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Efficacy and safety of steamed ginger extract for gastric health: a randomized, double-blind, placebo-controlled multi-center clinical trial

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The aim of this study was to investigate the efficacy and safety of steamed ginger extract (GGE03) for mild to moderate functional dyspepsia (FD) in a 12-week randomized, double-blind, placebo-controlled clinical trial. A total of 80 subjects who met the inclusion criteria without meeting the exclusion criteria were randomly assigned to a GGE03 group (n = 40, 480 mg day^{-1} as GGE03) or a placebo group (n = 40). Efficacy and safety evaluations were conducted before intervention and at 12 weeks after intervention. The GGE03 group showed significantly improved gastrointestinal symptom rating scale (GSRS) total score and sub-scores (abdominal pain, constipation, indigestion, and reflux) compared to the placebo group (p < 0.001 for all). Moreover, the 36-Item Short Form Survey (SF-36) sub-scales (general health, health change, pain, physical functioning, role limitations due to physical health, and social functioning) were significantly improved in the GGE03 group compared to those in the placebo group (p = 0.002, p = 0.016, p = 0.006, p = 0.001, p < 0.001, and p = 0.023, respectively). Safety evaluations (adverse events, complete blood count, blood chemistry, and urinalysis) revealed that GGE03 was safe without causing clinically meaningful changes. Therefore, GGE03 has the potential to be used as a health functional food for improving gastric health.

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1. Introduction

Functional dyspepsia (FD) is one of the most common functional gastrointestinal disorders (FGIDs) affecting the gastroduodenal region of the gastrointestinal (GI) tract without identifiable structural lesions.[1] Epidemiological studies have indicated that 10–30% of the global population suffers from FD.[2] Factors such as dietary habits, sociocultural differences, psychological issues, and GI infections can affect dyspeptic symptoms, resulting in differences in the distribution of prevalence.[3] Symptom-based diagnostic criteria for FD currently use the Rome IV criteria (fourth edition), developed by a group of experts in functional gastrointestinal disorders.[4] According to the Rome IV criteria, FD is diagnosed if a complex of symptoms (postprandial fullness, early satiation, epigastric pain, and epigastric burning) is present for the last 3 months with the symptom onset for at least 6 months before diagnosis without any evidence of organic, systemic, or metabolic disease that would explain symptoms on routine investigations.[4,5]

Risk factors for the onset of FD include being a female, smoking, *Helicobacter pylori* (*H. pylori*) infection, acute gastrointestinal inflammation, the use of non-steroidal anti-inflammatory drugs, and mental disorders.[6] Although FD does not affect survival, FD symptoms can be very troublesome and difficult to treat. They usually have a natural history of recurrence and remission. FD is believed to pose a serious burden to individuals and society. It can affect diet (quantity and quality of food) and quality of life, reduce productivity, cause emotional disorders and somatization, and lead to high medical costs.[7–10]

Considering the high prevalence of FD with a high disease burden and a large number of potential patients having FD and gastritis, effective symptomatic and therapeutic interventions are needed.[11] However, standard management of FD has not yet been established, and satisfactory pharmacotherapy is also unavailable.[12] The most commonly used medications include *H. pylori* inhibitors, acid suppressants, proton pump inhibitors, antidepressants, antacids, and prokinetics.[13–16]

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However, these treatments are often very complicated by their limited responses, high costs, and side effects.[17,18] Given the current limitations of pharmacotherapy, there is growing interest in natural products and their bioactive derivatives as alternative strategies for managing FD. Functional foods derived from natural compounds offer potential therapeutic benefits, particularly in nutritional interventions aimed at improving digestive health and promoting gastric mucosal protection.

Ginger (*Zingiber officinale*) is one of the world's best known spices. It has been used as a spice for over 2000 years.[19,20] Traditionally, ginger has been used to treat a wide range of ailments including gastrointestinal disorders (such as stomachaches, abdominal spasm, nausea, and vomiting), arthritis, and motion sickness.[21–23] Ginger and its active components exhibit various biological activities, such as antioxidant,[24–26] anti-inflammatory,[27–34] and anticancer[35] properties.

The heating process by steaming can affect the chemical profile of natural products, leading to changes in bioactivities.[36] Recently, the steaming process has been applied to enhance the functionality of ginger.[37] Steamed ginger extract (GGE03) has been reported to have lower toxicity, increased 1-dehydro-6-gingerdione (GD) content, and higher efficacy than ginger extract (GE).[38–40] In previous studies, steamed ginger extract has shown effects of improving gastric health through anti-inflammatory and antioxidant activities,[38,39] anti-osteoarthritis activity,[41] anti-obesity effects,[42–46] anti-diabetic activity,[40] and anticancer effects.[37]

GGE03 is processed to enhance bioactive compounds, including GD, which may provide superior gastric protection to raw ginger. According to a previous study,[38] GGE03 has gastroprotective effects by improving mucosal defensive factors [mucosal prostaglandin E_2 (PGE_2) synthesis and total nitric oxide] and gastric antioxidation capability. It also exhibits anti-inflammatory properties against ethanol/HCl-induced gastric mucosal injury in a rat model.[38] In addition, GGE03 shows anti-inflammatory effects through nuclear factor-κB (NF-κB) inhibition in *H. pylori*-infected gastric epithelial cells.[39]

GGE03 has been proven to be effective in protecting the gastric mucosa and improving gastric health in preclinical studies.[38,39] However, there have been no such studies on humans. With the rising scientific interest in functional foods for gastric health, well designed and controlled clinical trials are necessary to evaluate the efficacy and safety of GGE03 in human subjects. Thus, its efficacy needs to be confirmed in clinical trials. Therefore, we conducted a 12-week, randomized, double-blind, and placebo-controlled multi-center clinical trial to evaluate the effectiveness and safety of GGE03 in improving gastric health for those with mild to moderate FD.

2. Materials and methods

2.1. Study design

A 12-week, randomized, double-blind, and placebo-controlled multi-center clinical trial was conducted to evaluate the effectiveness and safety of GGE03 in improving gastric health. This study was conducted at Santosh Hospital (Bangalore, India) and Vagus Super Specialty Hospital (Bangalore, India) from June 2020 to November 2020.

