

# Progress of Chinese and Western medicine research on the treatment of functional dyspepsia based on intestinal microecology

Qiu Penghui<sup>1</sup>, Zhao Weihai<sup>2,\*</sup>, Wu Jinyue<sup>1</sup>, Chen Chen<sup>1</sup>, Luo Xingyu<sup>1</sup>, Meng Ge<sup>1</sup>

<sup>1</sup>Shaanxi University of Chinese Medicine, Xiayang, Shaanxi, 712046, China

<sup>2</sup>Affiliated Hospital of Shaanxi University of Chinese Medicine, Shaanxi, 712000, China

\*Corresponding author

**Abstract:** Functional dyspepsia (FD) is a disease in which gastroparesis and diet-related symptoms are the main clinical manifestations due to the dysfunction of the gastroduodenum, but there are no structural changes and its pathogenesis is still unclear. In recent years, intestinal microecology has been confirmed to be related to FD. In this paper, we intend to review the role and mechanism of microecological agents and Chinese medicine in the treatment of functional dyspepsia, starting from the relationship between intestinal microecology and FD, in order to provide reference for clinical treatment and research.

**Keywords:** intestinal microecology; intestinal flora; functional dyspepsia; microecological preparations; Chinese medicine

## 1. Introduction

Functional dyspepsia (FD) is one of the most common functional gastrointestinal disorders, affecting more than 20% of the population. According to the Rome IV diagnostic criteria, it is defined by the presence of one or more of the following symptoms: epigastric pain or burning sensation, early satiety, postprandial fullness, and no structural disease on imaging or endoscopy [1,2]. The pathophysiological pathogenesis of FD is not fully understood, and most studies currently suggest that the pathogenesis of FD may be related to gastrointestinal motility disorders, *Helicobacter pylori* (Hp) infection, brain-gut axis, psychosomatic factors, and the role of intestinal dysbiosis in the pathogenesis of FD has received much attention in recent years [3,4].

The current Western medical treatment of FD is mainly based on acid suppression, gastric mucosa protection, gastrointestinal motility, eradication of *H. pylori* and psychotherapy based on brain-gut axis [5]. However, it has many side effects, and long-term use will cause the body to develop drug resistance, resulting in recurrence of the disease, which seriously affects the life of patients. Recent studies have shown that microecological agents and Chinese medicine can improve FD symptoms to some extent by regulating intestinal flora, which are reviewed as follows.

## 2. The relationship between intestinal flora dysbiosis and FD

The human intestinal flora has multiple functions in the host, including intestinal development, homeostasis, and defense against pathogenic bacteria. The normal flora in the human body together constitute the intestinal microecology, which is a complex microbial ecosystem, and the microbial communities present within this special ecological environment are not only symbiotic, but also symbiotic and symbiotic with the host, together maintaining the stability of the internal environment of the gastrointestinal tract, whose beneficial flora have the ability to produce a variety of nutrients for the host, prevent infection by intestinal pathogens, and regulate the normal immune response. This affects the absorption, metabolism and immune defense of the human body [6,7]. Once the intestinal microecology is altered and the intestinal flora is disturbed, it can lead to multi-system diseases [8]. Recent studies have shown that dysbiosis of intestinal flora can lead to functional dyspepsia, and the dysbiosis of FD patients is mainly reflected in the change of intestinal flora abundance, species, and the decrease of beneficial flora. The relative abundance of *Bacillus* spp. decreased, and the relative abundance of *Aspergillus* spp. and *Cyanobacteria* increased. The study [9,10] found that the occurrence of

FD and its severity had a proportional relationship with pathogens such as *Aspergillus* and *Acidobacter*, while the numbers of *Proteus*, *Vibrio* and *Actinobacter* were negatively correlated with the occurrence of FD. The mechanism of FD occurrence due to dysbiosis of the intestinal flora is not clear and may be related to beneficial bacteria in the gut inhibiting the penetration and growth of pathogenic bacteria through competition for space and resources<sup>[11]</sup>. It may also be related to the impaired intestinal barrier, where the intestinal flora is dysbiosis, the decrease of beneficial bacteria in the intestine and the increase of pathogenic bacteria, whose metabolites activate the immune system, thus causing the release of inflammatory factors and mediating the development of FD<sup>[12]</sup>. Vanheel<sup>[13]</sup> et al. suggested that the impaired intestinal barrier function may be a potential mechanism for the development of FD, and that the impaired intestinal barrier is specifically manifested by the mucosa being in a state of hypo-inflammation, mucosa impairment of the intestinal barrier is manifested by a state of low inflammation and increased permeability of the mucosa; therefore, restoring the integrity of the intestinal barrier is considered a potential target for the treatment of FD.

