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ORIGINAL ARTICLE

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The effect of rikkunshito on gastrointestinal symptoms and gastric motor function: The first study in a Belgian functional dyspepsia population

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Abstract

Background: Rikkunshito, a traditional Kampo medicine, has shown efficacy to treat functional dyspepsia (FD) in controlled trials in Japan. Its putative benefit for European patients and mechanism of action has not been established.

Methods: This study examined the effect of rikkunshito on gastric motility and GI symptom perception in FD-PDS patients in a randomized, placebo-controlled, cross-over study. After a 2-week run-in period, patients received rikkunshito or matching placebo (2.5 g t.i.d.) for 4 weeks, separated by a 4-week washout period. Symptoms were assessed by the Leuven Postprandial Distress Scale (LPDS) diary throughout the study. At baseline and after both treatment arms, intragastric pressure (IGP) was measured to evaluate gastric accommodation and gastric motility. Simultaneously, GI symptoms were scored on a 100 mm visual analogue scale. Validated symptom questionnaires (PAGI-SYM, VSI, DSS, and PHQ) were completed each study visit.

Key Results: Twenty-three patients completed the study (33 ± 14 years, 22.7 ± 3.22 kg/m^2). Intragastric pressure was numerically, but not significantly, lower after rikkunshito compared with baseline and placebo (P = .14). No differences were found in gastric accommodation, nutrient volume tolerance, and symptoms assessed during IGP measurements. Early satiation and postprandial fullness (daily diary) decreased after rikkunshito compared with baseline (P < .041 for both). Placebo also improved most other symptoms assessed. No significant changes in VSI scores occurred. No adverse reactions occurred.

Conclusions: Rikkunshito did not alter gastric motility. Treatment with rikkunshito improved upper GI symptoms in FD patients but similarly high placebo effects were observed using the LPDS diary, PAGI-SYM, SF-NDI, and DSS scores. Rikkunshito was safe and well-tolerated.

KEYWORDS
functional dyspepsia, gastrointestinal symptoms, intragastric pressure, rikkunshito

1 | INTRODUCTION

Functional dyspepsia (FD) is, with its prevalence of 5%-20% worldwide, one of the most common functional gastrointestinal disorders for which patients seek medical care.[1] FD is defined as the presence of recurrent or chronic symptoms thought to originate from the gastroduodenal region, in the absence of any structural abnormalities found during routine diagnostic procedures. According to the Rome III criteria, FD can be subdivided into two subgroups based on the most prominent symptoms. One subgroup is referred to as postprandial distress syndrome (PDS), characterized by meal-related symptoms. Cardinal PDS symptoms are postprandial fullness and early satiation. The second subgroup is the epigastric pain syndrome (EPS) subgroup, defined by meal-unrelated symptoms, including epigastric pain and epigastric burning.[2,3] The recently renewed Rome IV criteria decreased the overlap between both subgroups by considering epigastric pain manifesting after meal intake as belonging to PDS.[2,4] Although the underlying pathophysiology of FD remains unclear, different pathophysiological mechanisms have been proposed to be involved, including impaired gastric motility.[5] Gastric accommodation, the relaxation reflex of the stomach upon food intake, is impaired in approximately 40% of FD patients and has been shown to be associated with early satiation and weight loss.[6-8] Other pathophysiological mechanisms involved in FD include delayed gastric emptying, visceral hypersensitivity and brain-gut axis dysfunction.[5,9]

Due to the heterogeneous nature of FD in terms of symptoms and underlying pathophysiology, finding effective treatment options for FD has been challenging. Furthermore, the few available pharmacological options do not seem to be efficacious for the majority of patients.[10] Hence, there is an unmet medical need for new treatment options that can relieve FD symptoms efficiently. In Japan, rikkunshito, a traditional herbal Kampo medicine, has been widely prescribed to patients with a range of upper GI symptoms for more than 20 years. Recent Japanese studies indicated efficacy of rikkunshito in FD as well.[11] The effect of rikkunshito is thought to rely on comparable mechanisms as prokinetic agents as it counteracted the attenuation of gastric dysmotility resulting from inhibition of nitric oxide (NO) synthesis.[12,13] A barostat study in healthy subjects suggested that rikkunshito is able to enhance gastric accommodation, and an ultrasound study in FD patients found increased volume of the proximal stomach in response to nutrient ingestion during rikkunshito treatment.[14,15] Furthermore, rikkunshito was shown to improve delayed emptying, to exert antistress effects in gastric hypersensitivity and to be involved in motility regulation via ghrelin secretion.[12,16-18] Hence, it is reasonable to assume that rikkunshito treatment can improve abdominal symptoms related to disturbed motility. However, studies evaluating the effect of rikkunshito on gastric accommodation and nutrient volume tolerance in FD patients are lacking. Therefore, the aim of the present study was to evaluate the effect of rikkunshito on intragastric pressure, as a measure for gastric motility and gastric accommodation, and nutrient volume tolerance in FD. We hypothesized that gastric motility and symptom levels improve after a 4-week treatment with rikkunshito.

Key Points

- Rikkunshito improved early satiation and postprandial fullness in Belgian FD patients.
- Rikkunshito was safe and well tolerated.
- Rikkunshito numerically decreased intragastric pressure compared to baseline and placebo, but this did not reach statistical significance in this pilot cohort.

