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Functional Dyspepsia: Recent Advances in Integrated Chinese and Western Medicine Therapeutics

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Abstract: ***Functional dyspepsia (FD) is a prevalent functional gastrointestinal disorder characterized by primary clinical manifestations such as postprandial fullness and early satiation. Its pathogenesis is complex. Contemporary medical research indicates that its primary mechanisms involve gastrointestinal motility dysfunction, visceral hypersensitivity, Helicobacter pylori (H. pylori) infection, and brain-gut axis dysregulation. Current therapeutic strategies primarily focus on prokinetic agents, acid suppression, neuromodulation, and H. pylori eradication. Traditional Chinese Medicine (TCM) posits that the core pathogenesis of FD lies in spleen-stomach disharmony. TCM treatment primarily encompasses pattern differentiation and treatment (bian zheng lun zhi) and characteristic TCM therapeutic modalities. Integrated Chinese and Western medicine therapy for FD demonstrates synergistic effects in clinical practice, achieving effective therapeutic outcomes. However, current research on FD within both medical paradigms still presents unresolved issues. Future studies necessitate elucidating the underlying mechanisms and optimizing diagnostic and therapeutic strategies.***

Keywords: Functional Dyspepsia, Etiology and Pathogenesis, Integrated Chinese and Western Medicine, Pattern Differentiation and Treatment (Bian Zheng Lun Zhi)**.**

1. Introduction

Functional dyspepsia (FD) is a prevalent clinical disorder of the digestive system, characterized by chronic dyspeptic symptoms including postprandial fullness, early satiation, epigastric pain, and epigastric burning sensation. It is classified as a functional gastrointestinal disorder (FGID) [1], typically unrelated to organic, systemic, or metabolic diseases. According to the Rome IV criteria, FD is categorized into two primary clinical subtypes: Postprandial Distress Syndrome (PDS), predominantly manifesting as meal-induced fullness and Epigastric Pain Syndrome (EPS), characterized by epigastric pain [2].In recent years, the global prevalence of FD has risen progressively. This condition substantially impairs patients' quality of life and work productivity, while concurrently consuming considerable healthcare resources.

The pathogenesis of functional dyspepsia (FD) remains incompletely elucidated. Contemporary medical management primarily focuses on prokinetic agents, acid suppression, neuromodulation, and Helicobacter pylori (H. pylori) eradication. While these interventions may alleviate clinical symptoms in the short term, long-term medication adherence remains suboptimal due to patient reluctance. Traditional Chinese Medicine (TCM) correlates the cardinal symptoms of FD with disorders such as "Wei Pi" (stomach stuffiness), "Pi Sai" (fullness obstruction), and "Wei Tong" (stomach pain). TCM pathogenesis attributes FD to the spleen-stomach system with involvement of the liver, employing therapeutic strategies centered on soothing liver qi stagnation and regulating qi to fortify the spleen. TCM exhibits distinct advantages in FD management through pattern differentiation and treatment (Bian Zheng Lun Zhi) tailored to specific etiologies and pathomechanisms, often yielding favorable clinical efficacy and prognosis. Integrated Chinese and Western medicine therapy synergistically leverages the strengths of both paradigms and has been validated as an effective clinical approach for FD. This review concise overviews the pathogenesis of FD from both TCM and Western medical perspectives and synthesizes recent advances in integrated therapeutic strategies for FD.

2. Pathogenesis

2.1 Western Medical Pathogenesis

Contemporary medical research indicates that the pathogenesis of functional dyspepsia (FD) primarily involves: Gastrointestinal motility dysfunction; Visceral hypersensitivity; Helicobacter pylori (H. pylori) infection; Abnormal gastric acid secretion; Duodenal low-grade inflammation; Brain-gut axis dysregulation; Gut microbial dysbiosis [3]. Current evidence suggests these pathophysiological mechanisms interact synergistically rather than acting independently. The development of FD represents a multifactorial process, with brain-gut axis dysfunction serving as the pivotal pathological mechanism underlying both FD onset and progression. This central pathway integrates signals from multiple contributing factors [4].

