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Treatment of Gastroesophageal Reflux Disease Based on the Intestinal Flora Theory from Sweetness Reaches Spleen

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Abstract: ***Context**: Cases of gastroesophageal reflux disease (GERD) have shown an increasing trend over time, severely impacting patients' quality of life. Gut flora issues are a hot research topic, and their metabolites are strongly associated with host disease. Studies have shown that intestinal flora dysbiosis is not only related to diseases of the digestive system, but also has a certain connection with the endocrine system, nervous system and rheumatoid immune system. Recent national and international studies have shown a strong association between intestinal flora dysbiosis and GERD. Spleen-boosting herbs have also been found to help regulate the intestinal flora. The digestive system is synergized by the spleen and stomach of Chinese medicine and the intestinal flora; **Purpose**: Explore the connections between intestinal flora, TCM spleen and stomach, and GERD; Methods: Based on the pathomechanism of GERD, we will explore the mechanism of intestinal flora and its metabolites, the spleen and stomach of TCM, and the influence of TCM on related diseases to build a "hub" connecting TCM, intestinal flora, and GERD; **Results**: Through the anatomical structure and physiological properties of the digestive system, the scientific arguments related to the influence of intestinal flora on GERD through immunity and the central nervous system were constructed, which also revealed the importance of traditional Chinese medicine in regulating intestinal flora and influencing GERD; **Conclusion**: Herbal medicine can be used to treat GERD by regulating the intestinal flora. Dysbiosis of the intestinal flora influences the development of GERD through several pathways, The interconnection between spleen and stomach and flora in Chinese medicine and the effects of both on GERD were explored with the clue that sweetness reaches the spleen. It also provides a new therapeutic concept for the clinical treatment of GERD.*

Keywords: Intestinal flora, Short chain fatty acids, Spleen and stomach, Plant polysaccharides, Gastroesophageal reflux disease.

1. Introduction

Statistically, gastroesophageal reflux disease (GERD) is categorized into: non-erosive reflux disease (NERD), reflux esophagitis (RE), and Barrett's esophagus (BE) [28]. It has a global prevalence of approximately 8% to 33%, with the highest prevalence in Western countries and a lower prevalence (<10%) in East Asia, and affects all age groups. A worldwide study shows: Approximately 13.0% of the population surveyed had at least one GERD-related symptom in a week, which is higher in Western countries, and this percentage is increasing over time in the Asia-Pacific region. A survey in our country showed this: Approximately 1.9% to 7.0% of the study population had heartburn symptoms ≥1 time per week. Reflux esophagitis (RE) accounts for approximately 30.0% to 40.0% of all cases of GERD [1][13]. Intestinal bacteria and esophageal microbiome (EM) can influence the mechanisms of GERD through immunologic pathways, and intestinal flora play an important role in the pathogenesis of GERD [2]. Current research has found that probiotics may relieve GERD-related symptoms through certain mechanisms, but the mechanism of their effect on GERD needs to be explored in depth by relevant professionals [3]. Guo's argues: Spleen and Stomach weakness appears as a malfunction of the transportation and transformation of the spleen, a malfunction of the qi circulation and descent of the stomach, resulting in symptoms such as acid reflux and heartburn because the yang qi of the spleen does not rise and the qi of the stomach rises [4]. The many physiological effects of intestinal flora in the body are closely related to the corresponding functions of the spleen and stomach in Chinese medicine [5]. Therefore, the aim of this paper is to provide a new theoretical basis for the clinical treatment of GERD by exploring the interrelationships between intestinal flora and spleen, stomach and GERD.

