

Efficacy and safety of *Aurantii Fructus Immaturus* flavonoid Tablets vs. domperidone for functional dyspepsia: a multicenter, double-blind, double-dummy, randomized controlled phase III trial

M. Wei¹, Y. Chai², H. Shen³, M. Du⁴, X. Zhou³, T. Liu⁵, X. Yang⁶, S. Li⁷, J. Sun⁷, Y. Ge⁸

(1) Department of Traditional Chinese Medicine, Jiangsu Provincial Hospital, Nanjing, China; (2) GCP center of Jiangsu Province Hospital, Nanjing, China; (3) Department of Gastroenterology, Jiangsu Province Hospital of Traditional Chinese Medicine, Nanjing, China; (4) Department of Nuclear Medicine, Jiangsu Province Hospital of Traditional Chinese Medicine, Nanjing, China; (5) Department of Liver, Spleen and Stomach Diseases, Affiliated Hospital of Changchun University of Traditional Chinese Medicine, Changchun, China; (6) Department of Hepatobiliary, Spleen and Stomach, Affiliated Hospital of Henan Academy of Traditional Chinese Medicine, Zhengzhou, China; (7) Department of Traditional Chinese Medicine, The First Hospital of Shanxi Medical University, Taiyuan, China; (8) Department of Gastroenterology, Guangdong Second Hospital of Traditional Chinese Medicine, Guangzhou, China.

Abstract

Background: The clinical management of functional dyspepsia (FD) is challenging. This study evaluated the efficacy and safety of *Aurantii Fructus Immaturus* flavonoid (AFIF) tablets vs. domperidone for FD.

Methods: This multicenter, randomized, double-blind, double-dummy, positive-controlled trial recruited FD patients, who were randomized 1:1 to the AFIF (AFIF and domperidone placebo) and domperidone (domperidone and AFIF placebo) groups. The primary endpoint was the rate of disappearance of all four FD symptoms (postprandial feeling of fullness, early satiety, upper abdominal pain, and upper abdominal burning sensation) after 4 treatment weeks.

Results: Totally 120 and 119 patients were included in the AFIF and domperidone groups, respectively. The rates of disappearance of all four symptoms after 4 treatment weeks were 28.33% and 31.93% in the AFIF and domperidone groups, respectively ($p=0.5748$). The rate of disappearance of all four symptoms 4 weeks after treatment discontinuation was significantly higher in the AFIF (21.05%) compared with the domperidone group (4.39%, $p=0.0002$). The gastric emptying rates 2h after a meal were significantly increased in both AFIF (7.58%, $p<0.0001$) and domperidone (6.95%, $p=0.0121$) groups versus baseline, without a significant between-group difference ($p=0.8457$). Twenty-two (1 moderate) and 43 (3 moderate) adverse events occurred in the AFIF (19.17%) and domperidone (36.13%) groups, respectively.

Conclusion: The efficacy of AFIF tablets is similar to that of domperidone after 4 treatment weeks, while AFIF tablets may have a better safety profile than domperidone. Additionally, AFIF tablets have a significant advantage over domperidone in the rate of symptom disappearance 4 weeks after treatment discontinuation. (*Acta gastroenterol. belg.*, 2024, 87, 484-493).

Keywords: disappearance of symptoms, gastric emptying, traditional Chinese medicine.

Introduction

Disorders of gut-brain interaction (DGBI), previously known as functional gastrointestinal disorders, include a broad range of digestive symptoms in the absence of organic lesion or definite etiology, associated with significant decrease in patient's quality of life and increase in health care use (1). Functional dyspepsia (FD) is a common DGBI with an impaired barrier function and immune activation focused in duodenum, and symptoms that include postprandial fullness, early satiety, epigastric pain, epigastric burning, sometimes aggravated to

nausea, vomiting or heartburn (2-4). Due to differences in the definition of FD, the changes in its prevalence over the years is hard to track (3,5), but according to the most recent systematic review it is currently affecting about 8% of the global population (6). Symptoms of FD are often severe enough to interfere with daily activities of patients and, although pathophysiological mechanisms are still not fully understood, the search for effective treatment strategies is ongoing.

Most FD treatment modalities are symptomatic, with no curative treatment available and symptom relief periods often very short (2,7,8). Moreover, conventional proton pump inhibitors (PPIs) cause various adverse effects, including elevated risk of intestinal infection, small intestinal bacterial overgrowth, and nutrient malabsorption (9,10). Increasing gastric and small intestinal motility with domperidone could promote gastric emptying and enhance gastroduodenal coordination, but carries a risk of sudden cardiac death (11,12) and should be used with caution (13). Recent studies note that some neuromodulators have a promising efficacy in FD, but conclusive evidence is lacking (14).

