proliferation, differentiation and development in the gastrointestinal tract, leading to abnormal slow-wave rhythms that reduce smooth muscle motility and slow down the dynamics of the gastrointestinal tract, thereby inducing gastrointestinal motility dysfunction-related diseases such as FD (Chai et al., 2017).

Chen Qiao used the “Using the acu-points of shu to regulate the center of shu” method to treat rats with gastrointestinal motility disorders to observe the expression of SCF and its C-kit protein and mRNA. Studies have shown that “Using the acu-points of shu to regulate the center of shu” acts on the Back-Shu point through acupoint pointer therapy to generate the corresponding bioelectric signal, and through the operation of the meridian Qi, the extracellular signal is transmitted and acts on the SCF/C-kit signaling pathway to improve the mechanism of gastrointestinal dynamics (Chen et al., 2019). By observing the gastric ICCs and their SCF/C-kit signaling pathways in FD rats, Deng found that SCF and C-kit decreased significantly in FD model rats compared with normal rats, SCF and C-kit increased in the low, medium and high dose groups of Aurantii Fructus Immaturus compared with the model group, so Aurantii Fructus Immaturus could promote the proliferation of ICCs through upregulating the expression of SCF and C-kit to promote gastric motility (Deng et al., 2018). It was found that mild moxibustion at the Zusanli could promote ICC proliferation by upregulating SCF and C-kit expression through the SCF/C-kit pathway, resulting in a significant increase in gastric emptying rate to improve gastrointestinal motility (Han, 2020). By observing the effects of magnolol on digestive fluid secretion and gastrointestinal motility in FD mice, Wang found that magnolol could upregulate SCF and C-kit expression and improve symptoms in FD mice, and that gastrointestinal hormones and gastrointestinal motility were significantly improved (Wang et al., 2020a). Based on the SCF/C-kit signaling pathway, Weichangshutai granules increased the expression of SCF and C-kit in the gastric sinus of mice and promoted the proliferation of ICCs, thus improving gastrointestinal motility and effectively improving their symptoms (Wang et al., 2022).

## 5 CRF signalling pathway

CRF is a 41-amino acid neuroendocrine peptide that is widely distributed in the central nervous system and peripheral tissues such as the gastrointestinal tract. CRF is found in the hypothalamus, paraventricular nucleus and amygdala in the central system and in the adrenal glands and gastrointestinal tract in the peripheral system (Giannogonas et al., 2016). CRF is a key regulator of the stress response, and various stressors can stimulate the pituitary-adrenal axis by inducing CRF release, and can act as a neuromodulator of behavioural and autonomic nervous system activity, regulating visceral function under stressful conditions, and is closely related to gastrointestinal dynamics and increased visceral sensitivity (Peng and Liu, 2007; Larauche et al., 2009). Animal studies have shown that intracerebral injection of CRF or related peptides can inhibit gastric emptying and gastric motility, and Tache found that intracerebellar CRF injection into the medullary pool of the rat cerebellum can similarly inhibit gastric emptying of liquid food in rats (Taché et al., 1987; Tache et al., 2018). The CRF receptor family includes two G-protein-coupled receptors, corticotropin releasing factor-receptor 1 (CRF-R1) and corticotropin releasing factor-receptor 2 (CRF-R2), which in terms of mood regulation, bind mainly to CRF-R1, which enhances anxiety-depression-like behaviours, and to CRF-R2, which inhibits anxiety-depression-like behaviours (Jezova et al., 1999). Stress can trigger alterations in the brain-gut axis, which can ultimately lead to the development of Gastrointestinal diseases such as FD (Konturek Peter et al., 2011). A study of FD patients showed that CRF levels were significantly higher in FD patients than in controls, and higher CRF levels were associated with higher anxiety-depression scores, suggesting that CRF participates in the development of FD and has an impact on anxiety-depression (Li et al., 2016). Studies have shown that CRF can cause a low inflammatory state in FD patients by regulating the levels of mast cells and cytokines (Shin-Ichiro et al., 2019).

By observing the distribution and expression of peripheral duodenal CRF and CRF-R1 in the central nervous system of FD rats, Zhu found that CRF expression was up-regulated in FD rats and that Jianpiliqi Fang could inhibit CRF expression levels and participate in brain-gut interaction, thus treating FD (Zhu et al., 2020). Li showed that the expression of CRF in the gastric sinus of FD rats was higher than that of the normal group, and the expression of urocortin 2 (UCN2) was lower than that of the normal group, and Xiangsha Liujunzi Decoction could reduce the level of CRF in the gastric sinus of FD rats with spleen deficiency, and the effect was more significant at higher doses, which could increase the expression of UCN2 mRNA and protein, improve gastric emptying rate and promote gastric motility (Li et al., 2022b). 5-HT is an important neurotransmitter in the gastrointestinal tract that is regulated by the hypothalamic CRF for synthesis and release and binds to

specific receptors (Nakade et al., 2007; Qin et al., 2019). Xiangsha Liujunzi Decoction can reduce 5-HT secretion by reducing CRF levels in FD rats. It was found that Sinisan could reduce the expression of CRF in the central system and peripheral tissues of FD model rats, and also reduce the expression level of CRF-R1 in the duodenum to regulate brain-gut interaction (Zhu, 2020).