2.2 Traditional Chinese Medicine (TCM) Etiology and Pathogenesis

Traditional Chinese Medicine (TCM) classifies functional dyspepsia (FD) under "Wei Pi" (gastric stuffiness) or "Wei Wan Tong" (epigastric pain) based on symptom correspondence, as no direct disease equivalent exists in classical texts. Etiologically, TCM attributes FD primarily to emotional dysregulation, chronic fatigue, congenital deficiency, dietary irregularities, and pathogenic invasion. The disease locus centers on the stomach with close involvement of the liver and spleen. Initial manifestations typically present as excess patterns caused by cold congelation, food stagnation, qi stagnation, or

phlegm-dampness obstruction. Chronic progression leads to deficiency patterns or deficiency-excess complexes due to protracted pathogen retention depleting vital qi. Consequently, FD predominantly exhibits a root-deficiency with manifestation-excess pattern: spleen deficiency constitutes the root deficiency, while qi stagnation, food accumulation, phlegm-dampness retention, and blood stasis obstructing collaterals represent the excess manifestations. The core pathogenesis involves impaired spleen transport function and qi dynamic obstruction, ultimately causing failure of stomach qi descent [5].

3. Therapeutic Strategies

3.1 Western Medical Treatment

3.1.1 Prokinetic Agents

Prokinetic agents are first-line pharmacotherapy for postprandial distress syndrome (PDS) [6]. Commonly used agents include dopamine D_2 receptor antagonists, muscarinic receptor modulators, and 5-HT_4 receptor agonists. Dopamine D_2 antagonists (e.g., domperidone) enhance gastric emptying and promote peristalsis by blocking dopaminergic neurotransmission. 5-HT_4 receptor agonists such as mosapride improve esophageal peristalsis, gastrointestinal coordinated contractions, and proximal colonic emptying through 5-HT_4 receptor activation. Cisapride—a representative 5-HT_4 agonist—is clinically restricted due to significant cardiotoxic risks (QT prolongation), whereas mosapride is widely prescribed given its favorable safety profile. Acotiamide, a selective muscarinic M_1/M_2 receptor antagonist, exerts prokinetic effects by enhancing acetylcholine release at neuromuscular junctions. Clinical trials in Japanese cohorts and systematic reviews confirm its superiority over placebo in improving global FD/PDS symptoms [7].

3.1.2 Acid-Suppressing Agents

Clinically utilized acid-suppressing agents include histamine H_2-receptor antagonists (H_2RAs), proton pump inhibitors (PPIs), and potassium-competitive acid blockers (P-CABs). Although no direct evidence confirms gastric acid hypersecretion in functional dyspepsia (FD), studies report impaired duodenal acid clearance and duodenal hypersensitivity to acid infusion in FD pathophysiology. The American College of Gastroenterology/Canadian Association of Gastroenterology (ACG/CAG) guidelines recommend PPIs as first-line therapy for Helicobacter pylori-negative FD [8]. Commonly prescribed PPIs include rabeprazole and omeprazole. Compared to PPIs, H_2RAs demonstrate moderate acid suppression and inferior efficacy in controlling FD symptoms [9], establishing PPIs as preferred initial therapy. Current evidence regarding P-CAB efficacy in FD remains insufficient for robust clinical evaluation.

3.1.3 Neuromodulation Therapy

Recent evidence implicates brain-gut axis dysregulation as a pivotal pathomechanism in functional dyspepsia (FD), with growing clinical data linking FD to emotional disorders and somatization. Neuromodulatory agents encompass:

- Tricyclic antidepressants (TCAs)
- Tetracyclic antidepressants
- Antispasmodics
- Guanylate cyclase-C (GC-C) receptor agonists
- Serotonin receptor agonists/antagonists
- Selective serotonin reuptake inhibitors (SSRIs) [10].

Per ACG/CAG guidelines, TCAs are recommended for FD patients unresponsive to proton pump inhibitors (PPIs) and Helicobacter pylori eradication [8]. A meta-analysis demonstrated significant efficacy of TCAs for FD symptom management (RR=1.3; 95%CI1.1-1.6) [11], whereas the SSRI escitalopram showed no significant clinical improvement versus placebo (p=0.24).

The superior symptom remission rate with TCAs is attributed to their multi-target mechanisms affecting multiple neurotransmitter systems (norepinephrine, serotonin, histamine). However, this polypharmacology increases susceptibility to anticholinergic adverse effects (dry mouth, constipation, tachycardia) and cognitive impairment [12].

Notwithstanding, low-dose antidepressant therapy (e.g., amitriptyline 10-25 mg/day) represents an effective option for refractory FD, balancing symptom control (NNT=8), patient satisfaction, and adverse event minimization [13].

3.1.4 Helicobacter pylori Eradication

Although conclusive evidence establishing Helicobacter pylori (Hp) as a direct etiological agent of functional dyspepsia (FD) remains elusive, multiple studies demonstrate that Hp infection elevates calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and substance P levels, thereby delaying gastric emptying and impairing gastric accommodation [14]. Clinical observations confirm that eradication therapy in Hp-positive FD patients significantly improves clinical symptoms and enhances therapeutic outcomes [15].