The study protocol (Protocol No: FT15-9H1) and informed consent form were reviewed and approved by the Institutional Ethics Committees of Santosh Hospital (date of approval: March 19, 2020) and Vagus Super Specialty Hospital (date of approval: July 10, 2020). This study was registered with the Clinical Trials Registry India (CTRI) on April 03, 2020 (CTRI number: CTRI/2020/04/024448). It was performed in accordance with the Declaration of Helsinki. The trial was conducted in agreement with the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP). This trial was conducted according to Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized clinical trials. All subjects participated in this study after signing an informed consent form.

A screening visit (visit 1) to select subjects based on the inclusion/exclusion criteria was conducted within two weeks. After baseline assessment, 80 study subjects were randomly assigned at a 1 : 1 ratio to a GGE03 group (n = 40) or a placebo group (n = 40) according to a randomization list generated by a computer. The block randomization technique was used for equal allocation of subjects in each treatment arm. The block size was 4, which was 2 × the number of treatment arms. The randomization list was computer generated using CRAN R software version 3.6.3. During the study period, all research investigators and subjects remained double-blinded from the randomization code. Subjects performed a total of five visits (visit 1: week −2; visit 2: week 0; visit 3: week 4; visit 4: week 8; and visit 5: week 12) during the 12-week study period. Baseline data were measured at visit 2 (week 0).

2.2 Study participants

A total of 80 subjects with mild to moderate FD participated in this clinical trial. Inclusion criteria were as follows: (1) male and female over 19 to 60 years of age; (2) subjects diagnosed with FD (Rome IV criteria) who did not require immediate medication due to upper abdominal discomfort or persistent/recurrent pain; (3) subjects who agreed to the written consent of the applicant and who could cooperate with the necessary visits and related tests and surveys for the study process. Exclusion criteria were as follows: (1) subjects who were allergic to natural products and drug ingredients; (2) subjects who had undergone endoscopic examination of stomach: Los Angeles (LA)-Grade A reflux esophagitis, gastric ulcer diagnosis, and acute gastritis requiring treatment; (3) subjects who had undergone past gastric acid suppression surgery or stomach and esophagus surgery except for closure of the ulcer or over sewing surgery; (4) subjects who needed to take steroids, bestero-inflammatory drugs, aspirin, or other drugs that could cause ulcers every day (but low-dose aspirin for cardiovascular disease); (5) subjects who were diagnosed with malignant tumors within five years; (6) subjects who consumed alcoholic beverages more than 4 times a week; (7) sub-

jects with severe liver dysfunction (>2.5 times normal upper limit of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT)) or serious liver dysfunction; (8) subjects with chronic kidney disease or severe renal disease including kidney dysfunction (>2 times normal upper limit of creatinine at screening visit); (9) subjects with unregulated diabetes or cerebrovascular disease and subjects who had been diagnosed within 3 months of the disease requiring surgery; (10) subjects who were diagnosed within three months of the following diseases: Zollinger–Ellison syndrome, primary esophageal motility disorder esophageal stricture, malignant disease of the gingival ulcer or upper GI tract, pancreatitis, absorption disorder, severe cardiovascular disease or pulmonary disease; (11) subjects who had undergone endoscopy within two weeks or before the first visit and subjects who consumed GI drugs such as proton pump inhibitors (PPIs), H2 receptor antagonist, gastroesophageal reflux disease (GERD) treatment, or prokinetics; (12) subjects who continued to take the following drugs: diazepam, hydantoin derivative, warfarin, anticholinergic, prostaglandin analog, antineoplastic agent and more than 165 mg of salicylate, steroid, non-steroidal aromatase inhibitors (NSAIs), osteoporosis treatment; (13) pregnant, nursing women or those who had a plan to become pregnant within 3 months; (14) subjects who had participated in other clinical trial within the 4 weeks; (15) subjects who are judged to be unable to comply with the requirements of the test.

2.3 Study products and interventions

The study products used in this study were provided by SD Biotechnologies (Seoul, Republic of Korea). GGE03 was prepared as described previously.[38,39] Briefly, ginger was washed three times with distilled water, dried at 50 °C for 30 h, and then steamed at 2–2.5 kgf cm^{-2} and 97 °C for 2 h. GGE03 was obtained by extracting steamed ginger with 15-fold 70% ethanol (v/v) for 15 hours at 85 °C and 1.5 kg cm^{-2} followed by passing through a 60-mesh filter and concentrating at −650 mmHg and 55 °C. GGE03 was spray-dried to obtain a powder and stored at −20 °C until use. The GD content in GGE03 was standardized to 1.15 mg g^{-1}.

All subjects were randomly assigned to a group administered with GGE03 (480 mg day^{-1} as GGE03) or a placebo group (0 mg day^{-1} as GGE03). Subjects took 1600 mg per day (2 tablets per day with morning meal intake) for 12 weeks. Placebo products were manufactured with ingredients that did not affect effectiveness. The placebo was composed of inactive ingredients such as microcrystalline cellulose, calcium carboxymethyl cellulose, and cocoa color. GGE03 and placebo products had the same appearance, weight, and properties.

2.4 Efficacy outcome measures

Primary outcomes were the gastrointestinal symptom rating scale (GSRS) and the 36-Item Short Form Survey (SF-36) questionnaire. Secondary outcomes were superoxide dismutase (SOD), malondialdehyde (MDA), and mucin 1.

The GSRS is a self-reported gastrointestinal symptom scale with a total of 15 symptom items combined. The questionnaire is divided into five sub-scores: abdominal pain (abdominal pain, nausea, and hunger pains), reflux (acid regurgitations, heartburn), indigestion (borborygmus, abdominal distension, eructation, and increased flatus), diarrhea (diarrhea, loose stools, and urgent need for defecation), and constipation (constipation, hard stools, and feeling of incomplete evacuation).[47] We measured the total score and individual scores of the GSRS. The scale was used to assess symptom severity using a seven-grade Likert scale, ranging from 1 (no discomfort at all) to 7 (very severe discomfort).[48] The reliability and validity of the GSRS have been well documented,[48,49] with higher scores indicating worse symptoms.[50] GSRS was completed before initiation of this study and at 12 weeks post-intervention.