## 6 PERK signalling pathway

Endoplasmic reticulum stress (ERS) and its mediated unfolded protein response (UPR) play an important regulatory role in the cellular response to external stimuli, controlling cell survival and extinction through the expression of apoptosis and autophagy-related genes (Wu et al., 2016; Hetz and Papa, 2018). Appropriate endoplasmic reticulum stress is beneficial to intracellular homeostasis, but excessive endoplasmic reticulum stress can lead to associated apoptosis. The ERS activates the unfolded protein response (UPR) pathway, which is mainly activated by PKR-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6), three endoplasmic reticulum transmembrane sensing proteins (Banerjee et al., 2016). PERK is the first activation pathway in response to endoplasmic reticulum stress (Vandewynckel et al., 2015). Under physiological conditions, all three pathway initiator proteins are bound to endoplasmic reticulum molecular chaperone regulatory protein 78 (GRP78) in the lumen of the endoplasmic reticulum in an unactivated state. When stress occurs, the three proteins dissociate from GRP78, accelerating the degradation of misfolded proteins, reducing endoplasmic reticulum stress and promoting cell survival. If the endoplasmic reticulum is in a state of continuous stress and PERK is chronically activated then cell viability will be impaired (Ye et al., 2013). The interconnected nerve fibres of ICC and smooth muscle cells jointly regulate gastrointestinal motility, and the presence of autophagy in their cells, causing a reduction in their number, may be an important cause of FD gastrointestinal motility disorders (Jan et al., 2009; Wang and Jiang, 2009; Ji et al., 2013).

By observing the expression of PERK protein in the PixulFormula, FD rats and the treatment of FD with Spleen Deficiency Formula 1, Lv showed that the expression of PERK protein was elevated in model FD rats compared with the normal group, and after the drug intervention with Spleen Deficiency Formula 1, the expression of each PERK protein was reduced compared with the model group, which could improve the cellular UPR phenomenon (Lv et al., 2017). Zhou used a cycle-length modelling method to show that the degree of ERS occurrence in this model FD rats was persistent, and whether ERS occurred in the gastric tissues of FD rats was confirmed by comparing the PERK expression. The experimental results showed that the PERK level was higher in the model FD rats compared with the normal group, and the



PERK decreased significantly after the drug treatment with Chaihushugan Powder was given, indicating that Chaihushugan Powder promotes gastric motility through the ERS (Zhou, 2018). Separation of PERK from GRP78 leads to phosphorylation of Ser51 of eIF2 $\alpha$ , or p-eIF2 $\alpha$ , thus reducing the burden of protein synthesis by the endoplasmic reticulum (Heather et al., 2000). It was found that p-eIF2 $\alpha$  protein expression was elevated in FD model rats, indicating that eIF2 $\alpha$  was heavily phosphorylated in the gastric tissues of FD rats. After Chaihushugan Powder intervened in FD rats, p-eIF2 $\alpha$  expression was reduced, indicating that eIF2 $\alpha$  phosphorylation was inhibited, from which it can be deduced that Chaihushugan Powder has an inhibitory effect on the PERK/eIF2 $\alpha$  pathway, suppressing endoplasmic reticulum stress and promoting gastric motility (Zhou, 2018).

## 7 NF- $\kappa$ B signalling pathway

NF- $\kappa$ B is a group of nuclear protein factors that regulate the expression of a wide range of genes and play an important role in the regulation of cell proliferation, differentiation, inflammatory response and apoptosis in the body (Yarandi and Christie, 2013). NF- $\kappa$ B family includes five subunits, including p65 and p50, and the typical NF- $\kappa$ B is a dimer composed of p50 and p65. p65 is present in the resting state with inhibitor kappaB(I $\kappa$ B) and exists in the cytoplasm as a homo- or heterodimeric form in an inactive state. When it receives pathological stimuli, it activates the apoptotic signaling pathway (Cramer et al., 2012). Previous studies on FD have mainly been related to abnormalities in gastric structural function; recent studies have shown a close association between inflammatory cell infiltration in the duodenum, elevated local inflammatory factors and impaired expression of barrier function-tight junction proteins (Chang et al., 2017). toll-like receptor 9 (TLR9) and toll-like receptor 4 (TRL4) play an important role in the stress-induced inflammatory response, which induces disease.

It was found that NF- $\kappa$ B expression was elevated in gastric smooth muscle cells of model FD rats, and after drug intervention with Chaihushugan Powder, NF- $\kappa$ B expression was significantly reduced in FD rats, indicating that Chaihushugan Powder could inhibit excessive apoptosis of gastric smooth muscle tissue cells by inhibiting the activation of NF- $\kappa$ B signaling pathway in order to promote gastric motility and improve FD symptoms (Shang, 2017). By observing the gastrointestinal motility and NF- $\kappa$ B p65 expression in the hypothalamus tissue of FD rats with liver-depression and spleen-deficiency type and the treatment of liver-depression and spleen-deficiency type with Chaizhu Liweiyin, Fan found that the NF- $\kappa$ B p65 protein and gene expression in the hypothalamus tissue of FD rats in the model group was elevated, and different dose groups of the formula could reduce the NF- $\kappa$ B p65 expression to different degrees (Fan

et al., 2021). TLR9 and TRL4 play an important role in stress-induced inflammatory responses. TLR9 was elevated in the duodenum, and its level decreased significantly after treatment with Chinese herbal gavage. NF- $\kappa$ B is the most important signaling molecule downstream of TLR9, and activated TLR9 activates NF- $\kappa$ B, which promotes the expression of inflammatory factors such as TNF- $\alpha$  (Chang et al., 2018). Chaihu Shugan San can not only inhibit apoptosis by inhibiting the activation of NF- $\kappa$ B signaling pathway, but also have an inhibitory effect through PERK/eIF2 $\alpha$  pathway, inhibiting endoplasmic reticulum stress and promoting gastric motility. When NF- $\kappa$ B is stimulated, a detached I $\kappa$ B in NF- $\kappa$ B enters the nucleus to bind to DNA and regulate the inflammatory response. Electroacupuncture intervention in FD model rats resulted in a decrease in duodenal TLR4 expression and a decrease in inflammatory factors such as IL-6 and TNF- $\alpha$ , which inhibited the inflammatory response and repaired the mucosal barrier, thereby reducing FD-related symptoms (Wang et al., 2020b).