2 | METHODS

2.1 | Study population

Patients aged between 18 and 75 years old were included in this study. Until the publication of the updated Rome IV criteria in 2016, patients fulfilling the Rome III criteria for FD with PDS were eligible to participate in the study. Upon the release of the Rome IV consensus, these criteria were used to select FD-PDS patients, also including patients with meal-related pain symptoms. All patients underwent careful anamnesis and clinical examination. Overlap with other GI symptoms related to epigastric pain syndrome and irritable bowel syndrome was allowed, provided they were of mild intensity and PDS symptoms were predominant. Patients presenting with significant diseases or other GI disorders including chronic idiopathic nausea, gastroesophageal reflux disease, or excessive belching were not eligible to participate. Furthermore, patients with an active psychiatric condition were excluded. Additional exclusion criteria comprised pregnancy, diabetes type 1 or type 2, heart diseases or concomitant extra-digestive disease, major GI surgeries or surgeries affecting upper gut motility, and known hypersensitivity to ginseng or ginger. Patients receiving *Helicobacter pylori* eradication treatment during the last 3 months or taking drugs affecting gut secretion, mucosal integrity (with exception for aspirin at cardio-protective doses), motility, and/or gastrointestinal sensitivity were considered not eligible to participate. The use of proton pomp inhibitors was allowed provided that FD symptoms were predominant, and heartburn was limited to a maximum of two episodes of no more than mild intensity per week. Treatment with a stable dose of a single antidepressant (with the exception of amitriptyline and mirtazapine) during the last 3 months was accepted. Lastly, only patients who reported at least moderate postprandial fullness and/or early satiation for at least 4 days during the 2-week run-in period were randomized in the study. The study was designed to have 80% power to detect a 30% difference in intragastric pressure with a sample size of 30 subjects and $P < .05$. The study was approved by the Ethics Committee of the University Hospitals, Leuven, Belgium (EC number: S56924) and was performed in accordance with the Declaration of Helsinki and the BMJ guidelines. The study was registered on http://www.clinicaltrials.gov as NCT03856294. Informed consent was obtained from all subjects before performing any study procedure.

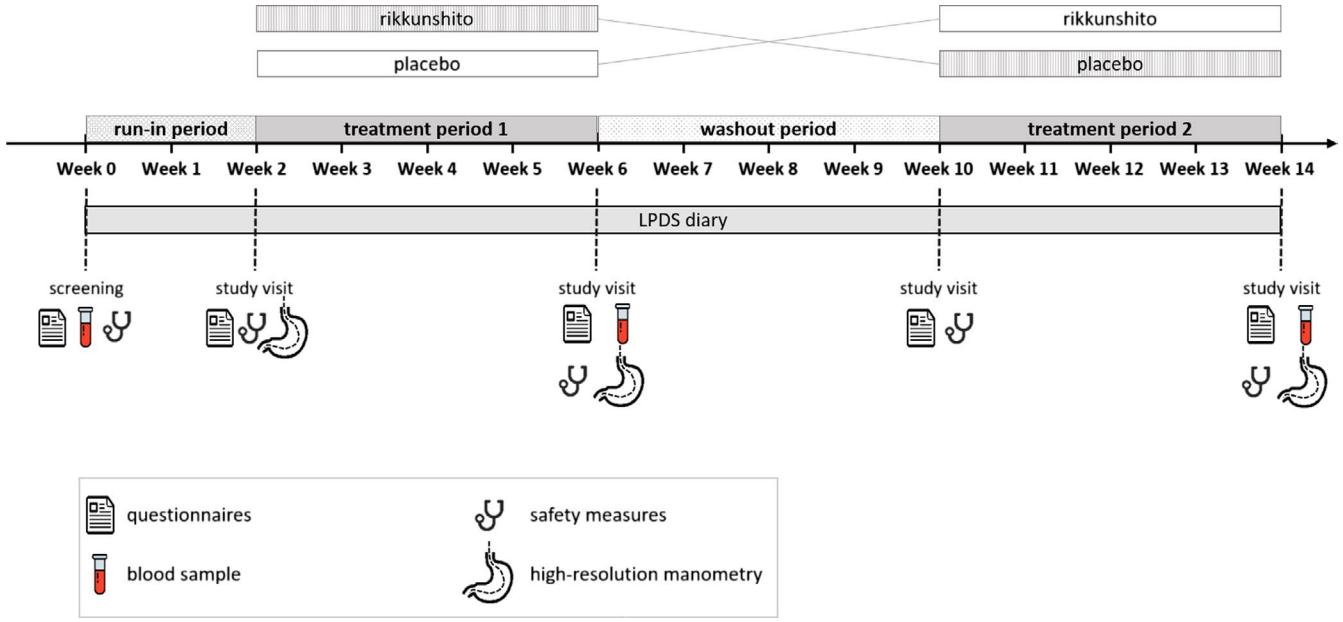

FIGURE 1 Overview of study design. The effect of rikkunshito on intragastric pressure and FD symptoms was evaluated in a randomized, counterbalanced, placebo-controlled, double-blind, cross-over study. The study had a total duration of 14 wk, consisting of a run-in period (2 wk) and two treatment phases (4 wk) separated by a washout period (4 wk). Intragastric pressure, assessed using high-resolution manometry, was measured at baseline and after each treatment period. Each study visit, questionnaires on gastrointestinal symptoms, and psychosocial state were completed, and safety measures (assessment of blood pressure, heart rate and weight, performing an electrocardiogram, evaluation of adverse event, and a physical examination) were performed. During screening and after each treatment period, blood samples were collected to evaluate liver and kidney function. The Leuven Postprandial Distress Scale (LPDS) diary was completed once daily throughout the entire study

2.2 | Study medication

Rikkunshito (TJ-43) is a traditional Japanese Kampo medicine with a granule formulation. It consists of extract powder of 8 mixed botanical raw materials: Atractylodes Lancea Rhizome, Ginseng, Pinellia Tuber, Poria Sclerotium, Jujube, Citrus Unshiu Peel, Glycyrrhiza, and Ginger. Excipients include sucrose esters of fatty acids (disintegrant), lactose hydrate (vehicle), and magnesium stearate (lubricant). The matching placebo contains corn starch (vehicle), lactose hydrate (vehicle), dextrin (vehicle), magnesium stearate (lubricant), FD&C blue and yellow aluminum lake (coloring agent), and red ferric oxide (coloring agent). Rikkunshito and placebo were administered orally as a solution, with 2.5 g of rikkunshito or placebo dissolved in 200 mL of lukewarm water. Study medication was taken three times daily 30 minutes before the meal.

Rikkunshito and matching placebo were manufactured by Tsumura & Co. Randomization of the treatment arms was performed by the pharmacy at the University of Leuven (Leuven, Belgium) and blinding procedures, and packaging and delivery of the blinded study medication was performed by Laboratoria Wolfs.