Traditional Chinese Medicine used the medical extract of *Aurantii Fructus Immaturus* for the treatment of FD in clinical practice for more than 2,000 years, with recorded safety and efficacy (15,16). The main components of *Aurantii Fructus Immaturus* that act in the gastrointestinal system are flavonoids, demonstrating antioxidant, analgesic, and anti-inflammatory effects along with safe preclinical and clinical profiles (17,18). The mechanism of action of *Aurantii Fructus Immaturus* flavonoids (AFIF) appears to involve nitric oxide synthase (NOS) regulation, potentially resulting in elevated cyclic Guanosine Monophosphate (cGMP) and Protein Kinase G (PKG) amounts, as well as reduced intracellular

Correspondence to: Yi Chai, 300 Guangzhou Road, Nanjing, China.
Email: littlechaiyi1@163.com

Submission date: 05/07/2024

Acceptance date: 21/10/2024

Ca²⁺ levels in smooth muscle (18,19), which might serve to enhance motility in safer ways than domperidone. A previous randomized controlled study of 60 patients reported significant advantages in the control of FD symptoms by AFIF compared to placebo, as well as a good safety profile (20). Still, AFIF has not yet been compared with other treatments, and its applicability in FD management needs to be discussed.

Therefore, this study aimed to evaluate the safety and efficacy of AFIF tablets vs. domperidone in FD treatment. The results could provide new management options for an incurable condition that affects the quality of life of numerous individuals.

Methods

Study design, ethical considerations, and participants

This multicenter, randomized, double-blind, double-dummy, positive-controlled phase III clinical trial recruited FD patients treated at the outpatient clinics of six research centers ([Supplementary Table S1](#)) across China, including Nanjing, Jiangsu; Changchun, Jilin; Zhengzhou, Henan; Taiyuan, Shanxi; and Guangzhou, Guangdong from January 2013 to February 2014. Delays in data disclosure were due to self-reviews requested by regulators. This trial had approval from the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University as the lead center (Ethical approval #2013-MD-034). All patients provided signed informed consent. The study followed the tenets of the Declaration of Helsinki and its amendments as well as Good Clinical Practices. The trial was registered with chictr.org.cn (ChiCTR2400083076).

Inclusion criteria were: 1) 18-65 years old males or females; 2) FD diagnosis according to the Rome III criteria (detailed explanation in the Discussion section); 3) gastric motility drugs, gastric mucosal protective agents, and antacids stopped 4 weeks before enrollment. Exclusion criteria were: 1) esophagitis, atrophic gastritis, gastroduodenal ulcers, erosion, bleeding, tumors, or other organic diseases; 2) liver, gallbladder, or pancreas organic diseases; 3) diabetes, kidney disease, connective tissue disease, or mental illness; 4) serious heart, brain, lung, kidney, hematopoietic system, or endocrine system diseases; 5) a history of abdominal surgery; 6) renal insufficiency, defined as serum creatinine levels above the upper limit of normal; 7) liver insufficiency, defined as aspartate transaminase or/and alanine transaminase 1.5 times the respective upper limit of normal; 8) pregnancy or lactation; 9) participation in another clinical trial within 3 months before enrollment.

Randomization and blinding

Randomization was performed by the stratified block randomization method, with research center as the stratification factor and a block size of four. Statistical

experts from the Peking University Clinical Research Institute generated and preserved a random number table with SAS 9.1 (SAS Institute, Cary, NC, USA). The patients were randomized 1:1 to the AFIF and domperidone groups and administered the corresponding drug. Each patient also received the active-matched placebo (Jiangxi Qingfeng Pharmaceutical Co., Ltd) that was similar with the active drug in packaging, smell, and taste. Drug administration was facilitated via a consecutive numbering system, enhancing allocation concealment and further reinforcing the blinded nature of the study. All patients and onsite study members remained blinded to treatment allocation until statistical analyses were completed unless a patient experienced serious adverse events (SAEs) or required urgent resuscitation.

Interventions

Patients in the AFIF group took three AFIF tablets (Jiangxi Qingfeng Pharmaceutical Co., Ltd) (previously named *Aolanti Weikang Tablets* and renamed AFIF tablets with approval from the Chinese Pharmacopoeia Commission) per time (0.29 g/tablet) and one domperidone placebo tablet (10 mg/tablet), with warm water 30 min before meal, three times per day for 4 weeks. Patients in the domperidone group took three AFIF placebo tablets per time (0.29 g/tablet) and one domperidone tablet (Xian Janssen Pharmaceutical) (10 mg/tablet), with the same frequency and timing. Upon allocation of all investigational drugs to respective research units according to the numbers provided by the Clinical Research Institute of Peking University, principal investigators at various sites designated specific personnel to assume sole responsibility for the secure storage of these drugs in designated cabinets. The investigator in charge of drug dispensation, upon confirming a patient's eligibility, assigned a drug number in accordance with the order of visit.

Concomitant use of other gastric motility drugs, gastric mucosal protective agents, Proton Pump Inhibitors (PPIs), antacids, antidepressants/neuromodulators, or other Chinese or Western medicine drugs that may affect evaluation was prohibited.

Assessments

Baseline data were collected at enrollment, including demographic indexes, TCM symptoms, and clinical symptoms. Routine laboratory tests and electrocardiography were performed. Gastric emptying was measured by radionuclide imaging. Follow-up visits were performed once weekly during the treatment period. Drugs for 1 week were distributed at each visit, and the remaining drugs of the previous week were collected. Concomitant medications were recorded, and the detected symptoms and signs were recorded and scored at each visit. The tests and symptom evaluation were repeated 4 weeks after treatment discontinuation.