## 8 Other signalling pathways

C-type natriuretic peptide (CNP) binds specifically to natriuretic peptide receptor B (NPR-B) on smooth muscle cell membranes, which activates pGC, causing an increase in the intracellular second messenger cyclic guanosine monophosphate (cGMP). cGMP inhibits the voluntary contraction of smooth muscle (Gower et al., 2000; Guo et al., 2003). Zhong observed the CNP and cGMP contents and NPRB expression in gastric smooth muscle in FD rats after the intervention of Sijunzi Decoction, and showed that the CNP and cGMP contents decreased and NPR-B expression decreased after the intervention of Sijunzi Decoction, indicating that Sijunzi Decoction could regulate the CNP-NPR-B-cGMP signalling pathway and increase gastric emptying capacity to normalize it (Zhong et al., 2017). Huang found that after 2 weeks of treatment with Shuwei Decoction in FD rats, the expression of pGC protein, CNP protein and mRNA was significantly reduced compared to the model group to inhibit the CNP/pGC signalling pathway and restore gastric motility (Tang et al., 2017). MEK signalling pathway is regulated by extracellular signal-regulated protein kinase (ERK) protein kinase (ERK), c-junh2-terminal kinase (JNK) and p38, a cascade of three protein kinases involved in cell proliferation, differentiation and apoptosis (Kang et al., 2018). The effect of electroacupuncture on the MEK/ERK1/2 signalling pathway in FD rats was observed by Kang who used tail-clamping stimulation with irregular diet to model FD rats. The studies found that MEK, ERK1/2 and their phosphorylated proteins p-MEK and p-ERK1/2 proteins were elevated in FD model rats, and that the expression of MEK and ERK1/2 and their phosphorylation levels were inhibited by electroacupuncture at

the Zusanli. Prostaglandin E2 (PGE2) is a mucosal protective endogenous factor, upon binding to its receptor, elevates intracellular cyclic adenosine monophosphate (cAMP) and has a regulatory effect on the opening of tight junction proteins and epithelial paracellular pathways (Su et al., 2008; Tan et al., 2017). It was found that the expression of PGE2 and cAMP decreased in FD model rats, and that Jianpi Yiqi Recipe could up-regulate PGE2-cAMP expression and improve the structure and function of duodenal tight junction protein in FD rats, which is one of the mechanisms for the treatment of FD (Zhao et al., 2019).

Information transfer between cells is a fundamental law of life activity. Molecular signals stimulate the cell membrane or intracellular receptors, and the ligand binds to the receptor, initiating a cascade of intracellular signaling, which transmits extracellular signals to the nucleus, altering the transcriptional activity of target genes and ultimately generating a series of cellular responses that cause physiological reactions in the body (Huang and Zhu, 2005; Yang and Guo, 2015). The pathogenesis of FD is related to a variety of signalling pathways. With the continuous progress of molecular biology research, the understanding of FD-related cell signalling pathways has been deepened, and the mechanism of Chinese medicine intervention in FD has gradually become a research hotspot in recent years. The 5-HT signaling pathway, AMPK signaling pathway, C-kit signaling pathway, CRF signaling pathway, PERK signaling pathway and NF- $\kappa$ B signaling pathway are the pathways of FD treatment in Chinese medicine. The 5-HT signaling pathway and CRF signaling pathway play an important role in mediating visceral hypersensitivity. AMPK, C-kit and PERK signaling pathways are closely related to mediating cellular autophagy and regulating gastric motility. NF- $\kappa$ B signaling pathway is mainly related to mediating inflammatory response.

FD is a psychosomatic disorder and is closely related to the spleen and stomach. The liver is the master of drainage, which affects the spleen and stomach's ability to raise and lower turbidity, so the basic clinical principle is to clear the liver and relieve depression, regulate qi and strengthen the spleen. Chinese medicine has a long history of treatment for FD, with the advantages of multi-component, multi-target and multi-level, and combined with modern medicine multiple cell signaling pathways, it plays a unique advantage in reducing visceral sensitivity, regulating gastric dynamics and reducing inflammatory response.

Current research related to the prevention and treatment of FD in Chinese medicine reflects some of the shortcomings, and there is still a gap with Western medical research: (1) Due to the insufficient level of research in Chinese medicine, too much research is focused on single and compound herbs, and research on single herbs is slightly thin. (2) Lack of multi-pathway research on the prevention and treatment of FD by

Chinese medicine compounding, which cannot better exploit the therapeutic advantages of Chinese medicine with multi-pathways and multi-targets. (3) Chinese herbal compounding has not been analysed for specific components of action in the course of the study. (4) Research on the treatment of FD with TCM is still dominated by basic research and there is a need for high quality randomized controlled clinical trials to provide assurance on the clinical role of TCM. In summary, there is still much room for exploring the mechanism of TCM in the treatment of FD. Future research should be based on TCM theory as a guide, discriminating evidence, making full use of modern medicine's advanced experimental instruments and science and technology to summarize research involving all pathways of a single compound formula, to comprehensively, thoroughly, systematically and objectively explore the mechanism of TCM in the treatment of FD, and to provide a more favourable evidence-based medical basis for the clinical application and promotion of TCM.