2.3 | Study design

This randomized, placebo-controlled, double-blind, cross-over study had a total duration of 14 weeks, consisting of a 2-week run-in period, two treatment phases of 4 weeks each and a 4-week washout period separating the treatment phases to prevent carryover effects. Study visits were held at baseline (screening) and after the run-in period, treatment phases, and washout period (Figure 1).

The primary endpoint of the current study was the change in intragastric pressure after rikkunshito treatment. To assess the effect of rikkunshito on intragastric pressure as an indirect measure for gastric motility, high-resolution manometry (HRM) was performed after the run-in period (baseline measurement) and after both treatment phases. During intragastric pressure measurement, a nutrient tolerance test was performed and symptom questionnaires were completed. Throughout the entire study, patients scored their gastrointestinal symptoms on a daily basis using the Leuven Postprandial Distress Scale (LPDS) diary. In addition, questionnaires on gastrointestinal symptoms and psychosocial state were completed each study visit.

Safety measures performed each study visit included assessment of blood pressure, heart rate and weight, performing an electrocardiogram, evaluation of adverse event, and a physical examination. Furthermore, blood samples were collected during screening and after each treatment phase to evaluate liver and kidney function. Serum levels of potassium, creatine kinase, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, and gamma-glutamyl transferase were assessed. Women of childbearing potential were asked to undergo a pregnancy test before study enrollment and before each treatment period.

2.3.1 | High-resolution manometry

Intragastric pressure (IGP) was measured using a high-resolution solid-state manometry system (Manoscan 360, Sierra Scientific Instruments) as previously described.[19] After an overnight fast, the manometry probe (ManoScan ESO catheter, Given Imaging) with 36 circumferential pressure-sensing channels spaced at 1-cm intervals, was transnasally positioned into the stomach, as far as possible toward the duodenum with at least one of the pressure-sensing channels positioned in the lower esophageal sphincter (LES). In addition, a nasogastric feeding tube (RT10/100, Eurosteriel Medical) was positioned in the proximal stomach to intragastrically administer a liquid meal (Nutridrink, Nutricia). The position of both probes was verified fluoroscopically. Hereafter, both probes were fixed to the subject's nose with adhesive tape to prevent displacement. The patients were asked to take place in a hospital bed in upright position for the remainder of the experiment.

After a stabilization period of 20 minutes, 200 mL lukewarm water (baseline measurement) or the study medication (rikkunshito or placebo) dissolved in 200 mL lukewarm water was administered. Thirty minutes later, a liquid meal (Nutridrink, 150 kcal, 6 g proteins, 18.4 g carbohydrates, and 5.8 g lipids per 100 mL) was infused intragastrically at a constant speed of 60 mL/min. Patients scored satiation on a 0-5 Likert scale on 1-minute intervals. The infusion was stopped when the participant reached maximal satiation (score of 5). Hereafter, IGP measurement continued for two more hours.

Appetite-related sensations (hunger and satiation) and gastrointestinal symptoms (bloating, fullness, nausea, belching, heartburn, epigastric burning, thoracic cramps, epigastric cramps, and pain) were scored on a visual analogue scale (VAS) throughout the IGP measurement. Symptom scores were collected every 5 minutes from the start of the stabilization period until the end of liquid meal infusion, and every 10 minutes hereafter until the end of the measurement.

2.3.2 | Questionnaires

Throughout the study, patients were asked to fill out the Leuven Postprandial Distress Scale (LPDS) diary on a daily basis. This diary is a reliable patient-reported outcome instrument that assesses functional dyspepsia symptoms.[20] It comprised eight symptoms with verbal descriptors ranging from 1 (absent) to 5 (very serious) accompanied by "smiley faces". Symptoms assessed were early satiation, postprandial fullness, bloating, epigastric pain, epigastric burning, nausea, belching, and heartburn. Furthermore, a weekly overall treatment evaluation (OTE) was included in the LPDS diary to evaluate whether the patients indicated their symptoms improved remained unchanged to worsened compared with before treatment. Overall treatment evaluation scores ranged from −4 (completely unbearable) to +4 (completely disappeared).[20]

Additionally, each study visit, the following questionnaires on gastrointestinal symptoms and psychosocial state were completed: Dyspepsia Symptom Severity Scale (DSS), Patient Assessment of upper Gastrointestinal Symptom severity index (PAGI-SYM),[21] Short Form Nepean Dyspepsia Index (SF-NDI),[22] and the Visceral Sensitivity Index (VSI).[23]

2.4 | Data analysis

Manometric measurements were analyzed with ManoView Analysis 2.0.1 software (Sierra Scientific Instruments). The original data were converted into a text file and imported in Excel for further analysis. In order to avoid artefacts caused by movement, coughing, sneezing, or swallowing, a moving median was calculated per channel from the original data. From the moving median, a baseline value was calculated per channel as the average pressure over the last 5 minutes before intake of study medication. Pressures in the proximal stomach were calculated by averaging the pressure of the first five pressure channels that were clearly positioned below the LES or the pressure area influenced by the LES.[19]

For the LPDS diary, symptom scores of the last 2 weeks of each study phase (run-in, treatment periods, and washout) were averaged and compared between the study phases. Furthermore, average DSS and VSI scores were compared between the study phases. The PAGI-SYM measures the intensity of 20 upper gastrointestinal symptoms grouped into 6 subscales: heartburn/regurgitation, nausea/vomiting, fullness/satiety, bloating, upper abdominal pain, and lower abdominal pain. The average scores per subscale were compared between the study phases. For the SF-NDI scores, used as a measure of quality of life, the impairment of the subject to participate or enjoy relevant aspects of life (work, study, eating, etc) was assessed.

2.5 | Statistical analysis

Statistical analysis was performed in Statistical Analysis Software 9.4 (SAS). Only data from patients who completed both treatment arms were included in the analysis dataset. All data were analyzed using linear mixed models. Symptom scores that did not follow Gaussian distribution were divided into tertiles or quartiles and analyzed using generalized linear mixed models with a cumulative logit link function for ordinal response variables. Study phase and time (for IGP and VAS scores) were the categorical independent variables included in the models. Effects of interest included the main effect of study phase, testing the difference between the study phases over time, and, if applicable, the study phase-by-time two-way interaction effect, testing the differences in the time course between the study phases. Post hoc analyses were performed to elucidate which study phases differed significantly. A Tukey-Kramer correction for multiple pairwise comparisons was performed in every post hoc analysis. For all analyses, the variance-covariance structure providing the best fit was chosen based on the minimum value of Akaike's information criterion (AIC). Data were considered statistically significant when $P < .05$. All data were presented as mean ± SEM.