AEs were recorded during the study, and their severity was evaluated as no discomfort (0 point), mild discomfort (1 point), moderate discomfort (2 points), and severe discomfort (3 points). AEs were recorded for up to 8 weeks after the first study drug dosing.

Endpoints

The primary endpoint was the rate of disappearance for all four FD symptoms, including postprandial feeling of fullness, early satiety, upper abdomen burning sensation and pain (21), after 4 treatment weeks.

Secondary endpoints included the rate of disappearance of each symptom and gastric emptying function after 4 treatment weeks, as well as the rate of disappearance of all four FD symptoms and the rate of disappearance of each symptom 4 weeks after treatment discontinuation. Solid gastric emptying function was assessed with ^{99m}Tc-DTPA as a tracer by Single-Photon Emission Computed Tomography (SPECT) (SKYLight, Philips), with a focus on gastric emptying rate 2 h after meal and gastric half-emptying time.

Safety indicators included treatment-emergent AEs (TEAEs), serious AEs (SAEs), adverse drug reactions (ADRs), serious treatment-related AEs (STRAEs), and AEs and ADRs resulting in treatment discontinuation. The data management process is described in [Supplementary Material Text 1](#).

Sample size

According to previous clinical experience, the rate of disappearance of all four FD symptoms after 4 weeks of treatment with domperidone approximates 20%. It was estimated that the rate of disappearance of all four FD symptoms in the AFIF group after 4 treatment weeks would be at least 35%. With $\alpha=0.05$, a power (1- β) of

0.70, 1:1 randomization, and two-sided tests, the required sample size for each group was 109 patients, i.e. 218 in total. Considering a dropout rate of 10%, at least 120 patients were needed per group, for a total of 240.

Statistical analysis

Efficacy analysis was based on the full analysis set (FAS), which included all patients after randomization. In the FAS, missing values resulting from patient dropout were addressed by the Last Observation Carried Forward (LOCF) method, in which subsequent missed visit points were replaced by the last available measurements. For complete cases with intermediate missing values, the most recent non-missing data point was carried forward for the final estimation. A sensitivity analysis was carried out in the per-protocol set (PPS), which included patients who fully complied with the protocol and completed all required tests with available data. In the PSS, missing data were not carried forward or replaced. Safety analysis used the safety set (SS), defined as all patients administered at least one dose of the study drug.

SAS 9.4 (SAS Institute, Cary, NY, USA) was used for data analysis. Continuous data with normal distribution were reported as mean $\pm$ standard deviation (SD) and compared by the Student's t-test; those with skewed distribution were presented as median and interquartile range (IQR), and compared by the Mann-Whitney U-test. Categorical data were reported as n (%) and compared by the chi-squared test or Fisher's exact test. The normal approximation method was applied to determine differences in disappearance rates (AFIF group – domperidone group) and the corresponding two-sided 95% confidence intervals (CIs). Descriptive analyses were performed for safety events. Two-sided $P<0.05$ was considered statistically significant.

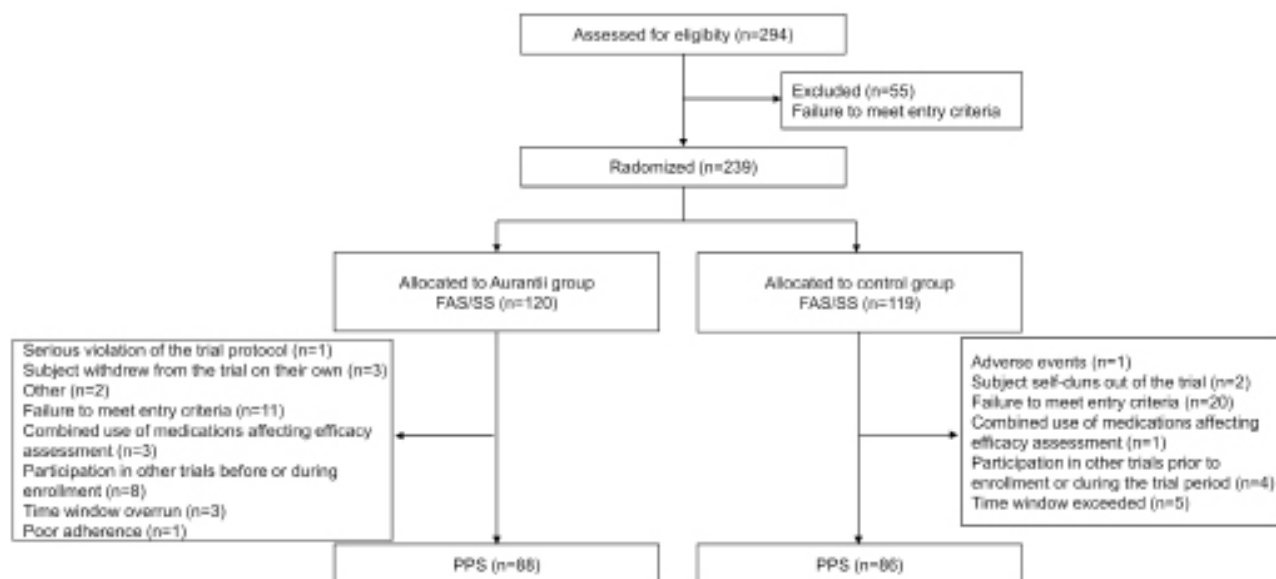


Fig. 1. — Study flowchart. FAS: full analysis set; PPS: per-protocol set; SS: safety set.