## Author contributions

YS participated in the proposal of the research topic, the design of the research scheme, the implementation of the research process, the drafting, revision and final review of the paper; DY participated in the proposal of the research topic, the design of the research scheme, the revision and final review of the paper; LC provided material support for the paper and guide the writing of the paper, participated in the final review of the paper; ZZ participated in the collection and collation of the paper data, the investigation and collation of references, and the revision of the paper.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## References

- Banerjee, A., Ahmed, H., Yang, P., Czinn, S. J., and Blanchard, T. G. (2016). Endoplasmic reticulum stress and IRE-1 signaling cause apoptosis in colon cancer cells in response to andrographolide treatment. *J. Oncotarget* 7, 41432. doi:10.18632/oncotarget.9180
- Barbera, R., Feinle, C., and Read, N. W. (1995). Abnormal sensitivity to duodenal lipid infusion in patients with functional dyspepsia. *[J]. Eur. J. gastroenterology hepatology* 7 (11), 1051–1057. doi:10.1097/00042737-199511000-00007
- Bashambo, A., Taylor, A. H., Samuel, K., Panthier, J. J., Whetton, A. D., and Forrester, L. M. (2006). The survival of differentiating embryonic stem cells is dependent on the SCF-KIT pathway. *J. Cell Sci.* 119 (15), 3039–3046. doi:10.1242/jcs.03038
- Bharath, L. P., Rockhold, J. D., and Conway, R. (2021). Selective autophagy in hyperglycemia-induced microvascular and macrovascular diseases. *J. Cells* 10 (8), 2114. doi:10.3390/cells10082114
- Bravo-San Pedro, J. M., Kroemer, G., and Galluzzi, L. (2017). Autophagy and mitophagy in cardiovascular disease. *Circ. Res.* 120 (11), 1812–1824. doi:10.1161/CIRCRESAHA.117.311082
- Buschmann, M. M., Shen, L., Rajapakse, H., Raleigh, D. R., Wang, Y., Wang, Y., et al. (2013). Occludin OCEL-domain interactions are required for maintenance and regulation of the tight junction barrier to macromolecular flux. *[J]. Mol. Biol. Cell* 24 (19), 3056–3068. doi:10.1091/mbc.E12-09-0688
- Chai, Y., Huang, Y., Tang, H., Tu, X., He, J., Wang, T., et al. (2017). Role of stem cell growth factor/c-Kit in the pathogenesis of irritable bowel syndrome. *[J]. Exp. Ther. Med.* 13 (4), 1187–1193. doi:10.3892/etm.2017.4133
- Chang, X. F., Zhao, L. Q., Jia, M. D., et al. (2018). Effect of Jianpi Liqi Formula on TLR9-NF- $\kappa$ B-iNOS pathway in the duodenum of functional dyspepsia rats[J]. *Beijing J. Traditional Chin. Med.* 37 (07), 606–609.
- Chang, X., Zhao, L., and Wang, J. (2017). Sini-san improves duodenal tight junction integrity in a rat model of functional dyspepsia. *BMC complementary Altern. Med.* 17 (1), 432. doi:10.1186/s12906-017-1938-2
- Chen, J. Y., Dang, S. P., Wu, Y., et al. (2022). Role of autophagy in occurrence of diabetic cardiomyopathy[J]. *Med. Recapitulate* 28 (09), 1751–1757.
- Chen, Q., Xie, S., Zhou, X. L., et al. (2019). Effects of “regulating the pivot through the shu points” on the expression of SCF, c-kit protein and mRNA in rats with gastrointestinal motility disorder[J]. *China J. Traditional Chin. Med. Pharm.* 34 (03), 1174–1177.
- Chen, S. H., Zhu, L. J., Zhi, Y. H., Wu, H. S., Li, L. Z., Li, B., et al. (2022). Pitongshu alleviates the adverse symptoms in rats with functional dyspepsia through regulating visceral hypersensitivity caused by 5-HT overexpression. *Comb. Chem. high throughput Screen.* 25. doi:10.2174/1386207325666220827152654
- Cramer, F., Christensen, C. L., Poulsen, T. T., Badding, M. A., Dean, D. A., Poulsen, H. S., et al. (2012). Insertion of a nuclear factor kappa B DNA nuclear-targeting sequence potentiates suicide gene therapy efficacy in lung cancer cell lines. *J. Cancer Gene Ther.* 19 (10), 675–683. doi:10.1038/cgt.2012.54
- Deng, J., Ling, J. H., Shang, G. X. C., et al. (2018). Effects of Citrus aurantium L. on interstitial cells of Cajal (ICCs) and SCF/c-Kit signaling pathway in the antrum of rats with functional dyspepsia[J]. *China J. Traditional Chin. Med. Pharm.* (6), 2304–2309.
- Douglas, A. D. (2016). Functional gastrointestinal disorders: History, pathophysiology, clinical features, and Rome IV. *Gastroenterology* 150, 6, 1262–1279.e2. doi:10.1053/j.gastro.2016.02.032
- Drossman, D. A., and Hasler, W. L. (2016). Rome IV-functional GI disorders: Disorders of gut-brain interaction. *Gastroenterology* 150 (6), 1257–1261. doi:10.1053/j.gastro.2016.03.035
- Duffey, K. C., Shih, O., Wong, N. L., Drisdell, W. S., Saykally, R. J., and Cohen, R. C. (2013). Evaporation kinetics of aqueous acetic acid droplets: Effects of soluble organic aerosol components on the mechanism of water evaporation. *Phys. Chem. Chem. Phys.* PCCP. 15 (28), 11634–11639. doi:10.1039/c3cp51148k
- Fan, M. M., Han, H., Lin, W., et al. (2021). Effect of Chaizhu Liwei Yin on the expression of p38MAPK and NF- $\kappa$ B p65 in the functional dyspepsia rats with the pattern of liver qi stagnation and spleen deficiency[J]. *Jilin J. Chin. Med.* 41 (12), 1631–1635.
- Fan, M. N., Zhang, B., and Chen, S. N. (2020). Effect of weitong Xiaopi prescription on expressions of 5-HT and receptor in rats with liver-qi depression and spleen-deficiency type of functional dyspepsia[J]. *Chin. Archives Traditional Chin. Med.* 38 (11), 229–232+299.