For evaluating health-related quality of life (HRQoL), the SF-36 questionnaire was used. SF-36 is a widely used general health profile questionnaire with 36 question items of eight scales:[51,52] physical functioning (10 questions), role limitations due to physical health (4 questions), role limitations due to emotional problems (3 questions), pain (2 questions), general health (5 questions), energy or fatigue/vitality (4 questions), social functioning (2 questions), emotional well-being (5 questions), and a single question on changes in the state of health.[53] The higher the score, the better the quality of life. There is considerable evidence supporting the reliability and construct validity of SF-36.[54] The questionnaire was completed before interventions and at 12 weeks post-intervention.

Blood biomarkers such as SOD, MDA, and mucin 1 related to gastric health were measured before intervention and at 12 weeks after intervention.

2.5 Safety outcome measures

Safety outcomes included adverse events (AEs), complete blood count (CBC), blood chemistry, and urinalysis. AEs were monitored continuously throughout the study period. CBC analysis included white blood cells (WBCs), red blood cells (RBCs), hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Blood chemistry analysis included AST, ALT, GGT, alkaline phosphatase (ALP), total bilirubin, total protein, albumin, total cholesterol, triglyceride, high-density lipoprotein (HDL)-C, low-density lipoprotein (LDL)-C, blood urea nitrogen (BUN), creatinine, uric acid, and glucose. Urinalysis included pH and specific gravity. CBC analysis, blood chemistry analysis, and urinalysis were performed before and after intervention with a 12-hour fast. Vital signs including systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, and temperature were measured at each visit.

2.6 Statistical analysis

The sample size was calculated based on previous studies with similar designs.[49] It was calculated based on the change in the GSRS score before and after intervention in the test and placebo groups. GSRS and SF-36 were considered co-primary endpoints to assess symptom severity and quality of life, respectively. According to the ICH E9 guidelines,[55] multiplicity

adjustment is not required when co-primary endpoints are jointly necessary to demonstrate efficacy and are interpreted together. The sample size was determined based on the GSRS, which has been shown to be more sensitive to change in functional dyspepsia.[11,49,56] Based on a two-sided test for this calculation with a power of 80% and a significance level of 5%, the sample size for each group was determined by allowing a dropout rate of 20%. Based on the calculation, a total of 80 subjects (40 subjects per group) were needed. Therefore, 80 subjects were enrolled for a 1 : 1 randomization to the GGE03 and placebo groups.

All statistical analyses were performed using R 4.0.2 (R Foundation, Vienna, Austria). Continuous variables are presented as mean ± standard deviation (SD) and categorical variables are presented as number (percentage). Data analysis for efficacy was performed using the full analysis set (FAS). The FAS was defined as having data of efficacy evaluation collected more than once after administration of the trial product. Analysis for safety was performed using the safety set. The safety set was defined as those being randomly assigned to this clinical trial who took trial products at least once. Statistical analysis was performed on data according to protocol criteria. Comparison between groups was performed using an independent *t*-test for changes in values between before and after 12 weeks of intervention. Within each group, the comparison between before and 12 weeks after intake was analyzed using a paired *t*-test. Differences were considered statistically significant when *p*-values were less than 0.05.

3. Results

3.1. Subject characteristics

To select eligible participants, 81 volunteers were screened. Of these, one participant was excluded due to withdrawal of consent, resulting in 80 subjects who were randomized into GGE03 and placebo groups (n = 40 each). Fig. 1 presents a flowchart of the subjects' progression through this study. Demographic characteristics of each group are summarized in Table 1. They were generally comparable across groups.

3.2 Efficacy outcomes

Efficacy evaluation biomarkers were measured before intervention and at 12 weeks after intervention.

The results of the GSRS analysis are shown in Table 2 and Fig. 2. In the GGE03 group, the GSRS total score significantly decreased by 15.8 ± 19.8 after 12 weeks of intake compared to that at the baseline (p < 0.001). On the other hand, in the placebo group, the score decreased by 1.8 ± 12.2, showing no statistically significant change. When the change in GSRS total score was compared between groups, there was a statistically significant difference (p < 0.001). As a result of analyzing subscores of the GSRS, abdominal pain and indigestion scores significantly decreased by 5.0 ± 4.4 and 6.1 ± 5.8, respectively, in the GGE03 group (both p < 0.001), and by 1.2 ± 3.2 and 1.8 ± 4.4, respectively, in the placebo group (p = 0.018 and p = 0.012, respectively). There was a statistically significant decrease between the two groups (both p < 0.001). Constipation score significantly decreased by 1.5 ± 4.4 in the GGE03 group (p = 0.036), while it significantly increased by 1.4 ± 2.9 in the placebo group (p = 0.004), showing a statistically significant difference between the two groups (p < 0.001). Reflux score significantly decreased by 2.8 ± 3.2 in the GGE03 group (p < 0.001), but decreased by 0.6 ± 2.1 in the placebo group without reaching statistical significance, showing a statistically significant decrease between the two groups (p < 0.001).

Analysis results of SF-36 are shown in Table 3 and Fig. 3. Compared to those before intake, changes in the general health, health change, and pain scales of the SF-36 after 12 weeks of intake significantly increased by 20.5 ± 18.7, 31.9 ± 39.2, and 30.8 ± 36.9, respectively, in the GGE03 group (all p < 0.001), and by 8.5 ± 15.0, 11.9 ± 33.5, and 10.2 ± 27.1, respectively in the placebo group (p < 0.001, p = 0.031, and p = 0.022, respectively). This resulted in statistically significant differences between the two groups (p = 0.002, p = 0.016, and p = 0.006, respectively). The physical functioning scale significantly increased by 9.2 ± 24.1 in the GGE03 group (p = 0.020), but significantly decreased by 6.5 ± 16.9 in the placebo group (p = 0.020), showing a statistically significant difference between the two groups (p = 0.001). Role limitations due to physical health and social functioning scales significantly increased by 44.4 ± 43.3 and 19.7 ± 32.6, respectively, in the GGE03 group (both p < 0.001), whereas they increased by 6.9 ± 21.9 and 5.0 ± 23.0, respectively, in the placebo group without reaching statistical significance, showing statistically significant difference between the two groups (p < 0.001 and p = 0.023, respectively). Blood biomarkers (SOD, MDA, and mucin 1) showed no statistically significant difference between the two groups (data not shown).