2. Correlation between Intestinal Flora and GERD

2.1 Mechanisms by which the Intestinal Flora May Influence GERD

(1) Abnormal neurotransmitter secretion affects gastrointestinal tract (GIT) function; (2) Gastroesophageal dyskinesia due to neuropathy caused by type 2 diabetes; (3) Autonomic nervous system dysfunction caused by anxiety and depression; (4) Abnormal body mass index (BMI) with resultant elevation of intra-abdominal pressure; (5) Delayed gastric emptying increases the probability of refluxing gastric contents; (6) Estrogen causes relaxation of the lower esophageal sphincter (LES); (7) Fatty liver-associated metabolic inflammatory response affects LES; The intestinal flora interacts with the body to form a dynamic balance system that regulates and maintains the body's metabolism [6][7], **Which** affects the development and treatment of many diseases and is also a hot topic for in-depth research at both national and international levels [8]. The central aspect of intestinal flora that affects GERD is that dysbiosis leads to a decrease in beneficial metabolites, a proliferation of harmful bacteria, and the production of large amounts of harmful substances. Further onwards affects digestive functions or induces immune-inflammatory and other disorders, ultimately leading to esophageal pathology.

2.2 Specific Ways in Which the Intestinal Flora May Influence GERD

2.2.1 Autonomic and Psychosomatic Pathways

Autonomic dysfunction is not only a mediator of psychoactive factors that induce GERD, but also leads to digestive hypersensitivity and altered gastrointestinal motility. Psychoactive factors play an important role in the development of GERD and in the management of its treatment. Depression and Depressive Disorder (MDD) are two of the most important influences of psychosomatic factors and are also important unfavorable factors that hinder the treatment of GERD with acid suppressive drugs [9]. Brain and gut peptides are mediators of communication between the central nervous system (CNS) and the enteric nervous system (ENS). For example, cholecystokinin (CCK) can cause relaxation of the gastric fundus and affect the LES during meals, Glucagon-like peptide (GLP-1) may act on MDD by binding to specific receptors in the gut and CNS [10][28][33]. Intestinal flora influences the CNS and regulates depression through endocrine, neural, and immune pathways [11].

The balance between sympathetic and parasympathetic nerves may affect the tonicity of the esophageal sphincter, and dysregulation of the sympathetic nervous system may lead to sphincter relaxation [34]. Intestinal flora can act on the CNS via the vagal nerves to influence conduct [12]. Its metabolites, short-chain fatty acids (SCFAs), can affect the immune system of the CNS by modulating neurons and glial cells, and also modulate CNS physiology across the blood-brain barrier (BBB) by binding to MCT receptors [13][14]. Microorganisms in the body can have a role in CNS-related diseases through the “microbe-gut-brain axis” (MGB) [15]. Han randomly divided 60 mice into control, MDD, and SCFAs groups in an experiment to investigate whether SCFAs exert antidepressant effects by regulating the composition of the intestinal flora and modulating the TLR4/MyD88/Nuclear Transcription Factor κB (NF-κB) inflammatory pathway in depressed mice, The 16S rRNA gene sequence was used to analyze the composition of the intestinal flora of mice, The activation of astrocytesin hippocampal tissue and the TLR4/MyD88/NF-κB inflammatory pathway was determined by immunofluorescence staining and Western blot. The protein expression levels of TLR4, MyD88, and NF-κB in mice in the MDD group were higher than those in the control group and the SCFAs group (all $P<0.05$). Conclusion: SCFAs can improve depressive-like behavior and decrease astrocyte activation in MDD mice, which may be related to the improvement of intestinal flora dysbiosis and down regulation of TLR4/MyD88/NF-κB pathway protein overexpression [16]. Sun found that modulation of acetic acid, propionic acid, and n-butyric acid improved MDD behavior in mice in a study on “modulation of short-chain fatty acids to improve MDD” [17]. The structure of the intestinal micro-ecosystem is altered, resulting in the proliferation of gram-negative bacteria and the weakening of the intestinal barrier protection; lipopolysaccharide (LPS) produced by the harmful bacteria enters the bloodstream through the intestinal wall and activates TLR4 to induce MDD behavior. The interaction between the ENS and the CNS is reciprocal. Abnormalities in the structure of the intestinal flora and its metabolites will affect the ENS through certain mechanisms to a certain extent, which in turn affects the CNS, but ultimately may lead to digestive disorders, such as GERD.