- Garcia, D., and Shaw, R. J. (2017). AMPK: Mechanisms of cellular energy sensing and restoration of metabolic balance. *Mol. Cell* 66 (6), 789–800. doi:10.1016/j.molcel.2017.05.032
- Giannogonas, P., Apostolou, A., Manousopoulou, A., Theocharis, S., Macari, S. A., Psarras, S., et al. (2016). Identification of a novel interaction between corticotropin releasing hormone (Crh) and macroautophagy. *J. Sci. Rep.* 6 (1), 23342. doi:10.1038/srep23342
- Gower, W. R., Salhab, K. F., Foulis, W. L., Pillai, N. Bundy, J. R., Vesely, D. L., et al. (2000). Regulation of atrial natriuretic peptide gene expression in gastric antrum by fasting. *Am. J. physiology. Regul. Integr. Comp. physiology* 278 (3), R770–R780. doi:10.1152/ajpregu.2000.278.3.R770
- Guo, H. S., Cui, X., Cui, Y. G., Kim, S. Z., Cho, K. W., Li, Z. L., et al. (2003). Inhibitory effect of C-type natriuretic peptide on spontaneous contraction in gastric antral circular smooth muscle of rat. *Acta Pharmacol. Sin.* 24 (10), 1021–1026.
- Han, Y. L. (2020). *Regulation of moxibustion at Zusanli point on SCF/C-kit signaling pathway in FD rats[D]*. Wuhan, China: Hubei University of Traditional Chinese Medicine.
- He, Jieying, Gui, Bei, Chen, Yanfen, al, ea, Tao, S. H., Shen, Z. B., et al. (2022). Mechanism of liangfu pills in treatment of functional dyspepsia: Based on network pharmacology and experimental verification. *China J. Chin. Materia Medica* 47 (14), 3853–3862. doi:10.19540/j.cnki.cjcm.20211230.705
- Heather, P. H., Zhang, Y. H., Bertolotti, A., Zeng, H., Ron, D., and Bertolotti, A. (2000). Perk is essential for translational regulation and cell survival during the unfolded protein response. *Mol. Cell* 5 (5), 897–904. doi:10.1016/s1097-2765(00)80330-5
- Hetz, C., and Papa, F. R. (2018). The unfolded protein response and cell fate control. *Mol. Cell* 69 (2), 169–181. doi:10.1016/j.molcel.2017.06.017
- Huang, J. L., Guo, X., Wang, X. J., et al. (2017). Effect of Shuwei Decoction on gastric emptying function and CNP/pGC signaling pathway in rats with functional dyspepsia[J]. *Chin. Tradit. Pat. Med.* 39 (11), 2389–2393.
- Huang, W. L., and Zhu, X. F. (2005). *Signal transduction[M]*. Beijing: People's Medical Publishing House.
- Jan, D. H., Natalia, Z., and Gianrico, F. (2009). Physiology, injury, and recovery of interstitial cells of cajal: Basic and clinical science. *Gastroenterology* 137 (5), 1548–1556. doi:10.1053/j.gastro.2009.09.023
- Jezova, D., Ochedalski, T., Glickman, M., Kiss, A., and Aguilera, G. (1999). Central corticotropin-releasing hormone receptors modulate hypothalamic-pituitary-adrenocortical and sympathoadrenal activity during stress. *Neuroscience* 94 (3), 797–802. doi:10.1016/s0306-4522(99)00333-4
- Ji, Y. X., Ling, J. H., Pang, L. M., et al. (2013). Cajal interstitial cells, Ca<sup>2+</sup> and gastrointestinal motility in the gastrointestinal tract[J]. *J. Pract. Med.* 29 (11), 1872–1873.
- Jiang, S. H., Wang, Y. H., Hu, L. P., Wang, X., Li, J., Zhang, X. L., et al. (2021). The physiology, pathology and potential therapeutic application of serotonylation. *J. Cell Sci.* 134 (11), jcs257337. doi:10.1242/jcs.257337
- Jing, Y., Shi, Y. Q., and Zhao, X. Y. (2015). Expression and significance of SCF and 5-HT in the intestinal mucosa of patients with diarrhoeal irritable bowel syndrome [J]. *Jilin Med. Journal* 36 (4), 646–647.
- Kang, Z. X., Xu, P. D., Tang, L., et al. (2018). Influence of eletro-acupuncture on MEK-ERK1/2 signaling pathway in functional dyspepsia rats[J]. *J. Emerg. Traditional Chin. Med.* 27 (12), 2079–2081+2085.
- Kang, Z. X., Zhang, H. X., Xu, P. D., Wang, J. Y., Han, Y. L., et al. (2017). Influence of electroacupuncture on ghrelin and mTOR expression in the gastric antrum of rats with functional dyspepsia. *[J]. World Chin. J. Dig.* 25 (17), 1553–1557. doi:10.11569/wcj.d.v25.i17.1553
- Konturek Peter, C., Brzozowski, T., and Konturek, S. J. (2011). Stress and the gut: Pathophysiology, clinical consequences, diagnostic approach and treatment options. *J. physiology Pharmacol. official J. Pol. Physiological Soc.* 62 (6), 591–599.
- Lang, X. M., Wang, Y. L., and Yang, Q. (2020). Effects of Shugan Jianpi Qingre formula on the expression of 5-HT receptor and CREB protein in gastric mucosa of rats with functional dyspepsia. *[J]. China J. Traditional Chin. Med. Pharm.* 35 (08), 4105–4108.
- Larauche, M., Kiank, C., and Tache, Y. (2009). Corticotropin releasing factor signaling in colon and ileum: Regulation by stress and pathophysiological implications. *J. physiology Pharmacol. official J. Pol. Physiological Soc.* 60 (7), 33–46.
- Li, H., Tang, H. T., Wang, X. Z., et al. (2016). The difference of CEF level and its relationship with anxiety/depression in subgroups of functional dyspepsia[J]. *Chin. J. Clin. Gastroenterology* 28 (06), 333–337.
- Li, J. J., Wang, F. Y., Lv, L., et al. (2022). Effect of Xiangsha Liujunzi tang on gastric motility and CRF and UCN2 expression in rats with functional dyspepsia due to spleen deficiency[J]. *Chin. J. Exp. Traditional Med. Formulae* 28 (03), 1–7.
- Li, J. X., Nie, Q. H., and Chen, H. Y. (2022). Clinical effect of acupuncture combined with traditional Chinese medicine application on the treatment of