3.3. Safety outcomes

The safety evaluation of GGE03 was analyzed in the safety set. During the clinical study period, a total of 15 subjects (6 in the GGE03 group and 9 in the placebo group) reported AEs. In the GGE03 group, adverse events included one case each of constipation, diarrhea, headache, and nausea, and two cases of fever. In the placebo group, adverse events included one case of body pain, one of headache, two of nausea, two of fever, and three cases of the cold. However, there was no significant difference in the incidence of AEs between the two groups. When AEs were evaluated by the investigator, they were found to be not related to the treatment received by subjects. In addition, AEs were mild or moderate. Medications were provided to treat AEs and all AEs were resolved. There were no serious AEs (SAEs).

Results of CBC analysis, blood chemistry analysis, and urinalysis are shown in Table 4. No significant differences between the two groups were found. All results were within their normal ranges. There were no clinically meaningful changes after intervention. Therefore, it was confirmed that the 12-week intake of GGE03 was safe for humans.

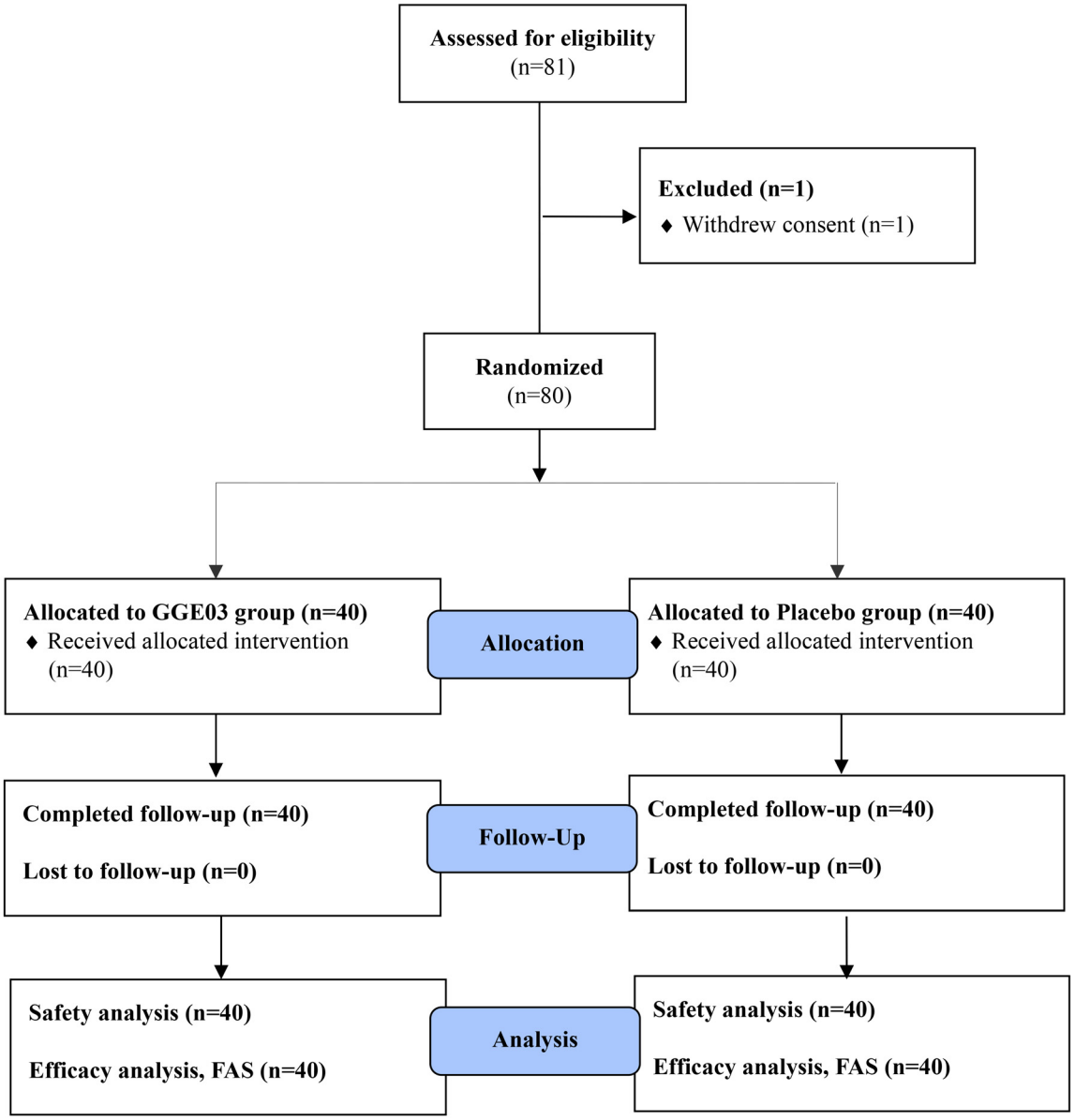

Fig. 1 Flow-chart of subjects. The number of study participants enrolled, allocated, followed, and analyzed is shown using the CONSORT 2010 flow diagram.

4. Discussion

This is the first 12-week randomized, double-blind, placebo-controlled, multi-center clinical study to evaluate the effectiveness and safety of GGE03 manufactured by extracting steamed ginger for improving gastric health. In mild to moderate FD, 12-week intake of GGE03 (480 mg day^{-1}) significantly improved the GSRS total score and sub-scores of abdominal pain, constipation, indigestion, and reflux compared to the control (intake of placebo). In addition, SF-36 sub-scales of general health, health change, pain, physical functioning, role limitations due to physical health, and social functioning were statistically significantly improved compared to those of the placebo group. This confirmed that GGE03 intake could improve gastric health and quality of life without side effects.