2.2.2 Immune and inflammatory response pathways

Disease Mechanisms: Due to the special biochemical environment of the distal esophagus, where Gram-negative bacteria are susceptible to parasitize. Microorganisms can also colonize the esophageal mucosa through swallowing and the gastroesophageal reflux pathway. In the case of a change in EM composition: (1) LPS from the shell of Gram-negative bacteria activates the NF-KB pathway via Toll-like receptor-4 (TLR-4) receptor, which promotes the release of interleukin-8 (IL-8), cyclo-oxygenase-2 (COX-2), and tumor necrosis factor-alpha (TNF-alpha), etc., and elicits inflammatory cascade responses; (2) LPS induces the release of prostaglandins (PGS) and nitric oxide (NO) from activated macrophages (MmI); Both of the above can cause changes in the morphology and function of smooth muscle cells resulting in decreased gastric emptying and relaxation of the LES, thus inducing GERD. Therapeutic aspects: SCFAs produced by intestinal flora catabolizing dietary fibers reduce pro-inflammatory factor secretion via the NF-KB signaling pathway. It can also down-regulate pro-inflammatory cytokines while promoting the expression of anti-inflammatory cells capable of inhibiting IL-6, IL-8, etc. Vitamin K and vitamin B synthesized by intestinal microbes have anti-inflammatory, antioxidant, immune-regulating, and DNA-repairing properties. Bacteriocins are ribosome-derived peptides produced by intestinal flora that can cross the "gut-blood barrier" to exert immunoregulatory, direct antimicrobial, and microbial compositional effects. Foreign studies have shown: “Prebiotics” and “probiotics” can improve some of the symptoms related to GERD, but the treatment of GERD by intestinal flora has not yet been widely used in clinical practice, and is still under constant research and exploration. In the future, scholars should continue to develop and explore the relevant theoretical system to provide a strong theoretical and practical basis for the treatment of GERD with intestinal flora [2][3][8]. Zhang in a study selected: 134 healthy individuals as control group and 128 patients with non-alcoholic fatty liver disease (NAFLD) as experimental group, using Pearson correlation analysis, the results showed that serum IL-17, IL-23, TLR4 levels of NAFLD patients were positively correlated with enterococci and Enterobacteriaceae ($P<0.05$), and with Lactobacillus, Bifidobacterium, Bacteroidetes, and B/E levels were negatively correlated ($P<0.05$). Conclusion: Abnormally elevated serum IL-17, IL-23, and TLR4 levels in patients with NAFLD are associated with the levels of Lactobacillus, Bifidobacterium, and Bacteroides immitis, and the regulation of intestinal flora is beneficial to improve the body's inflammatory response [18]. Animal models: (1) Bifidobacterium bifidum YIT10347 can adhere to the cells of the stomach wall and promote the production of mucin protein on the surface of the stomach wall, thus playing a certain protective effect on the gastric mucosa, and can regulate the NF-KB pathway signaling; (2) Lactobacillus johnsonii 1088 inhibits the secretion of gastric acid; (3) Lactobacillus casei LG21 increases pepsinogen (PGI) may promote gastric emptying; The above three pathways can maintain normal stomach function based on acid suppression and gastric protection to promote digestion, reduce the risk of gastroesophageal reflux, and help prevent inflammation [19]. Dysbiosis of the intestinal and esophageal flora results in the proliferation of Gram-negative bacteria, whose LPS can

induce inflammation through the pathways described above, including GERD.