Table 1. — Baseline characteristics

	AFIF group (n=120)	Domperidone group (n=119)	p
Age, median (IQR)	42.00 (28.00,50.00)	45.00 (30.00,52.00)	0.4154
Sex (female), n (%)	80 (66.67)	85 (71.43)	0.4260
Height, median (IQR)	163.50 (160.00,170.50)	162.00 (160.00,169.00)	0.1074
Weight (kg), median (IQR)	60.00 (52.00,70.00)	60.00 (52.00,67.00)	0.3725
Duration of FD (month), median (IQR)	12.60 (9.10,34.75)	13.90 (8.50,37.20)	0.7384
History of Western medicine, n (%)	31 (25.83)	35 (29.41)	0.5651
History of Chinese medicine, n (%)	19 (15.83)	22 (18.49)	0.6107
Complication, n (%)	37 (30.83)	52 (43.70)	0.0452
History of smoking, n (%)	19 (15.83)	16 (13.45)	0.7150
History of drug allergies, n (%)	6 (5.00)	1 (0.84)	0.1195
Postprandial distension score, n (%)			
0	3 (2.50)	0	0.2843
1	13 (10.83)	21 (17.65)	
2	63 (52.50)	64 (53.78)	
3	41 (34.17)	34 (28.57)	
Early satiety score, n (%)			
0	7 (5.83)	5 (4.20)	0.9976
1	31 (25.83)	31 (26.05)	
2	60 (50.00)	64 (53.78)	
3	22 (18.33)	19 (15.97)	
Epigastric burning score, n (%)			0.9802
0	14 (11.67)	19 (15.97)	
1	51 (42.50)	44 (36.97)	
2	42 (35.00)	40 (33.61)	
3	13 (10.83)	16 (13.45)	
Epigastric pain VAS score, median (IQR)	4.00 (2.45,5.00)	4.00 (3.00,5.50)	0.0813
2h GER (%), median (IQR)	50.00 (34.00,66.10)	46.00 (34.00,62.00)	0.4937
GET/2 (h), median (IQR)	2.06 (1.57,2.80)	2.24 (1.60,2.87)	0.2397
TCM syndrome			0.4101
Liver-stomach disharmony	41 (34.17)	38 (31.93)	
Damp heat of spleen and stomach	21 (17.50)	25 (21.01)	
Retention of food and drink	20 (16.67)	12 (10.08)	
Deficiency of spleen and stomach	38 (31.67)	44 (36.97)	
Clinical symptoms			0.2063
Postprandial distress syndrome	36 (30.00)	27 (22.69)	
Epigastric pain syndrome	27 (22.50)	22 (18.49)	
Complex symptom	57 (47.50)	70 (58.82)	
AFIF: <i>Aurantii Fructus Immaturus</i> flavonoid; IQR: interquartile range; FD: functional dyspepsia; VAS: visual analogue scale; GER: gastroesophageal reflux; GET/2: gastric semiempty time; TCM: traditional Chinese medicine.			

Results

Baseline patient characteristics

This study screened 294 FD patients, and 239 patients were randomized, of whom 120 and 119 were assigned to the AFIF and domperidone groups, respectively (Fig. 1). Table 1 presents the baseline patient characteristics. The recruitment of the first patient occurred on April 24, 2013, and the data-cutoff date was February 2014.

Symptom disappearance rates

In the FAS, the rates of disappearance of all four FD symptoms after 4 treatment weeks were 28.33% and 31.93% in the AFIF and domperidone groups, respectively, indicating a difference (AFIF group – domperidone group) of -3.60% (95%CI: -15.23% to 8.03%; $p=0.5748$) (Table 2). The PPS had consistent data, with 29.55% and 32.94% in the AFIF and domperidone groups, respectively (a difference of -3.39%, 95%CI: -17.21 to 10.41%; $p=0.7430$).

In the FAS, the rates of disappearance of all four FD symptoms 4 weeks after treatment discontinuation were 21.05% and 4.39% in the AFIF and domperidone groups, respectively, indicating a difference (AFIF group – domperidone group) of 16.66% (95%CI: 8.29-25.04%; $p=0.0002$) (Table 2). The PPS and FAS had consistent findings. The rates of disappearance of all four FD symptoms at each visit are shown in Fig. 2A.

In the FAS, from the first treatment week to the fourth, the rates of disappearance of the four individual FD symptoms in the AFIF and domperidone groups gradually increased (Fig. 2B-E). The rates of disappearance between the AFIF and domperidone groups were similar for postprandial feeling of fullness (40.17% vs. 44.54%), early satiety (53.98% vs. 51.75%), upper abdominal burning sensation (64.15% vs. 61.00%), and upper abdominal pain (40.17% vs. 42.86%) (all $p>0.05$, except for the rate of disappearance of upper abdominal pain after 1 week of treatment (8.55% vs. 2.52%, $p=0.0493$).