In this randomized clinical trial, GGE03 significantly improved gastrointestinal symptoms and quality of life scores in FD. These findings may be explained by mechanistic insights provided by previous preclinical studies,[38,39] which demonstrated that GGE03 exerts gastroprotective effects through mechanisms such as antioxidant, anti-inflammatory, and mucosal defense. In a rat model of ethanol/HCl-induced gastric injury,[38] GGE03 enhanced gastric mucosal defense by increasing PGE_2 and nitric oxide (NO) production, which significantly reduced the gastric lesion area and mucosal damage. It also improved antioxidant capacity by increasing glutathione (GSH) and the activity of antioxidant enzymes

Table 1 Baseline demographic characteristics of subjects

	GGE03 group (n = 40)	Placebo group (n = 40)	Total (n = 80)	p-Value[a]
Sex (M/F)	25/15	27/13	52/28	0.639[b]
Age (years)	39.7 ± 10.9	39.1 ± 11.4	39.4 ± 11.1	0.794
Height (cm)	167.6 ± 8.4	165.4 ± 8.6	166.5 ± 8.5	0.258
Weight (kg)	62.9 ± 9.5	64.4 ± 8.0	63.7 ± 8.8	0.460
SBP (mmHg)	117.3 ± 3.3	115.8 ± 4.1	116.6 ± 3.8	0.065
DBP (mmHg)	76.0 ± 5.6	75.7 ± 7.0	75.9 ± 6.3	0.833
Pulse (bpm)	78.0 ± 11.6	81.5 ± 10.5	79.7 ± 11.1	0.170
Temperature (°C)	36.6 ± 0.6	36.7 ± 0.5	36.7 ± 0.6	0.426
Alcohol (n, %)	11 (27.5%)	9 (22.5%)	20 (25.0%)	0.797[c]
Smoking (n, %)	6 (15.0%)	6 (15.0%)	12 (15.0%)	1.000[c]
GSRS total score	44.5 ± 5.4	43.0 ± 6.9	43.8 ± 6.2	0.317
SF-36 total score	55.7 ± 6.5	56.1 ± 5.9	55.9 ± 6.2	0.774

Values are presented as mean ± SD or number (%). [a] Analyzed using an independent t-test for the change values between the groups (GGE03 *vs.* placebo). [b] Analyzed using a chi-square test between the groups (GGE03 *vs.* placebo). [c] Analyzed using Fisher's exact test between the groups (GGE03 *vs.* placebo).

Table 2 Changes in GSRS before and after 12 weeks of intake

	GGE03 group (n = 40)				Placebo group (n = 40)				
	Baseline	12 weeks	Change value	p-Value[a]	Baseline	12 weeks	Change value	p-Value[a]	p-Value[b]
Total Score	44.5 ± 5.4	28.7 ± 19.2	−15.8 ± 19.8	<0.001***	43.0 ± 6.9	41.3 ± 13.9	−1.8 ± 12.2	0.363	<0.001***
Abdominal pain	10.8 ± 1.5	5.8 ± 3.7	−5.0 ± 4.4	<0.001***	10.5 ± 1.5	9.2 ± 3.4	−1.2 ± 3.2	0.018*	<0.001***
Constipation	6.9 ± 3.1	5.4 ± 3.7	−1.5 ± 4.4	0.036*	6.2 ± 3.1	7.6 ± 2.8	1.4 ± 2.9	0.004**	<0.001***
Diarrhea	6.1 ± 3.2	5.9 ± 4.2	−0.2 ± 5.0	0.778	6.3 ± 3.1	6.7 ± 2.8	0.4 ± 2.9	0.325	0.461
Indigestion	14.1 ± 1.5	8.0 ± 5.2	−6.1 ± 5.8	<0.001***	14.0 ± 2.6	12.2 ± 4.7	−1.8 ± 4.4	0.012*	<0.001***
Reflux	6.5 ± 1.6	3.7 ± 2.6	−2.8 ± 3.2	<0.001***	6.1 ± 1.8	5.5 ± 2.2	−0.6 ± 2.1	0.111	<0.001***

Values are presented as mean ± SD. [a] Analyzed using a paired t-test between the baseline and 12 weeks within each group (weeks 0 *vs.* 12). [b] Analyzed using an independent t-test for the change values between the groups (GGE03 *vs.* placebo). *p < 0.05, **p < 0.01, and ***p < 0.001.

such as SOD and catalase (CAT), while reducing MDA levels, a marker of lipid peroxidation. Furthermore, it exhibited anti-inflammatory effects by suppressing myeloperoxidase (MPO) activity, inhibiting NF-κB activation, and downregulating the expression of pro-inflammatory cytokines, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). Moreover, in an *H. pylori* infected gastric epithelial cell model,[39] GGE03 suppressed the growth of *H. pylori* and attenuated gastric inflammation by downregulating the expression of pro-inflammatory cytokines (IL-8, TNF-α, and IL-6), inducible NOS (iNOS), and interferon-γ (IFN-γ), inhibiting NF-κB activation, and reducing nitric oxide and MPO activity. Taken together, these preclinical findings provide mechanistic support for the observed clinical benefits of GGE03 in FD and highlight its potential as a promising functional ingredient for gastric health.