Myofibroblasts (MMs) distributed in the GIT myofibroblasts are categorized as “classically activated” (pro-inflammatory, M1) and “alternatively activated” (anti-inflammatory, M2).When LPS is involved, or the inflammatory stress state produces γ-interferon (IFN-γ) stimulation promotes the birth of the M1 type, which secretes pro-inflammatory mediators IL-12, IL-6, tumor necrosis factor-α (TNF-α), IL-1β, etc., which can promote inflammatory responses. The M2 type is predominantly expressed under stable conditions, expressing genes such as Mrc1, Cd163, Retnla, etc., and can secrete anti-inflammatory factors such as IL-4 and IL-10, which can inhibit inflammatory response, promote healing and have protective effects. MMs can secrete “bone forming protein” (BMP2) and act on “BMP2 receptors” on enteric neurons to affect GIT motivation, and the interaction between intestinal flora and MMs may delay gastrointestinal emptying through BMP2 receptors [20][21][22][27]. LPS, IL-12, IL-18, IFN-γ, and IL-17A induce MMs to activate the expression of "inducible nitric oxide synthase" (iNOS), which produces an NO-mediated emergency oxidative response that affects the LES or damages Cajal's interstitial cells (ICCs), affecting GIT movement [23][24][25]. Xu found a correlation between changes in gut microbiota and inflammatory response: The number of Escherichia coli and Enterococci in the intestine of the patients was positively correlated with serum IL-6, IL-8, TNF-α and CRP, and negatively correlated with serum NO, while Bifidobacterium and Lactobacillus were opposite to the above results [26] (all $P<0.05$).In the study “Pientzehuang (PTH) ameliorates autoimmune hepatitis (AIH) through macrophage (MΦ)-intestinal flora interaction” by Liu et al. 40 mice were randomly divided into the dexamethasone (DXM) group, model group, normal group, and PTH group. In the experiment, DNA extraction and PCR amplification of mouse feces were performed to obtain base sequences to study the correlation between intestinal flora and M1/M2 and the effect of PTH on intestinal dysbiosis in AIH mice, as well as the detection of M1/M2 by flow cytometry and the detection of inflammatory mediators by ELISA. Results: PTH inhibited the expression of IL-12, TNF-α, and L-1β ($P<0.01$), increased the expression of IL-4, IL-10 ($P<0.01$), significantly ameliorated AIH, and up-regulated the expression of M2, down-regulated the expression of M1 ($P<0.01$), and ameliorated the imbalance of intestinal flora in AIH mice. Conclusion: Improvement of AIH by PTH is achieved by regulating M1/M2 through the interaction between MΦ gut flora [27]. Eosinophilic esophagitis (EoE) is an immune-mediated disease triggered by food antigens. Evidence suggests that the flora and the innate immune system are involved in the pathogenesis of EoE [41]. Elevated leukotriene B4 (LTB4) levels have also been found in patients with GERD, suggesting that LTB4 could be used as a novel marker for the diagnosis of GERD. Bacteria of the Enterobacteriaceae family are associated with GERD and may mediate esophageal mucosal inflammation and intestinal chemotaxis, and there is growing evidence that structural components, metabolites, and toxins of pathogenic and opportunistic bacteria may cause immune damage to the body. SCFAs, which mainly include acetate, propionate, and butyrate, have been shown to have immune-modulating, regulating colonic motility, and maintaining intestinal homeostasis [28]. Dysregulation of the microbial system is an important cause of immune and inflammatory responses. Maintaining a balanced flora in the body strengthens the protective barrier of the mucous membranes and reduces the production of pathogenic bacteria and harmful substances, which plays a role in preventing immune and inflammatory responses.