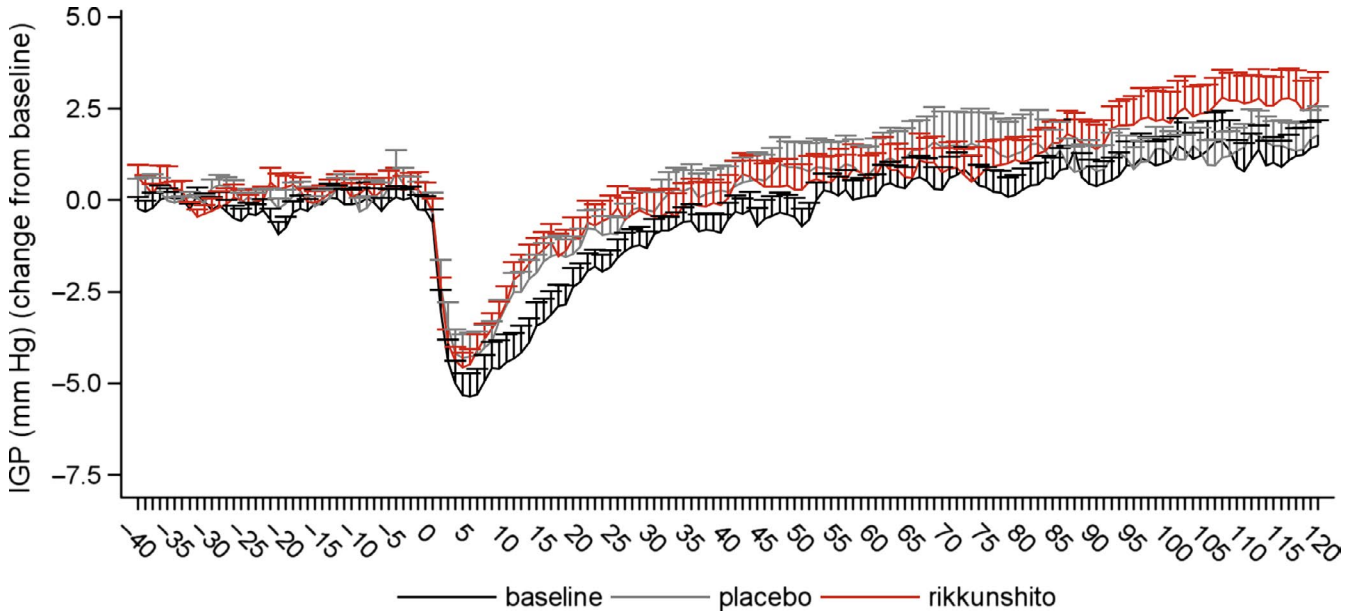

FIGURE 2 Change in intragastric pressure (IGP) from adjusted baseline. Baseline was determined as the IGP level 5 min before study medication (rikkunshito of placebo) or lukewarm water intake. A rapid IGP drop was observed upon intragastric liquid meal infusion, followed by a gradual increase (time main effect: $P < .001$). There was no significant difference between the study phases (main effect of study phase: $P = .23$; study phase-by-time interaction effect: $P = .072$)

3 | RESULTS

3.1 | Study population and compliance

A total of thirty-four patients were included in this study between December 2015 and July 2018. Eleven patients dropped out, resulting in 23 evaluable patients (33 ± 14 years, 22.7 ± 3.22 kg/m^2). Reasons for dropout were comorbidities (five patients), intolerance to the study procedures (two patients), time investment needed to participate (two patients), inability to stop prohibited medication (one patient), and hospitalization due to severe weight loss (one patient). There was no difference in age, BMI, PDS, and EPS scoring on the Rome III questionnaire between the group that dropped out and the group that completed the study ($P > .39$ for all).

Compliance with the study medication was high in both treatment groups: 96.7% for rikkunshito and 96.8% for placebo.

3.2 | Intragastric pressure measurement

Intake of study medication or lukewarm water (baseline measurement) did not affect IGP, indicated by stable pressures before the start of the liquid meal infusion. Intragastric liquid meal infusion induced a rapid decrease in IGP followed by a gradual increase (time main effect: $F = 22.04$, $P < .001$). For the baseline corrected IGP data (Figure 2), where baseline was determined as the IGP level 5 minutes before study medication or lukewarm water intake, there was no significant difference between the study phases (main effect of study phase: $F = 1.5$, $P = .23$; study phase-by-time interaction effect: $F = 1.28$, $P = .072$). These results were confirmed in the post hoc pairwise comparison test (Table 1).

TABLE 1 Pairwise comparison of intragastric pressure between study phases

Study phase (pairwise comparison)		*t*-value	*P*-value
Baseline corrected data			
Baseline	Placebo	−1.25	.43
Baseline	Rikkunshito	−1.67	.23
Placebo	Rikkunshito	0.73	.93
Raw data			
Baseline	Placebo	−0.18	.98
Baseline	Rikkunshito	1.76	.18
Placebo	Rikkunshito	1.61	.24

To assess global changes in IGP after the 4-week treatment period, the raw IGP data were explored. Rikkunshito was associated with numerically, although not statistically significant, lower IGP compared with placebo and baseline (main effect of study phase: $F = 1.96$, $P = .14$; phase-by-time interaction effect: $F = 0.67$, $P = .98$; Figure 3).

Nutrient volume tolerance did not differ between rikkunshito (532.17 ± 369.56 mL) and baseline (547.83 ± 259.84 mL), rikkunshito and placebo (526.96 ± 382.03 mL), and placebo and baseline ($P > .63$ for all).