After treatment discontinuation, the rates of disappearance of the four individual FD symptoms decreased slightly and significantly in the AFIF and

domperidone groups, respectively. The PPS and FAS had consistent results. Compared with the domperidone group, the AFIF group showed higher disappearance rates 4 weeks after treatment discontinuation regarding postprandial feeling of fullness (29.73% vs. 8.77%; 95%CI for the difference, 10.99%-30.92% [$p=0.0001$]), early satiety (37.96% vs. 16.36%; 95%CI for the difference, 10.13%-33.07% [$p=0.0004$]), upper abdominal burning sensation (37.62% vs. 17.53%; 95%CI for the difference, 7.99%-32.20% [$p=0.0024$]), and upper abdominal pain (32.43% vs. 11.40%; 95%CI for the difference, 10.55%-31.51% [$p=0.0002$]). The PPS and FAS had consistent results.

Gastric emptying rates 2 h after meal and gastric half-emptying times

In the FAS, the gastric emptying rate 2 h after meal ($57.76\pm18.47\%$) in the AFIF group after 4 treatment weeks increased by 7.58% versus baseline ($49.83\pm19.56\%$) (within group $p<0.0001$). The gastric emptying rate 2 h after meal ($53.75\pm22.69\%$) in the domperidone group only increased by 6.95% versus baseline ($47.21\pm21.68\%$, within group $p=0.0121$). The PPS and FAS had consistent results. The differences in gastric emptying rate between the two groups before and after treatment were not significant (FAS, $p=0.8457$; PPS, $p=0.6204$).

In the FAS, gastric half-emptying time in the AFIF group after 4 treatment weeks (1.99 ± 1.18 h) was shortened by 0.20 h versus baseline (2.21 ± 0.87 h, within group $p=0.1725$), while gastric half-emptying time in the domperidone group after 4 treatment weeks (2.37 ± 2.34 h) was shortened by 0.12 h versus baseline (2.46 ± 1.38 h, within group $p=0.6847$). The PPS and FAS had consistent trends (Table 2). The differences between the two groups in gastric half-emptying time before and after treatment were not statistically significant (FAS, $p=0.8108$; PPS, $p=0.8860$).

Subgroup analyses

In the FAS, there were no significant differences in the rates of disappearance of all four symptoms after 4 treatment weeks in various subgroups (all $p>0.05$) (Fig. 3A). The PPS and FAS had consistent trends.

In the FAS, the rates of disappearance of all four FD symptoms 4 weeks after treatment discontinuation were significantly higher in the AFIF group compared with

Table 2. — Efficacy

	AFIF group	Domperidone group	Difference	p
Disappearance rate of 4 symptoms after 4 treatment weeks (%), (95%CI)	28.33 (20.27,36.40)	31.93 (23.56,40.31)	-3.60 (-15.23,8.03)	0.5748
Disappearance rate of 4 symptoms 4 weeks after discontinuing treatment (%), (95%CI)	21.05 (13.57,28.54)	4.39 (0.63,8.15)	16.66 (8.29,25.04)	0.0002
Increased gastric emptying rate 2 hours after meal at week 4 week (%), mean $\pm$ SD	7.58 $\pm$ 13.25	6.95 $\pm$ 19.46	-	0.8457
Shortened gastric half-emptying time at week 4 (h), mean $\pm$ SD	0.20 $\pm$ 1.09	0.12 $\pm$ 2.19	-	0.8108

AFIF: *Aurantii Fructus Immaturus* flavonoid; CI: Confidence interval; SD: Standard deviation.