2.2.3 Microbial Fermentation Pathways

Intestinal fermentation of oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) to produce SCFA, methane (CH4), and hydrogen (H2) has been associated with increased GLP-1 production by L-cells, and the above mentioned fermentation products can increase the frequency of Transient Lower Esophageal Sphincter Relaxation (TLESR), and Small Intestinal Bacterial Overgrowth (SIBO) can also lead to excessive fermentation gas production, resulting in increased intra-abdominal pressure. Oral administration of oligosaccharides, as well as intracolonic infusion of oligosaccharides or SCFAs, reduces gastric tone by increasing YY peptide (PYY). GLP-1 and PYY can be released into the bloodstream to affect gastric emptying by inhibiting GIT motility and thus affecting TLESRs. acarbose can reverse the inhibitory effect of GLP-1 on gastric emptying. The reduction of gastric acid secretion by the use of proton pump inhibitors (PPIs) can cause changes in the microbiota of the GIT, leading to an increase in bacterial fermentation, which can lead to the development of GERD through the mechanisms described above [29][30][31][32]. In the study "Intestinal flora and GLP-1 levels in patients with MDD", Ma et al. divided 80 patients with MDD and 80 healthy patients into experimental and control groups, and detected GLP-1 levels by ELISA and bacterial flora by real-time fluorescence quantitative PCR.Results:GLP-1 levels were lower in the MDD group than in the control group (plasma $P<0.01$; feces $P<0.05$), fecal flora levels were lower in the MDD group than in the control group (both $P<0.05$), fecal GLP-1 levels were positively correlated with intestinal bifidobacteria and Lactobacillus spp. in the control group ($P<0.01$), and fecal GLP-1 levels were negatively correlated with the severity of the disease in the MDD group ($P<0.01$). Conclusion: In patients with MDD, GLP-1 levels are reduced and the relative levels of intestinal bifidobacteria and lactobacilli are decreased, and changes in the intestinal flora affect GLP-1 levels [33]. Probiotics may ameliorate the effects on intestinal motility due to small intestinal bacterial overgrowth [35]. Overseas studies have shown that a low FODMAP diet can improve reflux symptoms in people who also have irritable bowel syndrome (IBS) and GERD [43]. A decrease in beneficial bacteria and an increase in harmful bacteria in the intestinal tract leads to abnormalities in intestinal enzymes, which ultimately affects GIT and LES function and leads to the development of GERD symptoms.

2.2.4 Other pathways

Helicobacter pylori (HP) regulates the metabolism of gastrin and leptin, reduces gastric acid secretion, and is negatively associated with the risk of GERD. Studies have found that after eradication of H. pylori, the risk of GERD increases instead. Bifidobacterium bifidum and Bacillus fumigatus can prevent GERD by inhibiting potential pathogens. Probiotics

act on gastric mucosal receptors to increase gastric emptying, which can cause transient relaxation of the LES. Researchers found that 88% of GERD patients who took the prebiotic maltose-isomaltooligosaccharide (MIMO) for several weeks improved their reflux symptoms. In addition, intestinal dysbiosis causing constipation, IBS and inflammatory bowel disease (IBD) can lead to gastroesophageal reflux, so preventing certain diseases can play a role in preventing GERD [35]. Gan et al. selected 110 patients with RE in a randomized, double-blind, placebo-controlled trial and randomly assigned them to the placebo and probiotic groups (PPIs were used in both groups). Results: RE symptoms resolved earlier ($p<0.05$) and delayed relapse ($p<0.05$) in the probiotic group. CONCLUSION: The combination of Bifidobacterium animalis subspecies Lactobacillus helveticus MH-02 with PPI resulted in earlier relief of RE symptoms and delayed recurrence[36]. Gut flora is correlated with the pathogenesis of GERD, and efficacy can be enhanced by combination therapy with gut flora agents. Current research suggests that intestinal flora is associated with numerous diseases and that regulating intestinal flora can influence the development of GERD by preventing or alleviating certain diseases.