3.3 | Appetite-related sensations and gastrointestinal symptom scores

Hunger and satiation scores changed significantly over time (time main effect: $F = 6.96$, $P < .001$; $F = 13.96$, $P < .001$, respectively). No significant differences were observed between the study phases (main effect of study phase: $F = 0.81$, $P = .45$; $F = 0.23$, and $P = .79$,

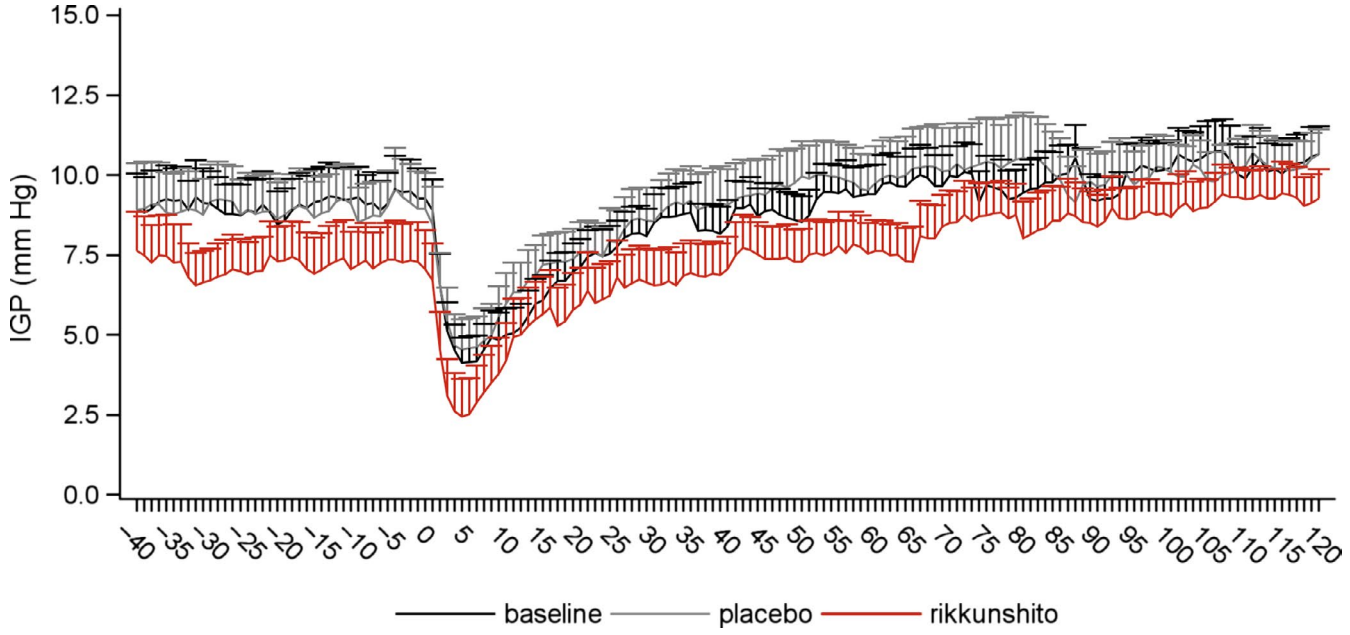

FIGURE 3 Raw intragastric pressure (IGP) changes over time. After rikkunshito treatment, IGP was numerically, but not significantly, lower compared with baseline and placebo (main effect of study phase $P = .14$) throughout the entire measurement

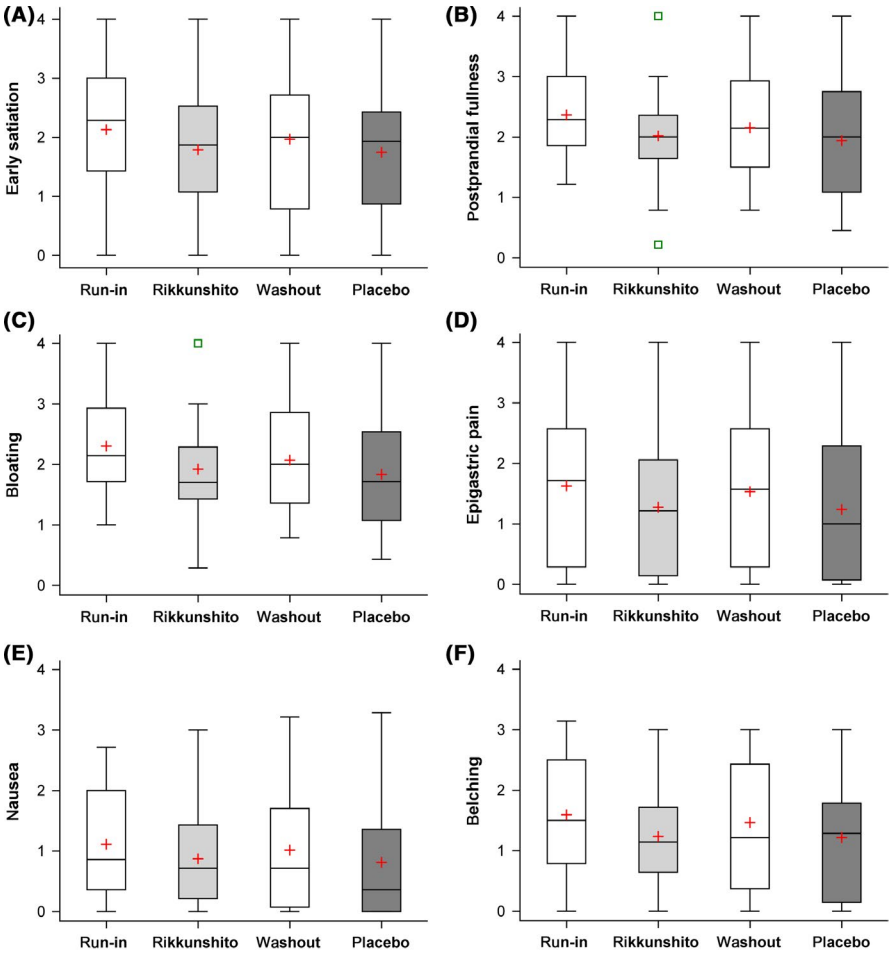

FIGURE 4 Symptom scores assessed by the Leuven Postprandial Distress Scale (LPDS) diary. Rikkunshito induced a decrease in early satiation (A) and postprandial fullness scores (B) compared with the run-in period ($P = .017$ and $P = .041$, respectively). No significant differences were observed between the other study phases. Bloating scores (C) were lower after both rikkunshito ($P = .007$) and placebo ($P = .006$) compared with run-in. Epigastric pain (D) decreased after rikkunshito ($P = .036$) and placebo treatment ($P = .017$) compared with run-in. Nausea (E) and belching (F) improved after placebo compared with run-in ($P = .021$ and $P = .028$, respectively), and belching scores were significantly lower after placebo treatment compared with the washout period ($P = .049$)