- functional dyspepsia in children and the influence on serum 5-HT and NO levels. *Comput. Intell. Neurosci.* 2022, 6800662. doi:10.1155/2022/6800662
- Li, X. L., Zhang, S. S., Yang, C., et al. (2014). Effects of Zhizhu pill on the gastric emptying function as well as Ghrelin, 5-HT and CGRP in rats with functional dyspepsia[J]. *Beijing J. Traditional Chin. Med.* 33 (11), 856–860.
- Li, Y., and Chen, Y. (2019). AMPK and autophagy[J]. *Adv. Exp. Med. Biol.* 1206, 85–108.
- Lv, L., Wang, F. Y., Tang, X. D., et al. (2017). Effects of Pixu I Formula on the PERK protein expression in gastric tissue of functional dyspepsia rats with syndrome of spleen deficiency[J]. *China J. Traditional Chin. Med. Pharm.* 32 (09), 3963–3967.
- Mao, L. F., Wang, L. D., Du, X. J., et al. (2021). Research thinking on the regulation of gastrointestinal motility disorder in functional dyspepsia by soothing liver and strengthening spleen based on ICC autophagy[J]. *J. Basic Chin. Med.* 27 (12), 1916–1919+1924.
- Nakade, Y., Fukuda, H., and Iwa, M. (2007). Restraint stress stimulates colonic motility via central corticotropin-releasing factor and peripheral 5-HT3 receptors in conscious rats. *Am. J. Physiol. Gastrointest. Liver Physiol.* 292 (4), G1037–G1044. doi:10.1152/ajpgi.00419.2006
- Peng, S. F., and Liu, S. (2007). CRF in relation to stress-related alterations in gastrointestinal motility dynamics and visceral sensation[J]. *Chin. J. Gastroenterology Hepatology* (03), 294–297.
- Pinna, A., Costa, G., Serra, M., Contu, L., and Morelli, M. (2021). Neuroinflammation and L-dopa-induced abnormal involuntary movements in 6-hydroxydopamine-lesioned rat model of Parkinson's disease are counteracted by combined administration of a 5-HT1A/1B receptor agonist and A2A receptor antagonist. *J. Neuropharmacol.* 196, 108693. doi:10.1016/j.neuropharm.2021.108693
- Qin, H. Y., Xavier Wong, H. L., Zang, K. H., Li, X., Bian, Z. X., et al. (2019). Enterochromaffin cell hyperplasia in the gut: Factors, mechanism and therapeutic clues: Factors, mechanism and therapeutic clues[J]. *Life Sci.* 239, 116886. doi:10.1016/j.lfs.2019.116886
- Ren, X. J., Ren, H. H., and Chen, Y. (2019). Advances in research on treatment of functional dyspepsia with traditional Chinese medicine[J]. *J. Liaoning Univ. Traditional Chin. Med.* 21 (01), 218–221.
- Sanders, K. M. (2019). Spontaneous electrical activity and rhythmicity in gastrointestinal smooth muscles. *Adv. Exp. Med. Biol.* 1124, 3–46. doi:10.1007/978-981-13-5895-1\_1
- Sanger, G. J., and Pasricha, P. J. (2017). Investigational drug therapies for the treatment of gastroparesis. *Expert Opin. Investig. Drugs* 26 (3), 331–342. doi:10.1080/13543784.2017.1288214
- Shang, G. X. C. (2017). *Effects of chaihui shugan san on apoptosis of gastric smooth muscle cell and expression of NF- $\kappa$ B protein in rats with functional dyspepsia [D]*. Nanning, China: Guangxi Medical University.
- Shin-Ichiro, H., Esha, K., Sreenivasan, P., et al. (2019). Gastric corticotropin-releasing factor influences mast cell infiltration in a rat model of functional dyspepsia. *J. PLoS ONE* 13 (9), e203704.
- Stasi, C., Bellini, M., Bassotti, G., Blandizzi, C., Milani, S., et al. (2014). Serotonin receptors and their role in the pathophysiology and therapy of irritable bowel syndrome. *[[J].Tech Coloproctol.* 18 (18), 613–621. doi:10.1007/s10151-013-1106-8
- Stevanovic, D., Janjetovic, K., Misirkic, M., Sumarac-Dumanovic, M., Micic, D., Vucicevic, L., et al. (2012). Intracerebroventricular administration of metformin inhibits ghrelin-induced Hypothalamic AMP-kinase signalling and food intake. *Neuroendocrinology* 96 (1), 24–31. doi:10.1159/000333963
- Su, H. X., Fu, Z. Y., Gao, Y. Z., et al. Correlation between 5-HT and diarrhea-type irritable bowel syndrome and regulation by traditional Chinese medicine. *[[J].Chinese General Pract.*, 1–9.
- Su, Y., Huang, X. J., Raskovalova, T., Zacharia, L., Lokshin, A., Jackson, E., et al. (2008). Cooperation of adenosine and prostaglandin E2 (PGE2) in amplification of cAMP-PKA signaling and immunosuppression. *J. Cancer Immunol. Immunother.* CII 57 (11), 1611–1623. doi:10.1007/s00262-008-0494-5
- Tache, Y., Larauche, M., Yuan, P. Q., and Million, M. (2018). Brain and gut CRF signaling: Biological actions and role in the gastrointestinal tract. *J. Curr. Mol. Pharmacol.* 11 (1), 51–71. doi:10.2174/1874467210666170224095741
- Taché, Y., Maeda-Hagiwara, M., and Turkelson, C. M. (1987). Central nervous system action of corticotropin-releasing factor to inhibit gastric emptying in rats. *[[J]. Am. J. physiology* 253 (21), G241–G245. doi:10.1152/ajpgi.1987.253.2.G241
- Tack, J., and Drossman, D. A. (2017). What's new in Rome IV[[J]. *Neurogastroenterol. Motil.* 29 (9), e13053. doi:10.1111/nmo.13053
- Tan, S. W., Chen, X. L., Xu, M. Y., Huang, X., Liu, H., Jiang, J., et al. (2017). PGE2/EP4 receptor attenuated mucosal injury via  $\beta$ -arrestin1/Src/EGFR-mediated proliferation in portal hypertensive gastropathy. *Br. J. Pharmacol. Chemother.* 174 (9), 848–866. doi:10.1111/bph.13752