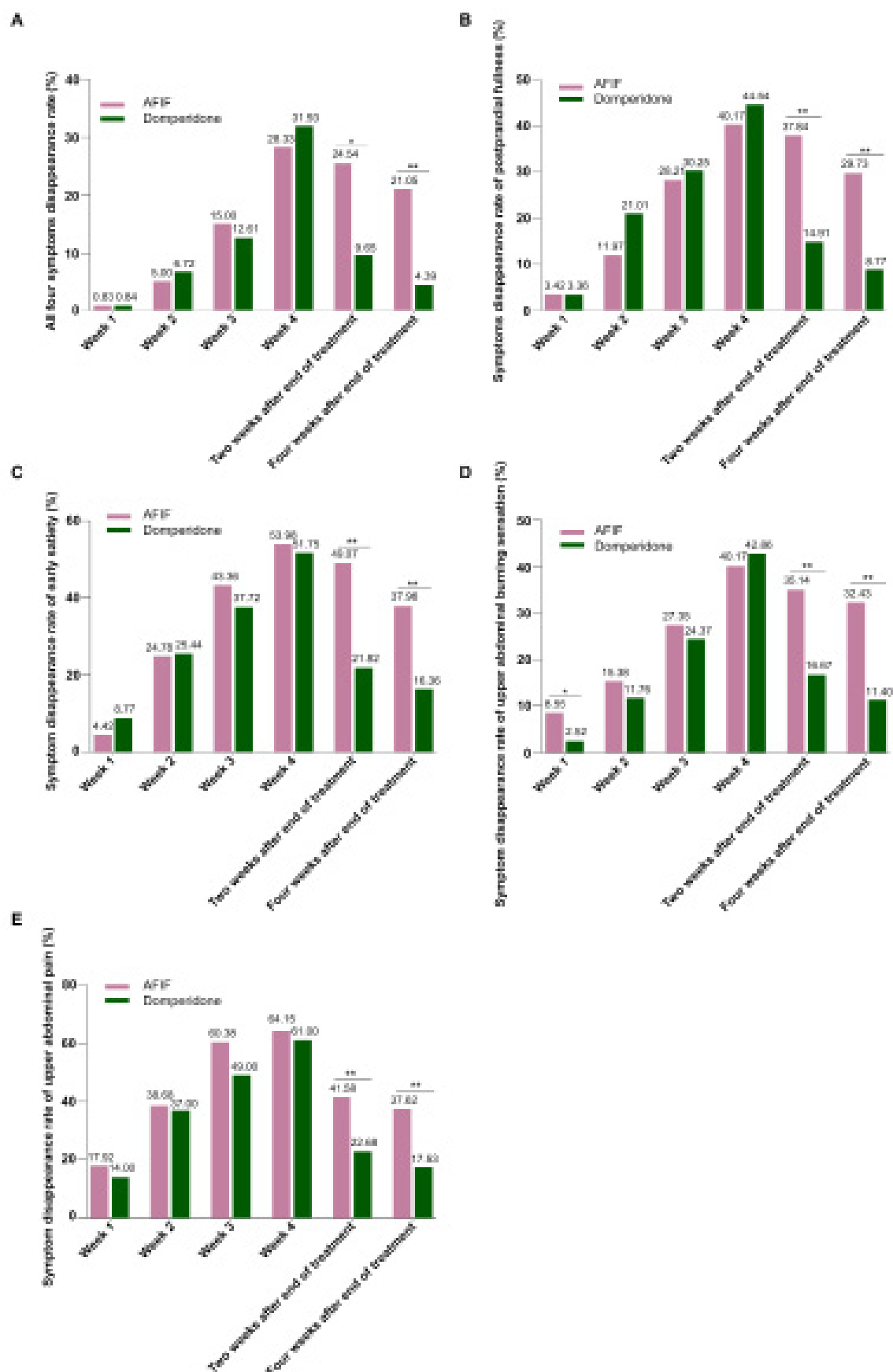


Fig. 2. — Rates of symptom disappearance at various visits. (A) All four symptoms. (B) Postprandial feeling of fullness. (C) Early satiety. (D) Upper abdominal burning sensation. (E) Upper abdominal pain. AFIF: *Aurantii Fructus Immaturus* flavonoid. * $p < 0.05$; ** $p < 0.01$.

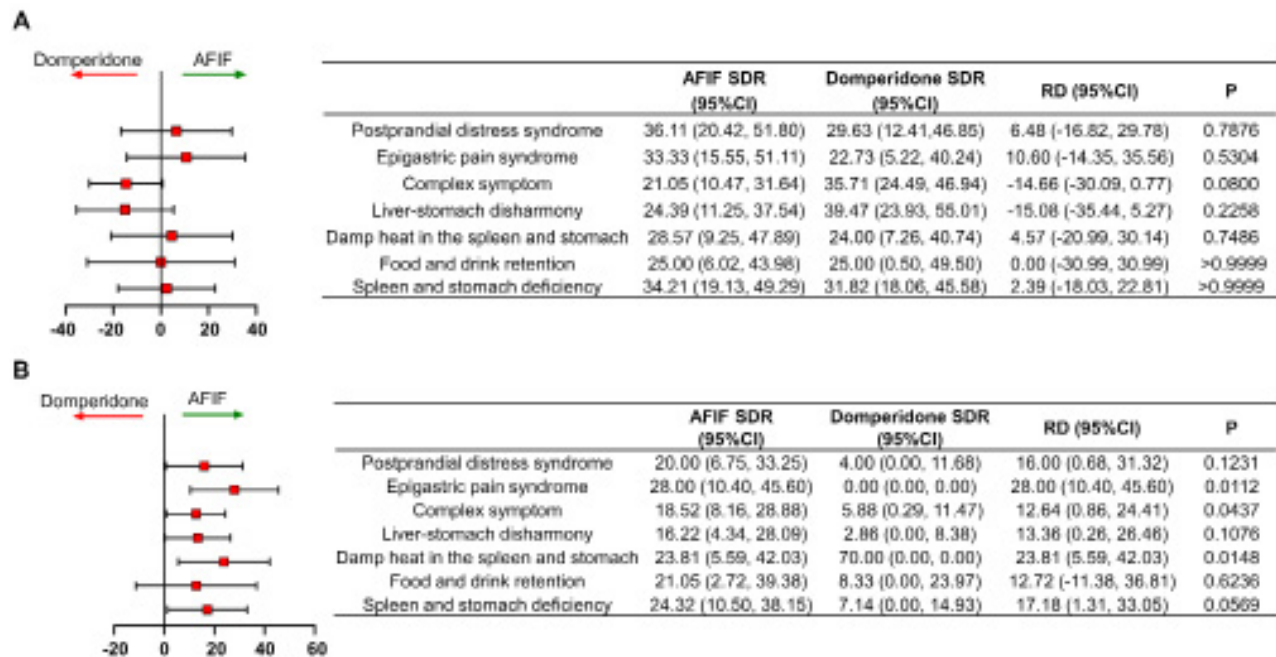


Fig. 3. — All four symptom disappearance rates (SDR) in different subgroups. (A) After four weeks of treatment. (B) At four weeks after the end of treatment. AFIF: *Aurantii Fructus Immaturus* flavonoid; RD: rate difference