FD is a chronic and relapsing disease. Its treatment is difficult due to its multifactorial etiology. A combination of drugs is required to correct its underlying pathology.[49,57] The overall symptom relief rate of treatments used for FD (*H. pylori* eradication, antacids, prokinetics, and antidepressants) is only 50%,[58,59] with 15–20% having persistent symptoms and 30–35% experiencing a change in symptoms.[60–62] Therefore, health functional foods that exhibit multiple mechanisms of action might be more effective and helpful than drugs that act through only one mechanism.[63] Ginger contains various bioactive phytochemicals, including phenol compounds (mainly gingerols, shogaols, and paradols) and terpene compounds (β-bisabolene, α-curcumene, zingiberene, α-farnesene, β-sesquiphellandrene, and so on).[41,64] In particular, the steaming process enhances the formation of GD, increasing its content by over threefold compared to raw ginger extract.[40] GD has been reported to downregulate pro-inflammatory signaling pathways, particularly NF-κB-related gene expression, and exhibits strong antioxidant activity.[65,66] Additionally, thermal processing facilitates the conversion of gingerols into shogaols, particularly 6-shogaol, which is recognized for its anti-inflammatory properties, including suppression of COX-2 and iNOS expression, leading to reduced nitric oxide production and inhibition of cytokines such as TNF-α and IL-6.[37,67] Overall, these mechanisms suggest that the steaming process enhances the bioactivity of ginger by increasing the levels of various active compounds, including GD and 6-shogaol, thereby supporting the therapeutic potential of GGE03 as an effective complementary intervention for the management of FD.

The GSRS is one of the most established and responsive disease-specific instruments with five symptom clusters

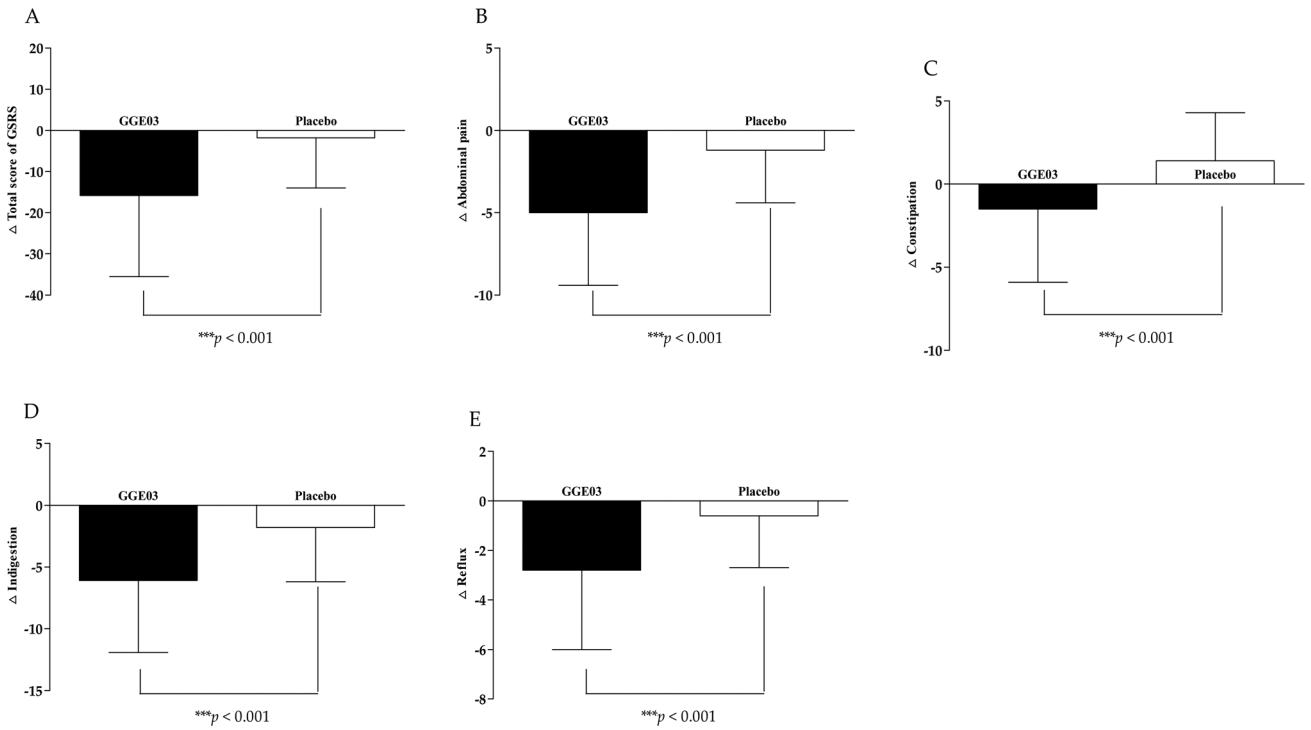

Fig. 2 Changes in GSRS. (A) Total score of GSRS, (B) abdominal pain, (C) constipation, (D) indigestion, and (E) reflux were measured in GGE03 and placebo groups at the baseline and at 12 weeks. Values are presented as mean ± SD. Analyzed using an independent *t*-test for the change values between the groups. **p* < 0.05, ***p* < 0.01, and ****p* < 0.001 *vs.* the placebo group.

Table 3 Changes in SF-36 before and after 12 weeks of intake

	GGE03 group (n = 40)				Placebo group (n = 40)				
	Baseline	12 weeks	Change value	p-Value[a]	Baseline	12 weeks	Change value	p-Value[a]	p-Value[b]
Total score	55.7 ± 6.5	64.4 ± 11.6	8.6 ± 12.5	<0.001***	56.1 ± 5.9	61.4 ± 18.9	5.3 ± 17.2	0.058	0.323
Emotional well-being	60.2 ± 6.3	56.9 ± 3.9	−3.3 ± 6.5	0.003**	62.2 ± 4.3	59.4 ± 5.9	−2.8 ± 5.6	0.003**	0.714
Energy or fatigue	58.0 ± 8.4	52.0 ± 5.5	−6.0 ± 11.0	0.001**	59.9 ± 6.0	57.6 ± 9.5	−2.2 ± 9.2	0.130	0.103
General health	37.0 ± 5.4	57.5 ± 17.7	20.5 ± 18.7	<0.001***	36.1 ± 3.7	44.6 ± 15.5	8.5 ± 15.0	<0.001***	0.002**
Health change	38.1 ± 13.9	70.0 ± 43.2	31.9 ± 39.2	<0.001***	41.9 ± 14.3	53.8 ± 33.3	11.9 ± 33.5	0.031*	0.016*
Pain	43.8 ± 8.3	74.6 ± 36.2	30.8 ± 36.9	<0.001***	44.6 ± 8.7	54.8 ± 26.3	10.2 ± 27.1	0.022*	0.006**
Physical functioning	70.8 ± 10.3	80.0 ± 26.6	9.2 ± 24.1	0.020*	72.1 ± 9.5	65.6 ± 17.1	−6.5 ± 16.9	0.020*	0.001**
Role limitations due to emotional problems	75.8 ± 28.2	76.7 ± 31.3	0.8 ± 38.8	0.893	67.5 ± 34.2	70.8 ± 33.1	3.3 ± 31.8	0.512	0.754
Role limitations due to physical health	31.2 ± 29.8	75.6 ± 35.1	44.4 ± 43.3	<0.001***	33.8 ± 29.7	40.6 ± 33.3	6.9 ± 21.9	0.054	<0.001***
Social functioning	49.7 ± 12.8	69.4 ± 34.5	19.7 ± 32.6	<0.001***	51.2 ± 8.9	56.2 ± 23.2	5.0 ± 23.0	0.176	0.023*