- Tang, F., Pacheco, M., Thiego, F., Liang, D., and Li, W. (2017). Secretogranin III promotes angiogenesis through MEK/ERK signaling pathway. *Biochem. Biophysical Res. Commun.* 495 (1), 781–786. doi:10.1016/j.bbrc.2017.11.080
- Tang, L., Zeng, Y., Li, L., Wang, J., Peng, D., Zhang, T., et al. (2020). Electroacupuncture upregulated ghrelin in rats with functional dyspepsia via AMPK/TSC2/Rheb-Mediated mTOR inhibition. *[[J]. Dig. Dis. Sci.* 65 (6), 1689–1699. doi:10.1007/s10620-019-05960-5
- Teng, W., Chen, H., Guo, F., et al. (2016). Expression and distribution of SP and its NK1 receptor in the brain-gut axis in neonatal maternally separated rat model with visceral hypersensitivity(J). *Genet. Mol. Res.* 15, 112–115.
- Wandewynckel, Y. P., Laukens, D., Bogaerts, E., Paridaens, A., Van den Bussche, A., Verhelst, X., et al. (2015). Modulation of the unfolded protein response impedes tumor cell adaptation to proteotoxic stress: A PERK for hepatocellular carcinoma therapy. *J. Hepatol. Int.* 9 (1), 93–104. doi:10.1007/s12072-014-9582-0
- Vanheel, H., Vicario, M., Vanuytsel, T., Van Oudenhove, L., Martinez, C., Keita, A. V., et al. (2014). Impaired duodenal mucosal integrity and low-grade inflammation in functional dyspepsia. *J. Gut* 63 (2), 262–271. doi:10.1136/gutjnl-2012-303857
- Villanueva-Paz, M., Cotán, D., Garrido-Maraver, J., [Exs, J], et al. (2016). *AMPK Regulation of Cell Growth, Apoptosis, Autophagy, and Bioenergetics*, 107.
- Wang, C. J., and Jiang, W. (2009). Relations of gastric motor dysfunction and gastric smooth muscle ultrastructure in functional dyspepsia model rats with Liver-Qi depression[J]. *Chin. J. Integr. Traditional West. Med. Dig.* 17 (02), 86–88.
- Wang, D., Zhang, H., Rong, P. J., et al. (2020). Effects of TLR4 and NF- $\kappa$ B p65 on duodenum with the intervention of electro-acupuncture in functional dyspepsia model rats with liver stagnation and spleen deficiency[J]. *J. Basic Chin. Med.*, , 26(09)1337–1340.
- Wang, D., and Pan, X. L. (2022). Progress in TCM research on functional dyspepsia based on duodenal abnormality[J]. *Mod. Traditional Chin. Med. Materia Medica-World Sci. Technol.* 24 (03), 925–932.
- Wang, L., Wang, J. H., Zhao, W. H., et al. (2022). Effect of weichang shutai granule SCF/c-kit signaling pathway on cajal stromal cells in rats with functional dyspepsia[J]. *Liaoning J. Traditional Chin. Med.* 49 (03), 202–205.
- Wang, Z. F., Huang, P., and Cai, G. H. (2020). Effects of magnolol on digestive fluid secretion and gastrointestinal motion function in mice with functional dyspepsia[J]. *Mod. Dig. Intervention* 25 (04), 454–458.
- Wang, Z. Y., Wang, N., Liu, P. X., et al. (2016). AMPK and cancer. *[[J]. EXS*, 107.
- Wauters, L., Talley, N. J., Walker, M. M., Tack, J., and Vanuytsel, T. (2020). Novel concepts in the pathophysiology and treatment of functional dyspepsia. *[[J].Gut* 69 (3), 591–600. doi:10.1136/gutjnl-2019-318536
- Wei, J., Li, N., Xia, X., Chen, X., Peng, F., Besner, G. E., et al. (2014). Effects of lipopolysaccharide-induced inflammation on the interstitial cells of Cajal. *[[J]. Cell tissue Res.* 356 (1), 29–37. doi:10.1007/s00441-013-1775-7
- Wu, J. S., Li, W. M., Chen, Y. N., Zhao, Q., and Chen, Q. F. (2016). Endoplasmic reticulum stress is activated in acute pancreatitis. *J. Dig. Dis.* 17 (5), 295–303. doi:10.1111/1751-2980.12347
- Wu, P. Q., Chen, M., and Han, L. Y. (2015). Correlation of the T102C polymorphism of serotonin 5-Hydroxytryptamine and its receptor gene and suicidal behavior by poison in Non-depressive patients. *[[J].West China Med. J.* 30 (8), 1411–1414.
- Yang, Z. C., and Guo, X. Z. (2015). Thinking about the correlation between cell signal transduction and experimental study on the theory of five internal organs responding to the season[[J]. *China J. Traditional Chin. Med. Pharm.* 30 (4), 974.
- Yarandi, S. S., and Christie, J. (2013). Functional dyspepsia in review: Pathophysiology and challenges in the diagnosis and management due to coexisting gastroesophageal reflux disease and irritable bowel syndrome. *[[J]. Gastroenterology Res. Pract.* 2013 (2), 351086. doi:10.1155/2013/351086
- Ye, Z., Wang, N., Xia, P. P., Liao, J., and Guo, Q. (2013). Parecoxib suppresses CHOP and Foxo1 nuclear translocation, but increases GRP78 levels in a rat model of focal ischemia. *[[J]. Neurochem. Res.* 38 (4), 686–693. doi:10.1007/s11064-012-0953-4
- Yu, F. Y., Huang, S. G., Zhang H. Y., Chi, H. G., Zou, Y., et al. (2016). Comparison of 5-hydroxytryptophan signaling pathway characteristics in diarrheapredominant irritable bowel syndrome and ulcerative colitis. *World J. Gastroenterol.* 22, 3451–3459. doi:10.3748/wjg.v22.i12.3451
- Zhang, L. M., Zeng, L. J., Deng, J., Zhang, Y. Q., Wang, Y. J., Xie, T. Y., et al. (2017). Investigation of autophagy and differentiation of myenteric interstitial cells of Cajal in the pathogenesis of gastric motility disorders in rats with functional dyspepsia. *[[J]. Biotechnol. Appl. Biochem.* 65 (4), 533–539. doi:10.1002/bab.1635
- Zhang, Y. L., Bian, L. H., Long, H., Zhang, W., and Hu, Y. (2021). Efficacy evaluation of acupuncture combined with Liujuanzi decoction in the treatment of