Table 3. — Adverse events and adverse reactions (SS) in the two groups

	AFIF group		Domperidone group	
	N	n (%)	N	n (%)
Adverse events	32	23 (19.17)	63	43 (36.13)
Adverse reactions	3	3 (2.50)	26	20 (16.81)
Serious adverse events	2	1 (0.83)	1	1 (0.84)
Drug-related serious adverse events	0	0	0	0
Adverse events leading to treatment discontinuation	0	0	1	1 (0.84)
Adverse reactions leading to treatment discontinuation	0	0	1	1 (0.84)

AFIF: *Aurantii Fructus Immaturus* flavonoid.

the domperidone group, in the epigastric pain syndrome (28.00% vs. 0, $p=0.0112$), complex symptom (overlap between epigastric pain syndrome and postprandial distress syndrome) (18.52% vs. 5.88%, $p=0.0437$), and damp heat in the spleen and stomach (23.81% vs. 0, $p=0.0148$) subgroups, while the remaining subgroups showed no significant differences (all $p>0.05$) (Fig. 3B). The PPS and FAS had consistent trends.

Safety

Ninety-five AEs occurred in 66 patients, including 23 (19.17%) and 43 (36.13%) in the AFIF and domperidone groups, respectively. There were no SAEs. Except for four cases of moderate AEs, all AEs were mild (Table 3).

The commonest AEs in the AFIF group included upper respiratory tract infection (1.67%), vaginal infection (1.67%), malabsorption (1.67%), elevated blood glucose (1.67%), and anxiety (1.67%). The commonest AEs in the domperidone group included upper respiratory tract

infection (4.2%), elevated alanine aminotransferase (4.2%), elevated aspartate aminotransferase (3.36%), abnormal electrocardiogram (3.36%), and dry mouth (3.36%) (Supplementary Table S2).

Twenty-three ADRs were detected, including 3 (2.50%) and 20 (16.81%) in the AFIF and domperidone groups, respectively. Adverse reactions included malabsorption (1.67%) and constipation (0.83%) in the AFIF group, versus elevated alanine aminotransferase (3.36%), dry mouth (3.36%), elevated aspartate aminotransferase (2.52%), dizziness (2.52%), constipation (1.68%), fatigue (1.68%), electrocardiographic ST-segment abnormality, abnormal electrocardiogram, diarrhea, lethargy, thirst, breast swelling, irregular menstruation (premenstrual period) and delayed menstruation (0.84% each) in the domperidone group (Supplementary Table S3).

No deaths occurred in this trial. Three moderate AEs occurred in two patients, including 2 (exacerbation of

chronic superficial gastritis and esophagitis leading to hospitalization) in one patient of the AFIF group (0.83%) and 1 (exacerbation of bronchitis leading to hospitalization) in the domperidone group (0.84%). One patient in the domperidone group had an adverse reaction leading to treatment discontinuation (0.84%). No serious adverse reactions occurred in this study (Table 3).

Discussion

This multicenter, randomized, double-blind, double-dummy, positive-controlled phase III clinical trial aimed to assess the safety and efficacy of AFIF tablets vs. domperidone in FD treatment. The results suggest that AFIF tablets were similar to domperidone after 4 weeks of treatment in terms of efficacy, but AFIF tablets had a significant advantage over domperidone in the rate of disappearance of symptoms 4 weeks after treatment discontinuation. The rates of AEs also appeared to be lower in the AFIF group compared with the domperidone group.

The exact pathogenesis of FD remains mostly unknown, but proposed mechanisms include motor dysfunction, changes in the duodenal microbiota, impaired immune activation and excessive mucosal permeability (4,22). Among other symptoms, incomplete gastric emptying often leads to notable decrease in the patient's reported well-being and quality of life in FD (23-25). Therefore, prokinetic agents are actively used to alleviate the symptoms of dyspepsia with notable efficacy: most recent systematic review and network meta-analysis, published in 2023, reported that domperidone, as well as mosapride, itopride, acotiamide and cinitapride may each induce symptom disappearance in individuals with FD. However, it was reported that while prokinetics alleviate dyspeptic symptoms in FD, they rarely significantly improve the quality of life in patients (26,27). As alternative, herbal preparations with a long history of use are known to be effective in FD treatment and demonstrated a better safety profile. A Persian herbal preparation based on celery and ajwain had similar efficacy to domperidone (28); STW 5 (Iberogast), peppermint oil plus caraway oil, and *Curcuma longa* were each shown to improve global symptoms of FD (29), as well as supplementation of ginger and artichoke leaf extracts (30). *Apium graveolens* and *Trachyspermum copticum* decreased symptom severity and frequency in adult patients with uninvestigated dyspepsia (31). Ongoing efforts are made to single out the acting components of those preparations and decipher their role in the FD pathogenesis.