TABLE 2 Mean DSS scores

	Mean ± SD	*P*-value		*P*-value
Rikkunshito vs	10.59 ± 3.76		Placebo vs	
Baseline	12.61 ± 4.06	.058	Baseline	<.001
Run-in	12.17 ± 3.37	.217	Run-in	<.001
Washout	12.00 ± 3.73	.329	Washout	<.001
Placebo	8.78 ± 4.11	.093		

respectively; study phase-by-time interaction effect: F = 0.84, P = .78; F = 0.81, and P = .83, respectively).

Regarding gastrointestinal symptoms, heartburn and cramp levels remained stable throughout the measurement (time main effect: P > .15 for both). Scores for bloating, fullness, nausea, belching, epigastric burning, abdominal cramps, and pain changed significantly over time (time main effect: P < .001 for all), increasing upon nutrient intake. However, rikkunshito treatment had no effect on any of the symptoms measured during IGP measurement compared with baseline and placebo (study phase main effect: P > .30 for all; study phase-by-time interaction effect: P > .22 for all).

3.4 | Leuven Postprandial Distress Scale (LPDS) diary

Early satiation and postprandial fullness differed significantly between the study phases (run-in, rikkunshito, washout, and placebo; study phase main effect: F = 5.09, P = .008; F = 5.37, P = .006, respectively). Post hoc analysis revealed a significant difference between rikkunshito and run-in (early satiation: t = −3.28, P = .017; postprandial fullness: t = −2.87, P = .041), but not between the other pairwise comparisons (P > .052 for all; Figure 4A,B).

Scores for bloating were significantly lower after rikkunshito and placebo compared with the run-in period (study phase main effect: F = 4.41, P = .007; rikkunshito: t = −2.77, P = .036; placebo: t = −3.39, P = .006; Figure 4C). No significant difference was found between the other pairwise comparisons (P > .32 for all). Epigastric pain significantly decreased after placebo and rikkunshito compared with the run-in period (study phase main effect: F = 4.50, P = .006; placebo: t = −3.05, P = .017; rikkunshito: t = −2.76, P = .036; Figure 4D). No significant changes were observed for epigastric burning (study phase main effect: F = 1.34, P = .27; post hoc pairwise comparisons: P > .25 for all; data not shown). Compared with the run-in period, placebo treatment significantly improved nausea (study phase main

TABLE 3 Comparison of PAGI-SYM scores (mean ± SD) between study phases. Significant *P*-values are underlined

	Total		Heartburn/regurgitation		Nausea/vomiting		Fullness/satiation	
	Mean ± SD	*P*-value	Mean ± SD	*P*-value	Mean ± SD	*P*-value	Mean ± SD	*P*-value
Rikkunshito vs	1.80 ± 0.75		0.77 ± 0.99		0.80 ± 0.78		2.80 ± 1.09	
Baseline	2.33 ± 0.72	<.001	0.96 ± 1.01	.516	1.13 ± 1.04	.047	3.62 ± 0.92	.002
Run-in	2.21 ± 0.74	.014	0.90 ± 1.04	.687	1.10 ± 1.13	.291	3.47 ± 0.91	.016
Washout	2.07 ± 0.73	.216	0.84 ± 1.02	.982	0.94 ± 0.92	.811	3.15 ± 1.08	.452
Placebo	1.64 ± 0.86	.669	0.71 ± 0.97	.313	0.84 ± 0.73	.477	2.65 ± 1.19	.948
Placebo vs								
Baseline		<.001		.109		.826		<.001
Run-in		<.001		.019		.999		.002
Washout		.007		.121		.975		.121

	Bloating		Upper abdominal pian		Lower abdominal pain	
	Mean ± SD	*P*-value	Mean ± SD	*P*-value	Mean ± SD	*P*-value
Rikkunshito vs	2.59 ± 1.22		2.39 ± 1.40		1.48 ± 1.42	
Baseline	3.30 ± 1.39	.007	3.39 ± 1.27	<.001	1.59 ± 1.40	.855
Run-in	2.93 ± 1.26	.457	2.98 ± 1.34	.110	1.87 ± 1.62	.665
Washout	2.76 ± 1.15	.919	2.87 ± 1.38	.273	1.85 ± 1.47	.682
Placebo	2.17 ± 1.36	.282	2.11 ± 1.48	.761	1.35 ± 1.39	.999
Placebo vs						
Baseline		<.001		<.001		.953
Run-in		.004		.004		.837
Washout		.046		.017		.851

effect: $F = 3.20$, $P = .029$; post hoc test: $t = -2.97$, $P = .021$) and belching (study phase main effect: $F = 4.23$, $P = .017$; post hoc test: $t = -3.05$, $P = .028$; Figure 4E,F). Furthermore, belching scores were significantly lower after placebo treatment compared with the washout period ($t = -2.79$, $P = .049$). No significant differences were found for the other pairwise comparisons ($P > .16$ for all). Scores for heartburn were too low throughout the study to analyze properly. Lastly, OTE scores did not significantly differ between placebo and rikkunshito ($F = 1.08$, $P = .30$; data not shown).

3.5 | Questionnaires

3.5.1 | DSS

DSS scores changed significantly between the study phases (study phase main effect: $F = 9.44$, $P < .001$). No significant difference in DSS scores was observed between screening and the run-in period, indicating that the symptoms remained stable during the run-in period ($t = 0.61$, $P = .97$). Placebo treatment significantly improved DSS scores compared with screening, run-in, and washout ($P < .001$ for all). No significant differences in DSS scores were observed after rikkunshito treatment compared with baseline, run-in, washout, and placebo ($P > .058$ for all; Table 2).