functional dyspepsia: A protocol of randomized controlled trial. *Medicine* 100 (8), e24528. doi:10.1097/MD.00000000000024528

Zhao, J. Y., Zhao, L. Q., Zhu, C. Y., et al. (2020). Effects of Xiangsha Liujunzi decoction on gastric sensitivity and expression of 5-HT and TRPV1 in duodenum of functional dyspepsia model rats[J]. *J. Traditional Chin. Med.* 61 (07), 613–618.

Zhao, L. Q., Chang, X. F., and Zhang, S. S. (2019). Effects of Jianpi Liqi formula on MLCK and PGE2-cAMP signal path in the duodenum of rats with functional dyspepsia[J]. *J. Cap. Med. Univ.* 40 (03), 335–339.

Zhong, Z. S., Huang, S. P., Zhang, W., et al. (2017). Disorder in CNP-NPRB-cGMP pathway of gastric antral smooth muscle of functional dyspepsia model rats

with spleen-deficiency syndrome and intervening mechanism of Sijunzi tang[J]. *Chin. J. Exp. Traditional Med. Formulae* 23 (13), 133–137.

Zhou, Z. (2018). *Effects of chaihu shugan san of the PERK/eIF2 $\alpha$  signaling pathways of Er stress in the antrum of rats with functional dyspepsia[D]*. Nanning, China: Guangxi Medical University.

Zhu, C. Y., Zhao, L. Q., Li, Y. X., et al. (2020). Effect of Jianpi liqi formula on CRF pathway in rats with functional dyspepsia[J]. *World J. Integr. Traditional West. Med.* 15 (01), 96–99+122.

Zhu, C. Y. (2020). *Study on the mechanism of sini san in the treatment of functional dyspepsia based on CRF pathway[D]*. Beijing: Beijing University of Chinese Medicine.