Values are presented as mean ± SD. [a] Analyzed using a paired *t*-test between the baseline and 12 weeks within each group (weeks 0 *vs.* 12). [b] Analyzed using an independent *t*-test for the change values between the groups (GGE03 *vs.* placebo). **p* < 0.05, ***p* < 0.01, and ****p* < 0.001.

depicting reflux, abdominal pain, indigestion, diarrhea, and constipation.[18] It has been widely used in FD studies.[68,69] In this study, the GSRS total score and sub-scores of abdominal pain, constipation, indigestion, and reflux were significantly improved at 12 weeks after taking GGE03 compared to those before taking GGE03. In addition, the improvement in the GGE03 group was larger than that in the placebo group, showing a statistically significant difference between the two groups. These results indicate that GGE03 has broad-spectrum efficacy in addressing multiple gastrointestinal symptoms associated with FD. In previous preclinical studies,[38,39] GGE03 significantly protected the gastric mucosa from damage by improving mucosal defense factors (NO and PGE2) and increasing antioxidant and anti-inflammatory actions, leading to an improvement in gastric health due to gastric mucosal protection. Therefore, GGE03 might play a crucial role in improving gastric health, indicating its potential as a therapeutic agent for subjects with FD. Similar clinical

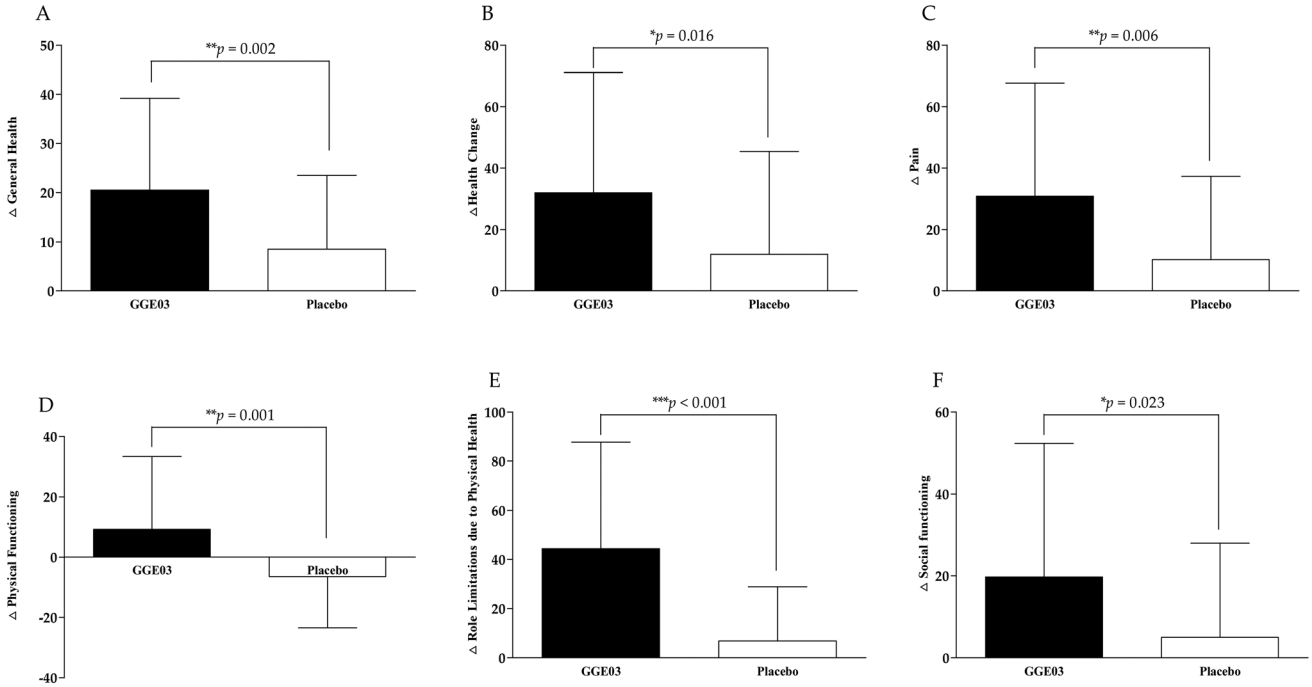

Fig. 3 Changes in SF-36. (A) General health, (B) health change, (C) pain, (D) physical functioning, (E) role limitations due to physical health, and (F) social functioning were measured in GGE03 and placebo groups at the baseline and at 12 weeks. Values are presented as mean ± SD. Analyzed using an independent *t*-test for the change values between the groups. $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$ *vs.* the placebo group.

studies[11,49,56] with an RCT design have been conducted to evaluate the efficacy of plant extracts in FD subjects. In clinical studies in which GCWB104 (*Flos Lonicera* extract),[49] *Cudrania tricuspidata* extract,[56] and fermented gold kiwi[11] were consumed for 8 weeks, the GSRS total score significantly improved after consumption, showing similar results to this study. However, the degree of improvement in the GSRS total score was significantly greater for GGE03, confirming the superiority of GGE03 in improving gastric health. Such a positive effect of GGE03 in improving gastric health might be due to the unique manufacturing process and sufficient intake period of GGE03.