3. Links between Spleen and Stomach, GERD, and Intestinal Flora in Chinese Medicine

“The large intestine and small intestine are both part of the stomach, and are part of the stomach meridian of foot-yang-ming.” according to “The Miraculous Pivot - This Transmission.” “Plain question - Jue Lun” discusses: “The spleen assists the stomach to carry out its fluids. “Jingyue Complete Book - acid swallowing” says: “Acid swallowing and belching, delirium and excessive thinking, is because the disease is in the spleen and stomach also.” “General Treatise on the Etiology and Symptomsology" said that: “The person who drinks and accumulates food, by drinking too much water, the water stays between the spleen and stomach, the spleen gets dampness, then it can't transport and transform the water and grains, and people burp with the smell of undigested food, abdominal distension and fullness, and also high fever, or swallowing acid”. Plain question - Zhi Zhen Yao Da Lun, which states that “sweetness reaches the spleen first”. The Plain question- Zangqi Fa Shi Lun wrote that “Liver qi tends to go upward, and can be eased by sweet medicines.” Li Dongyuan's Theory of Spleen and Stomach: “Herbal medicines with sweet and warm properties can nourish the middle jiao and help the spleen yang to rise and develop. Chinese medicine has its own unique theoretical system and efficacy in the treatment of GERD, but its pharmacological mechanism still needs to be explored by related scholars. The spleen and stomach in TCM play an irreplaceable role in guiding the treatment of GERD, and spleen deficiency is at the core of this guiding theory. This article mainly discusses the aspect of “sweetness reaches the spleen”.

GERD belongs to the category of Chinese medicine such as ergonomics and acid reflux. Disease Mechanisms: Dysregulation of qi, resulting in gastric qi upward reversal, the treatment is to tonify the middle jiao and benefit the qi, and harmonize the stomach to lower the reversal, for example: the addition of tonifying the middle jiao and qi soup, which consists of most of the herbs with a sweet nature. Chen selected 92 patients with GERD and randomly divided them into experimental and control groups (both groups were given PPI and mosapride).To the experimental group: (Astragalus 20 g, Atractylodes macrocephala 12g, Pericarpium Citri Reticulatae 6g, Ascophyllum Vulgare 6g, Radix Bupleurum Chinense 10g, Radix Codonopsis Pilosulae 12g, Radix Glycyrrhiza Glabra 12g, Radix Angelicae Sinensis 6g, Rhizoma Dandelionis 6g, Calcined Ulmus Bone 20g, Rhizoma Luteinis 5g, Rhizoma Cyperus Rotundus 20g, Citrus Aurantium Lepidodendron 12g, Fructus Pseudomembranosus 12g, Fructus Semen Rhei 10g, Fructus Ziziphirophyllae 6g, Fructus Zingiberus Gingko 3g,200 mL, warm, once in the morning and once in the evening, 1 dose/day, 8 weeks of treatment.), Results: The effective rate of the experimental group was significantly higher than that of the control group ($P<0.05$). Conclusion: The addition of tonifying the middle jiao and qi soup can improve the efficacy of clinical routine treatment of GERD [37]. There is a correlation between intestinal flora and the spleen and stomach in Chinese medicine, and studies have found that spleen tonic medicines can regulate intestinal flora imbalance, such as tonifying the middle jiao and qi soup. Metabolism of intestinal flora can promote the efficacy of Chinese herbal medicines. In an animal experiment, Yu et al. used (Astragalus membranaceus 18g, Atractylodes macrocephala 9g, Pericarpium Citri Reticulatae 6g, Radix Panax Ginseng 9g, Ascophyllum Chinense 6g, Radix et Rhizoma Glycyrrhizae Praeparatae 9g, Radix Achyranthes bidentatae 6g, Radix Angelicae Sinensis 3g) in a spleen-deficiency model of mice. It was found that tonifying the middle jiao and qi soup could enhance the immunity and regulate the intestinal flora of spleen-deficient mice [38]. Codonopsis, Poria, Chinese yam, Rhizoma Atractylodis Macrocephalae, Astragalus not only can replenish the spleen, but also its active ingredient “Chinese medicine polysaccharide” and intestinal flora can promote the proliferation of intestinal flora, but also to produce energy. The “herbal polysaccharides” in Lizhong Soup, Ginseng Ling Bai Zhu Powder and Si Jun Zi Soup can improve the function of the digestive system by increasing the beneficial bacteria in the body [39]. Prebiotics can regulate the structure of intestinal flora, and herbal polysaccharides are a natural prebiotic. In the classics of Chinese medicine, it is written that “sweetness reaches the spleen”, and sweet herbs have a tonic effect, They have the function of spleen strengthening and regulation of intestinal flora that can promote the function of the digestive system, so there is a consistency between prebiotics and glycyrrhizaids in strengthening the spleen and regulating intestinal flora. At present, many scholars have carried out in-depth studies on the association between TCM and intestinal flora, and it is believed that the potential of TCM in this area will be explored in the future, and the relevant theoretical mechanisms will become clearer.