### **3. Microecological agents in the treatment of FD**

#### **3.1 Probiotic treatment in FD**

Probiotics are defined by the Food and Agriculture Organization of the United Nations and the World Health Organization's Expert Advisory Committee on the Evaluation of the Health and Nutritional Properties of Probiotics. It is defined as "live microorganisms that, when injected in sufficient amounts, are beneficial to the health of the host. Probiotics are believed to have antibacterial, anti-inflammatory, and even anticancer effects, so they may help restore unbalanced intestinal flora, and recent studies have shown that probiotics may be effective for people with FD<sup>[14]</sup>. Cai Deen<sup>[15]</sup> observed that functional dyspepsia caused by *Hp* infection was significantly more effective with a probiotic combined with a quadruple eradication regimen than with a traditional quadruple therapy eradication regimen. A recent study<sup>[16]</sup> showed that *Lactobacillus* was the most commonly used agent for the treatment of FD, followed by *Bifidobacterium*, *Streptococcus* and *Bacillus*. Erna Sun<sup>[17]</sup> et al. found that the consumption of LC-37 lactic acid bacteria drink could increase the abundance of beneficial bacteria such as *Bifidobacterium* spp., *Prevotella* spp. and *Alternaria* spp. and significantly increase the abundance of *Lactobacillus* spp. and *Muribaculaceae* spp. and decrease the abundance of harmful bacteria *Dorea*, which could significantly alleviate the symptoms of functional dyspepsia and regulate the intestinal flora in the subjects.

#### **3.2 Prebiotic treatment in FD**

Prebiotics are digestible food components that produce beneficial physiological effects on the host by selectively modulating the composition or activity of the intestinal microbiota, thereby increasing the body's natural resistance to invading pathogens<sup>[18]</sup>. The increase in the number of beneficial intestinal flora and the fermentation of prebiotics are the main factors affecting the digestive health of the host. Bindels<sup>[19]</sup> et al. suggested that some beneficial effects from the metabolism of prebiotics may be dependent on the epithelium or through effects on bile acid metabolism, as well as neuroendocrine responses. There is no clear literature on the therapeutic effects of prebiotics in FD, but their effects in improving FD-related symptoms may be related to: (i) resistance to gastric acid, mammalian enzyme hydrolysis and gastrointestinal absorption; (ii) fermentation by the intestinal microbiota; and (iii) selective stimulation of the growth and activity of flora associated with intestinal health<sup>[20]</sup>. Most prebiotics have beneficial effects on host health by modulating the gastrointestinal microbiota and increasing the beneficial flora in the intestinal tract. In addition, intestinal flora can produce short-chain fatty acids through the fermentation of prebiotics, mainly through the metabolism of butyric, acetic and propionic acids, which provide energy to the cells of the intestinal wall<sup>[21]</sup>.

### **4. Regulation of intestinal microecology in FD patients by Chinese medicine**

#### **4.1 TCM understanding of FD and intestinal microecology**

FD has no name in ancient Chinese medical texts, but according to its clinical symptoms and manifestations, it can be classified as "fullness" and "gastric pain" in Chinese medicine<sup>[22]</sup>, which is located in the stomach and is related to the liver and spleen. FD is related to external evil, diet and emotion. The pathogenesis of the disease is the stagnation of gastric qi and the loss of harmony and