3.1.5 Histamine Receptor Antagonists

Histamine receptor antagonists have emerged as a potential therapeutic approach for functional dyspepsia (FD). This rationale stems from duodenal inflammation—a key pathophysiological mechanism in FD—characterized by aberrant eosinophil activation and a marked increase in mast cell density within the duodenal mucosa [16]. Histamine receptor antagonists demonstrate dual mechanistic actions: reducing eosinophil infiltration and alleviating mucosal inflammation. Preliminary clinical evidence indicates their capacity to ameliorate FD symptoms [17], though further large-scale trials are warranted to establish therapeutic efficacy.

3.2 Traditional Chinese Medicine (TCM) Therapy

3.2.1 Pattern Differentiation and Treatment (Bian Zheng Lun Zhi)

Per the 2023 Chinese Expert Consensus on TCM Diagnosis and Treatment of Functional Dyspepsia, FD is classified into five patterns: spleen deficiency with qi stagnation,

liver-stomach disharmony, spleen-stomach dampness-heat, spleen-stomach deficiency-cold, and cold-heat complex [18]. Core therapeutic principles focus on regulating qi dynamics and fortifying the spleen with qi-modulating herbs, utilizing modified classical formulas: Xiangsha Liujunzi Tang (Costus-Amomum Six Gentlemen Decoction) for spleen deficiency, Chaihu Shugan San (Bupleurum Liver-Soothing Powder) for liver-stomach disharmony, Lian Po Yin (Coptis-Magnolia Beverage) for dampness-heat, Lizhong Wan (Regulating the Middle Pill) for deficiency-cold, and Banxia Xiexin Tang (Pinellia Heart-Draining Decoction) for cold-heat complex. Clinical evidence demonstrates significant efficacy: Liu et al.'s RCT (n=60 PDS patients) showed modified Xiangsha Liujunzi Tang outperformed mosapride in alleviating postprandial fullness, improving quality of life, and reducing anxiety-depression scores [19]; meta-analyses confirm Chaihu Shugan San enhances gastric emptying (scintigraphy T½ Δ18min) and symptom relief [20]; Qi et al. (n=70) reported superior efficacy of modified Lian Po Yin versus mosapride, particularly for epigastric distension and sticky taste [21]; Wang et al. demonstrated modified Lizhong Wan's higher symptom resolution versus mosapride ± PPI in deficiency-cold FD [22]; Zeng et al.'s RCT (n=100) found Banxia Xiexin Tang achieved better clinical response than Western drugs for cold-heat complex FD [23].

Beyond classical formulas, empirical prescriptions developed by TCM practitioners demonstrate significant clinical efficacy in functional dyspepsia (FD) management. Yu et al. [24] reported superior outcomes with the self-formulated Ganmai Shunqi Decoction (Lilium brownii 40g, Toosendan fruit 15g, Lindera root 15g, Litchi seed 15g, honey-fried Glycyrrhiza 6g, light wheat 30g, jujube 10g) versus omeprazole + domperidone in liver-stomach disharmony FD. Li et al. [25] documented significantly higher efficacy of the empirical Shuyun Huazhi Decoction (Bupleurum chinense 6g, Citrus aurantium 12g, Bergamot 10g, Amomum villosum 5g, ginger-processed Pinellia 10g, Poria 12g, Glycyrrhiza 5g, Dioscorea 12g, Atractylodes macrocephala 6g, Magnolia bark 6g, Lindera 10g, fried rice sprout 15g, fried Gallus gallus endothelium 10g) compared to mosapride in spleen deficiency-qi stagnation PDS, with additional benefits in psychological symptom relief and recurrence prevention. Sun et al. [26] observed markedly enhanced efficacy of the empirical Liwei Decoction (Citrus aurantium 20g, Codonopsis 20g, Atractylodes 25g, Bupleurum 25g, Salvia miltiorrhiza 20g, ginger-processed Pinellia 12g, Citrus reticulata peel 20g, Paeonia alba 12g, Amomum villosum 10g, honey-fried Glycyrrhiza 20g) versus domperidone in liver depression-spleen deficiency FD (96.3% vs. 78.6% response rate, $p<0.01$), demonstrating significant improvements in both gastrointestinal symptoms and anxiety-depression scales. Collectively, pattern-differentiated TCM therapy demonstrates substantial efficacy in FD management, though limitations persist regarding incompletely elucidated mechanisms and suboptimal response in certain patient subsets.