Repeated exposure to GIT and reflux causes esophageal barrier dysfunction and decreased levels of esophageal DNA repair enzymes, which promotes the progression of esophageal inflammation. Cranberry proanthocyanidins (C-PAC) have prebiotic activity and ameliorate reflux-induced dysbiosis, Regulation of bile acid metabolism and transport ultimately inhibits bile reflux-induced esophagitis through the TLR/NF-κB/TP53 pathway ($P<0.05$), and also improves the body's metabolism [39]. As part of the barrier protection mechanism, the colony has a role in

promoting IL-22 production by MΦ-stimulated “innate lymphoid cells (ILCs)”.MΦ enables “innate lymphocytes” to promote the secretion of “retinoic acid” and IL-10 by “degenerate cells” (DCs) via IL-1β, which are key to the differentiation of “regulatory B cell (Breg) and T cell (Treg) subpopulations”. Flora-produced SCFAs prevent mucosal inflammation by increasing the number of Tregs. In addition to this SCFAs affect Treg, intestinal homeostasis, epithelial integrity, mucosal dendritic cell (DC) biology, and IgA antibody responses through G protein-coupled receptors [42]. SIBO can lead to: fatty liver, pancreatitis, gallbladder disease, diabetes, and other digestive and metabolic disorders [44]. The intestinal flora promotes digestive system function in agreement with the spleen's mastery of transportation and digestion. The Miraculous Pivot - Shi Chuan “the spleen, the main for the guard” and the intestinal flora also plays a role in the body's immune mechanism, “sweet reaches the spleen, most of the sweet herbs to tonify the spleen contains ‘Chinese medicine polysaccharides’ that can promote the proliferation of intestinal flora. At present, there are few Chinese medicinal preparations for regulating intestinal flora, so we can explore the mechanism of Chinese medicines in regulating intestinal flora and create highly effective Chinese medicinal preparations for regulating intestinal flora, so as to give full play to the powerful advantages of traditional Chinese medicine and to benefit the clinic.

4. Conclusion

A growing body of research suggests that GIT flora promotes the development of esophageal disease by influencing local or systemic inflammatory responses. However, there is little data from relevant domestic and international studies that can identify the causal mechanisms. Future relevant research directions should focus on establishing on clinical cohort, based on esophageal diseases, comprehensive analysis of GI microorganisms, and establishment of relevant animal models [45]. This paper explores the correlation between intestinal flora and GERD mainly through the following associations: (1) Gut flora can influence the CNS via the gut-brain axis; (2) Dysbiosis of the intestinal flora can cause an immune-inflammatory response; (3) Effects of FODMAPs on digestive system dynamics through intestinal fermentation; (4) From the perspective of sweetness entering the spleen, discussed the close relationship between spleen and stomach function and intestinal flora and the influence of spleen and stomach on GERD in Chinese medicine, and suggested that in the future we can explore the preparation of Chinese medicine to regulate intestinal flora by using "Chinese herbal polysaccharides" and other active ingredients in Chinese medicine, so as to make up for the lack of current Chinese medicine in this regard. Intestinal flora and its metabolites have an irreplaceable role in the health of the organism, and are also the hotspot of the current research. In the future, their mechanism of action should be explored through a large number of experimental studies to provide strong evidence for the clinical treatment of GERD.

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