descent of the stomach<sup>[23]</sup>. The *"Su Wen - The Treatise on Anger and the General Sky"* says: "The spirit is cured when yin and yang are in balance". The balance of yin and yang in Chinese medicine runs through the human physiology, and the balance of bacterial flora environment in the gastrointestinal tract also belongs to the balance of yin and yang in the human body. Recent scientific research also confirmed: intestinal flora and spleen and stomach as the impact of the body's food absorption<sup>[24]</sup>. It is confirmed that the balance of yin and yang in the intestinal tract is also a guarantee of the normal function of the spleen and stomach in raising the clear and lowering the turbidity, as well as the large intestine in transferring the meal. The beneficial bacteria in the intestinal tract can be regarded as positive qi, while the potentially pathogenic bacteria and harmful bacteria such as fungi and their metabolites can be regarded as evil qi. Various factors lead to disturbance of the intestinal flora, the fight between positive and evil, the imbalance between yin and yang, and the disruption of qi flow, resulting in "fullness" and "stomach pain"<sup>[25]</sup>.

#### **4.2 Regulation of intestinal flora by herbal medicine for FD**

Several studies have shown that traditional medicine and compounding can effectively regulate the intestinal micro-ecosystem and treat gastrointestinal diseases by restoring the intestinal micro-ecological balance<sup>[26]</sup>.

##### **4.2.1 Regulation of intestinal flora by herbal monotherapy**

Citrus aurantium, which enters the spleen and stomach meridians, has the function of breaking up qi and dispersing lumpiness, resolving phlegm and eliminating stagnation. Its efficacy is essentially the same as that of promoting gastrointestinal motility in western medicine, and is one of the commonly used motility drugs in clinical practice, which is mostly used to treat gastrointestinal disorders caused by spleen and stomach qi disorders, and has a better effect on the treatment of FD<sup>[27]</sup>. Wang Ting<sup>[28]</sup> et al. found that the administration of Citrus aurantium could promote the growth of beneficial intestinal bacteria in rats with functional dyspepsia, and at the same time inhibit the reproduction of harmful bacteria, which eventually effectively improved the state of disordered intestinal flora. In an experimental study conducted by Zheng Minsi<sup>[29]</sup> to investigate the pharmacological effects of hexachinquefolium on FD and the intestinal flora-immune mechanism of its effects, it was found that hexachinquefolium could improve the pharmacological effects of functional dyspepsia by affecting the structural changes of intestinal flora of FD rats and causing changes in metabolites of SCFAs, which in turn could affect the immune function. A recent study<sup>[30]</sup> found that the interaction between intestinal flora and herbal medicines occurs mainly through two pathways. One way is that the intestinal microflora "digests" the herbs into absorbable active small molecules, which enter the body and cause physiological changes. The second is that herbal medicines regulate the composition of intestinal flora and its secretions, thus changing the intestinal flora and its secretions to induce physiological changes. The interaction between intestinal flora and herbal medicines can be attributed to the absorbable active small molecules and their altered intestinal flora and secretions.

##### **4.2.2 Regulation of intestinal flora by herbal compounding**

The pathogenesis of FD mainly lies in the stagnation of gastric qi and the loss of harmony and descent of the stomach. Therefore, to address the pathogenesis of FD, the main treatment is to strengthen the spleen and benefit the qi, and to restore the physiological function of the spleen to raise and lower the stomach. In clinical practice, for FD caused by weakness of the spleen and stomach, it is usually added or subtracted on the basis of Si Jun Zi Tang, which has been shown to regulate intestinal flora by improving intestinal barrier function<sup>[31]</sup> and regulating the intestinal immune system<sup>[32]</sup>. For dampness trapping the spleen and causing dysregulation of the spleen and stomach qi, the treatment is mostly based on the addition and subtraction of "Shen Ling Bai Zhu San" to resolve dampness, strengthen the spleen and harmonize the stomach. Jiang Hua<sup>[33]</sup> et al. showed that the mechanism by which "Shen Ling Bai Zhu San" regulates intestinal flora lies in the cultivation of anaerobic bacteria and the inhibition of aerobic bacteria. Yang Long<sup>[34]</sup> et al. found that "Shen Ling Bai Zhu San" can assist the growth of probiotics, inhibit the proliferation and colonization of pathogenic bacteria, improve the resistance of intestinal microbial colonization, maintain the homeostasis of intestinal local microecological environment, and protect the intestinal mucosa. In the study of the interaction between "Ban Xia Xie Xin Tang" and intestinal flora, Liang Kun<sup>[35]</sup> et al. found that the combination of ginseng, licorice and jujube in the formula is beneficial to the growth of healthy flora in the intestinal tract, while bitter and descending drugs such as "Huang Lian and Baicalin" can inhibit the growth of pathogenic bacteria in vitro, thus improving the intestinal microenvironment. Some studies have also shown that tonics also have regulatory effects on intestinal flora. Feng Xingzhong<sup>[36]</sup> et al. found that