In a previous randomized controlled trial that included 60 FD patients (45 and 15 administered AFIF and placebo, respectively), AFIF tablets demonstrated promising results (20), suggesting that it could be used as an alternative to prokinetic agents in restoring gastroduodenal motility. In the present study, the patients were administered AFIF tablets or domperidone for 4 weeks, with both groups showing similar rates of

disappearance of all four FD symptoms (28.33% vs. 31.93%). Although the present study was a superiority trial, the results suggest that the primary efficacy of AFIF tablets may be similar to that of domperidone. However, a non-inferiority trial is required for confirmation. Moreover, as the study was performed in 2014, the Rome III criteria for the definition of FD were used; despite published evidence that Rome III and Rome IV criteria do not result in the notable difference in diagnosis among Asian population (32), the subsequent studies should be based on the updated criteria.

On the other hand, despite similar rates of symptom disappearance between the two groups after 4 treatment weeks, the persistence of the treatment effect 4 weeks after treatment discontinuation was higher in the AFIF group, with only 4.39% of patients showing symptom disappearance 4 weeks after discontinuing domperidone treatment, versus 21.05% in the AFIF group. Such persistence of the treatment effect cannot be explained based on the current data. Although the AFIF group showed a trend of higher persistence versus the domperidone group in all subgroups 4 weeks after the end of treatment, no significant differences were detected between subgroups; the study was not powered enough to detect differences in smaller samples, which should be considered in the further research. Of interest, such sustained effect could provide a strategy of dosing over short periods, which could help limit the occurrence of AEs – this point should be also examined in future studies.

The elimination half-life of domperidone is 12.6-16.0 h, while dietary flavonoids appear to have elimination half-lives of 0-28 h (33); bioaccumulation and storage could also occur. Of note, it is likely that all flavonoids in AFIF tablets act together to improve FD symptoms, and symptom disappearance may not be attributable to a single flavonoid. For example, in the previous experimental study AFIF tablets improved the contraction of isolated gastric smooth muscle strips in rats (19). However, natural flavonoids have biological activities and potential health benefits such as antioxidant, antibacterial, and anti-inflammatory effects (34,35). The flavonoid resveratrol alleviates gastric mucosal damage induced by myocardial ischemia-reperfusion (36) and inhibits the expression of iNOS, NF- κ B, and IL-8 in mouse gastric tissue induced by *H. pylori* (10^8 CFU) (37). Citrus flavanones are the major active ingredients in AFIF, including naringin, neohesperidin and hesperidin, etc., which exert promoting effects on gastrointestinal motility through tryptophan metabolism, corticosterone metabolism and sphingolipid metabolism (38). Naringin induces both anxiolytic and sedative effects, which might be one of its mechanisms of action in FD (39). Its metabolites also affect microbiota composition and activity and exert beneficial effects on intestinal barrier function and gastrointestinal inflammation, potentially contributing to the improvement of gastrointestinal function and health (40). Neohesperidin alleviates gut

barrier damage, metabolic endotoxemia, and systemic inflammation (41). Nevertheless, compared with 1.1 traditional Chinese herbs, the AFIF tablet is a 1.2 preparation comprising purified flavonoids, which allows for more precise efficacy and a better safety profile. However, *in vitro* and *in vivo* studies and network pharmacology are still required to explore the exact mechanisms of AFIF tablets in FD and the factors explaining the sustained effects observed after treatment discontinuation.

Conventional treatment used to manage FD is known to increase the risk of extrapyramidal and endocrine AEs (42). In the present study, although there were no deaths or SAEs in either group, 3.36% of patients who received domperidone had abnormal electrocardiograms. Therefore, cardiac safety is still an issue with domperidone use for FD management, especially since FD is an incurable life-long condition. On the other hand, AFIF tablets showed no cardiovascular toxicity in the present study and had a lower rate of AEs than domperidone. Therefore, a large phase IV studies are required to observe such rare events.

This study had limitations. Firstly, clinical trials are performed in highly selected patient populations, which limits the generalizability of findings. Large-scale real-world studies are required to confirm the results. Secondly, the study was performed in 2014, and results were presented to China National Medical Products Administration, where they undertook a long verification process which was finished in October, 2023. Although the delay influenced the viability of study design to some degree (such as usage of Rome III criteria), the fact that the study drug was successfully approved and marketed despite such rigorous inspection further demonstrates the authenticity of the data. In the future, subsequent studies should be based on the Rome IV criteria for FD to increase generalizability. Thirdly, no validated score for assessing gastrointestinal symptom severity was used in this study, thus endpoints evaluation might be subjected to some degree of bias. And finally, the treatment period was only 4 weeks, and post-treatment follow-up was only 4 weeks. Therefore, the long-term treatment effect and safety of AFIF are still undocumented. Quality of life was also not examined in the present study and combinations of AFIF with other drugs require further investigation.

The efficacy of AFIF tablets appears to be similar to that of domperidone after 4 treatment weeks, but AFIF tablets have a significant advantage over domperidone in terms of sustained symptom disappearance 4 weeks after treatment discontinuation. Finally, AFIF tablets appear to be safe in FD patients.

Conflicts of interest

Authors declare no conflict of interest.

Financial disclosures

None

Funding

This study was supported by Jiangxi Qingfeng Pharmaceutical Co., Ltd. which provided study drug and placebo.

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