3.5.2 | PAGI-SYM

PAGI-SYM scores were significantly different between the study phases (study phase main effect: $F = 10.61$, $P < .001$). Rikkunshito and placebo both improved total PAGI-SYM scores compared with baseline ($P < .001$ for both) and compared with run-in ($P < .014$ for both). In addition, PAGI-SYM scores were significantly lower after placebo compared with washout ($t = -3.47$, $P = .007$). No significant differences were observed between rikkunshito and placebo ($t = 1\text{-}34$, $P = .67$; Table 3).

Regarding the PAGI-SYM subscales, heartburn/regurgitation was improved after placebo compared with run-in ($t = 3.48$, $P = .019$) whereas nausea/vomiting was improved following rikkunshito treatment ($t = 2.86$, $P = .047$). Fullness/satiation was improved after both rikkunshito and placebo compared with screening ($P < .001$ for both) and run-in ($P < .016$ for both). Bloating and upper abdominal pain were lower after placebo compared with baseline, run-in, and washout ($P < .045$ for all) and after rikkunshito compared with baseline ($P < .008$ for both). Lower abdominal pain was unaffected by rikkunshito or placebo treatment (Table 3).

3.5.3 | SF-NDI

The influence of FD symptoms on feelings of tension was reduced after placebo compared with baseline (study phase main effect: $F = 2.97$, $P = .023$, post hoc comparison: $t = 3.29$, $P = .009$). No significant differences were observed between the other pairwise comparisons ($P > .12$ for all). Similar results were found for the influence of FD complaints on work (study phase main effect: $F = 3.51$, $P = .010$, post hoc comparison baseline vs placebo: $t = 3.02$, $P = .022$; all other post hoc comparisons: $P > .12$ for all). No changes were found in the influence of symptoms on daily activities (study phase main effect: $F = 1.93$, $P = .11$, post hoc comparison: $P > .056$ for all), food intake (study phase main effect: $F = 2.54$, $P = .044$, post hoc comparison: $P > .054$ for all), and on control over symptoms (study phase main effect: $F = 1.85$, $P = .12$, post hoc comparison: $P > .10$ for all; data not shown).

3.5.4 | VSI

There was no significant difference in VSI scores for all pairwise comparisons ($P > .056$ for all; data not shown).

3.6 | Safety measures

3.6.1 | Adverse events

Table S1 shows all reported adverse events. All adverse events were of mild intensity and were considered not or unlikely to be related to the study therapy. Adverse events were reported equally frequent over all study phases, indicating that rikkunshito treatment is not associated with increased frequency of adverse events. These results demonstrate that rikkunshito is well-tolerated and safe.

3.6.2 | Blood pressure and heart rate

None of the patients experienced clinically relevant changes in blood pressure and heart rate throughout the study.

3.6.3 | ECG

No clinically significant abnormal ECG findings were reported throughout the study.

3.6.4 | Blood levels

No clinically relevant deviations in serum levels of potassium, creatine kinase, aspartate aminotransferase, alanine transaminase, alkaline phosphatase, and gamma-glutamyl transferase were observed throughout the study (Table S2). One patient showed transiently elevated creatine kinase levels (Table S1), likely due to muscle injury after strenuous exercise.

4 | DISCUSSION

Rikkunshito has been used for several decades to treat a variety of upper GI complaints in Japan. Previous research provided evidence for efficacy of rikkunshito in the treatment of FD as well.[11,15,24] The current study was the first study to explore the effects of rikkunshito in a European FD patient population. The study was designed to investigate the effects of rikkunshito on FD symptoms and gastric function and to assess its safety in a cross-over design. Regarding

symptoms scored by the daily LPDS diary, a validated patient-reported outcome measure for PDS, early satiation, and postprandial fullness improved after rikkunshito treatment. Using the same instrument, nausea and belching only improved after placebo and bloating and epigastric pain improved after both rikkunshito and placebo. In addition, total PAGI-SYM scores improved after rikkunshito and placebo, whereas DSS scores, and the influence of symptoms on tension and work as assessed by the SF-NDI only improved after placebo. Furthermore, no significant changes were found in VSI scores nor in IGP data. None of the reported scores differed significantly between placebo and rikkunshito. Finally, the use of rikkunshito was not associated with increased adverse events.

In the current study, patients with FD subtype PDS were included. According to the Rome III and Rome IV criteria, postprandial fullness and early satiation are the cardinal PDS symptoms. Interestingly, these symptoms, scored on the LPDS diary, were only improved after rikkunshito treatment compared with the run-in phase of the study. These results are in line with a previous study by Tominaga et al,[25] showing beneficial effects of rikkunshito on PDS symptoms. However, for several symptoms assessed with other questionnaires in the current study, significant improvements from run-in were found for both rikkunshito and placebo, or for placebo alone. Furthermore, no significant differences were found between rikkunshito and placebo for most of the symptoms assessed. These results reflect the small sample size of the current study and also confirm the presence of an important placebo effect in this study population. As patients were allowed to continue PPI treatment and treatment with a stable dose of a single antidepressant other than amitriptyline or mirtazapine in the current study, one could argue that the effects seen in the placebo treatment arm are elicited by the use of these drugs. However, in the current study, only seven patients continued PPI treatment and one patient was on concomitant treatment with a single antidepressant. Furthermore, concomitant medication intake remained stable throughout the study and was therefore the same in all treatment periods (baseline, run-in, rikkunshito, washout, and placebo) of this cross-over trial, where every patient serves as his/her own control. Hence, we conclude that stable concomitant medication use is unlikely to have affected responses assessed in this trial and that the effects seen in the placebo treatment arm are true placebo effects. It has been previously established that placebo effects are common in functional gastrointestinal disorders, including functional dyspepsia. A review of 2012 showed a variable placebo response in studies with FD ranging from 6% to 72%.[26] It should be pointed out that only the LPDS diary complies with current regulatory requirements for a PRO instrument and has received support from the European Medicines Agency.[27,28]