mice with intestinal mucosal damage model were treated with tonics, and the intestinal mucosal damage was repaired, which proved the effect of tonics in fostering the growth of beneficial bacteria in the intestine. In addition, Zhao Chunyi<sup>[37]</sup> found that the patients' sleep was improved after treatment with tonifying Zhong Yi Qi Tang, and the abundance of beneficial bacteria in the intestinal tract was increased, pathogenic bacteria were suppressed, and the immunometabolic function of the intestinal tract was improved. From the above, it can be seen that tonifying Zhong Yi Qi Tang can effectively regulate intestinal flora, which is mainly reflected in fostering the growth of probiotic bacteria in the intestine and accelerating the repair of damaged intestinal mucosa.

#### 4.3 Regulation of intestinal flora by acupuncture therapy

As an important part of Chinese medicine, acupuncture therapy plays a unique role in the treatment of certain functional diseases. Acupuncture therapy can regulate the body's qi, blood, yin and yang to restore the balance of yin and yang in the organism, which is essentially the same as the significance of maintaining the homeostasis of the intestinal flora. Acupuncture can improve the diversity of intestinal flora by stimulating acupuncture points and meridians, thus maintaining the stability of intestinal microecology and thus treating diseases. Hou Tianshu<sup>[38]</sup> et al. found that the beneficial intestinal flora and intestinal flora diversity in rats with ulcerative colitis model increased significantly after treatment with electroacupuncture points "Tian-shu, Zu-san-li and Shang-ju-xu". Wang Shudong<sup>[39]</sup> took two abdominal points "Tian-shu" and "Guan-yuan" from the rat model of intestinal flora disorders and treated them with warm acupuncture, the results showed that the number of Enterococcus, Enterobacter, Bifidobacterium and Lactobacillus in the intestine of the rats showed different degrees of increase, thus indicating that both electroacupuncture and warm acupuncture can improve the intestinal flora. This indicates that both electroacupuncture and warm acupuncture can improve the diversity of intestinal flora and increase the number of beneficial flora, and at the same time, they can also benignly regulate gastrointestinal motility, related brain and intestinal peptides and gastrointestinal hormones, thus benignly regulating the gastrointestinal tract and other related diseases in both directions. The mechanism is to improve the abundance and structure of intestinal flora, mainly by increasing the number of beneficial bacteria and reducing the number of harmful bacteria, thus stabilizing the intestinal flora<sup>[40]</sup>.

#### 5. Summary

Microecological preparations and TCM therapy can regulate the intestinal microenvironment of FD patients to restore the intestinal flora to a balanced state, and have achieved good efficacy in the treatment of functional dyspepsia, suggesting that an important part of the pathogenesis of functional dyspepsia lies in the imbalance of intestinal microecology. Therefore, in the clinical treatment of FD, we should pay attention to the intestinal microecology, and we can combine Chinese medicine therapy and microecological preparations to improve the intestinal microecology, so as to treat the disease. Since there are many factors affecting the intestinal environment, individual differences, and lack of uniform standards for detection methods, experimental data are scarce. Therefore, in the follow-up research, we can start from the following aspects: 1. to carry out the combination of disease and evidence animal models to verify the effect of TCM on the model of intestinal dysbiosis flora in multiple ways and multiple targets; 2. to carry out prospective clinical studies with large samples to explore the relationship between intestinal flora imbalance and FD from the perspective of evidence-based medicine.

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