3.2.2 Specialized TCM Therapies

Non-pharmacological TCM modalities demonstrate significant efficacy in functional dyspepsia (FD) management. Chen et al. [27] reported superior outcomes with acupuncture (core points: Zhongwan [CV12], Tianshu [ST25], Zusanli [ST36] plus pattern-specific adjuncts) versus domperidone (97.44% vs. 79.49% response rate, $p<0.05$) in 78 FD patients. Guo et al. [28] documented a 21.02% higher efficacy with warm-needling moxibustion at Qihai [CV6], Guanyuan [CV4], and bilateral Shenshu [BL23] compared to mosapride in deficiency-cold FD ($p<0.01$), particularly for cold-related symptoms and quality of life improvement. Yang et al. [29] demonstrated a hierarchical efficacy gradient in 120 liver-stomach disharmony FD patients: combined herbal patch application (Zhongwan [CV12], Shenque [CV8]) + wax therapy (40-45°C abdominal) + omeprazole (93.3%) > patches alone + omeprazole (73.3%) > wax therapy alone + omeprazole (66.7%) > omeprazole monotherapy (50.0%) ($p<0.01$), confirming synergistic benefits of integrated TCM therapies. Mechanistic studies reveal tuina (therapeutic massage) at key points like Zusanli [ST30] regulates gastrointestinal myoelectrical activity and enhances smooth muscle motility [30]; specialized techniques (e.g., abdominal vibration) elevate serum motilin and gastrin levels, improving gastric emptying. Additionally, tuina modulates brain-gut axis signaling, achieving high clinical response rates (typically>85%) that further improve when combined with pharmacotherapy. Emerging modalities including auricular acupuncture, herbal fomentation, and acupoint catgut embedding also show promising therapeutic potential for FD.

3.3 Integrated Chinese and Western Medicine Therapy

Integrated Chinese-Western therapy demonstrates superior efficacy in functional dyspepsia (FD) management by synergizing Western pharmacotherapy with TCM pattern differentiation. Shi et al. [31] reported significantly enhanced outcomes with itopride hydrochloride + Linggui Zhugan Decoction versus itopride monotherapy (94.44%) in 180 Rome IV-diagnosed FD patients, with notable improvements in gastrointestinal motility and quality of life. Deng and Peng [32] documented reduced adverse reactions and lower recurrence rates with Deanxit + Chaihu Shugan San versus prokinetics/acid suppressants in liver-stomach qi stagnation FD. Zhang [33] et al. observed significantly higher efficacy of domperidone + Pingwei Wendan Decoction versus domperidone alone, demonstrating advantages in gastric emptying, gastrointestinal hormone regulation, and reduced relapse. Yu and Tang [34] demonstrated comprehensive benefits of modified Xiangsha Yangwei Decoction (containing Magnolia officinalis, Lycium barbarum, Aucklandia lappa, etc.) + flupentixol/melitracen + mosapride versus Western drugs alone in 100 FD patients, with superior symptom resolution, overall response, and anxiety-depression improvement Collectively, integrated therapy offers enhanced clinical efficacy, favorable safety profiles, sustained symptom remission, and improved quality of life through multi-target modulation.

4. Conclusion

Functional dyspepsia (FD) represents a chronic relapsing-remitting functional gastrointestinal disorder characterized by complex, incompletely elucidated pathogenesis within both biomedical and Traditional Chinese Medicine (TCM) frameworks. Contemporary Western management relies primarily on symptomatic approaches—

prokinetic agents, acid suppression, neuromodulation, and Helicobacter pylori eradication—yet faces significant limitations: (1) high recurrence rates and adverse effects with long-term pharmacotherapy; (2) suboptimal efficacy in refractory FD; (3) absence of disease-modifying agents, necessitating polypharmacy due to symptom overlap with other digestive disorders.

Conversely, TCM demonstrates therapeutic advantages for FD through pattern differentiation (Bian Zheng Lun Zhi), delivering personalized interventions targeting both root causes (e.g., spleen deficiency) and symptomatic manifestations. Nevertheless, TCM research confronts methodological challenges: (1) insufficient statistical power in underpowered clinical trials; (2) heterogeneity in diagnostic pattern classification and treatment protocols; (3) predominant reliance on clinical studies without validated preclinical models.

Future research should prioritize elucidating the synergistic mechanisms of integrated Chinese-Western medicine, addressing existing limitations through rigorously designed trials and mechanistic studies. Optimizing this combinatorial approach will establish evidence-based, multidimensional therapeutic strategies that enhance clinical outcomes for FD patients while minimizing treatment burdens.

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