Notably, in previous literature available in English, only 2 recent rikkunshito studies in FD used placebo as a comparator. Additionally, both studies used a parallel design and an 8-week treatment period to assess the effects of rikkunshito on FD symptoms. They showed significant benefit at week 8 of treatment, but not at week 4.[24,25] These results imply that a 4-week treatment period with rikkunshito may be suboptimal for obtaining significant symptom improvement. However, a trend toward superiority of rikkunshito at week 4 was reported in both studies, which could not be observed in the current study. Several arguments can be put forward to explain these discrepancies, besides the small sample size in the present study. Firstly, ethnic differences between Asian and European patients can underlie the differences found in efficacy of rikkunshito. Secondly, the patients from the current study were recruited from tertiary care. Based on a subgroup analysis of a large randomized trial, Suzuki et al suggested rikkunshito to be more effective in primary care patients compared with patients recruited from hospitals. Most likely, this is related to the higher prevalence of therapy resistance in secondary and tertiary care patients.[24] Based on these findings, future research with rikkunshito in Europe should probably focus on primary care patients to gain more insight into the efficacy of rikkunshito.

Regarding the effects of rikkunshito on gastric motility, this study failed to show significant changes in IGP, assessed by high-resolution manometry, after 4 weeks of treatment. This is in contrast to two previous studies assessing the effects of rikkunshito on gastric accommodation and gastric volumes. Kusunoki et al[15] showed significant improvements in the expansion rate of the proximal stomach in FD, measured with ultrasound, after 2 weeks of treatment. Shiratori et al[14] measured gastric accommodation in nine healthy subjects using barostat and found an improvement of stress-induced reduced gastric volumes after 2 weeks of rikkunshito treatment. The incongruities between the current study and the previous studies can be explained by several factors. Firstly, both previous studies included more male than female subjects, whereas the opposite is true for the current study. Earlier research proposed, however, that rikkunshito is more effective in female patients.[29] Secondly, different techniques were used in the three studies. The gold standard to determine gastric accommodation is gastric barostat.[30] However, a number of important drawbacks are associated with the technique, including exaggeration of the gastric accommodation reflex, impediment of physiological responses to food intake, limited coverage of measured area, and invasiveness of the technique.[19,31-33] Similarly, the US method has a few limitations, comprising the user dependency and the required supine position of the subject to allow for partial distribution of the liquid test meal in the proximal stomach.[15,34] Consequently, gastric accommodation with normal distribution of the test meal cannot be evaluated with ultrasound.[15] Conversely, high-resolution manometry, used in the current study to indirectly measure gastric motility, is less invasive compared with barostat, includes measuring sensors over the full length of the stomach and can be used in a physiological upright position. Hence, we chose this technique to assess gastric motility in the current study.

In our opinion, the results concerning gastric accommodation reported thus far have to be interpreted with caution. Notably, in the study of Shiratori et al, impaired baseline gastric accommodation was induced by stress. In the current study, not all patients showed a reduced accommodation reflex at baseline. The presence of a floor effect, where gastric accommodation cannot be further improved, can explain the lack of significant results in our study. In

the ultrasound study, on the other hand, one subject showed a consistently increased expansion rate at all tested volumes. We have to consider the possibility that this can, at least partly, be driving the significant results observed by Kusunoki et al. This study was powered to show significant differences in the IGP drop as a marker of gastric accommodation. Moreover, measures of the IGP drop adjust for preprandial differences in resting pressure. Taken together, it seems reasonable to state that the effects of rikkunshito on gastric accommodation in FD patients are rather modest and that the reported beneficial symptomatic effects of rikkunshito are not exclusively elicited by an improvement of gastric accommodation. Surprisingly, in the current study, we did observe a numerical decrease in overall baseline IGP after 4 weeks of rikkunshito intake, although this did not reach statistical significance. Based on the simplified law of Laplace, a lower IGP for the same level of gastric filling is associated with lower gastric wall tension, a physical variable that has been implicated in the generation of FD symptoms.[35,36] These results might indicate that more focus should go to changes in overall gastric tone, rather than gastric accommodation. Furthermore, it is unclear whether a longer treatment period might exert more significant effects on gastric tone.

An important result of this first exposure of rikkunshito in Europe is the confirmed safety and tolerability of the herbal product. No relevant adverse drug reactions were reported in the current study. Furthermore, rikkunshito treatment was not associated with an increased amount of adverse events compared with placebo.

One of the limitations of the study is the difference in taste between placebo and rikkunshito. Several patients reported one of both treatments to have a stronger and, for some patients, more aversive taste. Although the patients in the study remained blinded for the received treatment as they could not associate the taste with the identity of the treatment, it cannot be ruled out that the perceived aversive taste hampered the putative positive effects on GI symptoms. Second, the small sample size can partly explain the lack of significant results. A sample size of 30 patients was calculated to yield a 30% change in intragastric pressure at $P < .05$. However, due to a high dropout rate, only 23 patients completed the entire study and were therefore included in the analysis. Consequently, this study might be underpowered to detect significant differences in intragastric pressure. Third, the current study was conducted in tertiary care. Hence, the results cannot be generalized to the general FD population. Additionally, as stated above, increased chances of therapy-resistance might have abolished beneficial effects of rikkunshito. It is important to note that, although in general the results fail to show superiority of rikkunshito over placebo, 11 patients reported symptom improvement in one of both treatment arms and opted to receive open-label treatment with rikkunshito after study completion. Of these, five patients continued rikkunshito treatment for at least 2 months after study participation because of maintained symptom improvement.

In conclusion, rikkunshito improved postprandial fullness and early satiation, typical PDS symptoms, as scored on the LPDS diary compared to baseline, but was not superior to placebo for the symptoms assessed in this study. Furthermore, no significant changes were found in gastric accommodation. However, a numerically lower IGP was observed after 4 weeks of treatment. Rikkunshito can probably be considered safe and well-tolerated by European patients. More large-scale studies, preferably with primary care patients and a longer treatment period, are needed to increase our knowledge of the benefits of rikkunshito in the treatment of FD.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

LH and JT were involved in scientific concept and design of the study; FC and IM were involved in the acquisition of data; IM analyzed the data and drafted the manuscript; IM, FC, LH, AV, TV, and JT critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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