Because FD subjects show significant impairment in HRQoL, measurement and improvement of HRQoL in FD are important.[70] SF-36 is a widely used and validated measure of generic HRQoL in gastroenterology.[71,72] In this study, we found that GGE03 intake improved SF-36 sub-scales (general health, health change, pain, physical functioning, role limitations due to physical health, and social functioning) of subjects with FD, thereby improving their health-related quality of life. This was an opportunity to confirm the extended effect of GGE03 in improving upper abdominal symptoms related to the stomach through preclinical trials.[38,39] In a clinical study in which ginger powder (1.2 g d^{-1}) was consumed for 14 days,[73] symptoms of indigestion were found to be improved, although quality of life did not change. This improvement is particularly notable when compared to a similar clinical study with analogous designs. Therefore, GGE03 can be considered an effective functional ingredient for restoring quality of life impaired by FD.

In preclinical studies,[38,39] GGE03 showed antioxidant effects by improving MDA, CAT activity, GSH, and SOD and anti-inflammatory effects by improving MPO, NF-κB, and pro-inflammatory cytokines (including IL-1β, IL-6, IL-8, and TNF-α). However, in the present study, blood biomarkers (SOD, MDA, and mucin 1) of FD subjects showed no significant changes following the consumption of GGE03. This might be because this study was conducted at the borderline level that did not require drug treatment in FD subjects, making it difficult to obtain significant results from blood biomarkers. Similar findings have been reported in the clinical trial,[74] where most laboratory parameters in FD patients remained within normal ranges. Additionally, in a clinical study[75] with an RCT design on the effect of *Nigella sativa* in patients with *H. pylori* infection and FD, biochemical markers IL-8, high-sensitivity C-reactive protein (hs-CRP), and MDA showed no significant changes. However, it is possible that GGE03 contributes to FD improvement through other mechanisms. This warrants further investigation.

Numerous studies[33,76–79] have reported the effectiveness of ginger in improving and treating FD symptoms. Clinical studies[33,79] with an RCT design have reported that ginger can reduce FD symptoms, including upper abdominal discomfort, compared to placebo. However, the hot and pungent taste of ginger makes it difficult to eat, leading to a decrease in its consumption. To solve this problem, various methods of processing ginger, including steaming, are used. Processing can reduce the pungent taste, extend the shelf life, increase the contents of health functional compounds, and improve the

Table 4 Changes in laboratory tests before and after 12 weeks of intake

		GGE03 group (n = 40)				Placebo group (n = 40)				
		Baseline	12 weeks	Change value	p-Value[a]	Baseline	12 weeks	Change value	p-Value[a]	p-Value[b]
CBC	WBC (cells per mcL)	6965.0 ± 1410.3	7012.5 ± 1412.8	47.5 ± 1014.5	0.769	6889.0 ± 1716.3	7016.2 ± 1464.3	127.3 ± 1409.4	0.571	0.772
	RBC (cells per mcL)	4.8 ± 0.8	4.8 ± 0.8	0.0 ± 0.4	0.890	4.8 ± 0.8	4.8 ± 0.8	−0.1 ± 0.4	0.367	0.489
	Hemoglobin (g dL^{-1})	14.3 ± 1.1	14.3 ± 1.6	−0.1 ± 1.2	0.711	14.3 ± 1.7	14.5 ± 1.1	0.1 ± 1.5	0.524	0.467
	Hematocrit (%)	40.6 ± 2.9	40.7 ± 3.9	0.1 ± 3.7	0.819	40.4 ± 3.0	40.9 ± 2.8	0.5 ± 3.5	0.349	0.632
	Platelets (lakhs per cu mm)	118.6 ± 157.6	119.4 ± 160.1	0.8 ± 57.6	0.934	122.5 ± 163.2	132.8 ± 171.9	10.3 ± 51.8	0.215	0.438
	Neutrophils (%)	57.5 ± 10.4	57.9 ± 10.7	0.4 ± 5.7	0.685	58.9 ± 11.1	59.4 ± 11.4	0.6 ± 6.4	0.572	0.880
	Lymphocytes (%)	31.3 ± 7.5	31.0 ± 8.2	−0.2 ± 6.0	0.818	31.0 ± 7.1	29.6 ± 7.5	−1.4 ± 5.8	0.128	0.363
	Monocytes (%)	5.2 ± 1.9	4.9 ± 2.1	−0.2 ± 2.0	0.448	5.2 ± 1.9	5.4 ± 2.0	0.2 ± 2.4	0.589	0.364
	Eosinophils (%)	3.7 ± 1.5	3.7 ± 1.4	−0.0 ± 1.5	0.943	3.7 ± 1.0	3.7 ± 1.5	0.0 ± 1.7	0.934	0.913
	Basophils (%)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	—	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	—	—
Blood chemistry	AST (IU L^{-1})	25.5 ± 5.7	25.1 ± 6.7	−0.4 ± 4.9	0.621	24.3 ± 7.2	25.9 ± 6.5	1.6 ± 5.5	0.067	0.087
	ALT (IU L^{-1})	24.8 ± 6.5	24.4 ± 7.2	−0.4 ± 5.0	0.588	26.4 ± 8.6	27.4 ± 8.3	1.1 ± 5.1	0.182	0.181
	GGT (IU L^{-1})	27.4 ± 10.3	26.7 ± 10.6	−0.7 ± 5.9	0.460	29.5 ± 10.7	28.2 ± 11.4	−1.3 ± 7.4	0.293	0.714
	ALP (IU L^{-1})	97.8 ± 32.1	94.7 ± 31.1	−3.1 ± 19.6	0.320	95.7 ± 32.4	100.3 ± 29.5	4.6 ± 15.5	0.065	0.053
	Total bilirubin (mg dL^{-1})	0.7 ± 0.2	0.7 ± 0.3	0.0 ± 0.2	0.849	0.7 ± 0.2	0.8 ± 0.2	0.0 ± 0.2	0.187	0.495
	Total protein (g dL^{-1})	7.0 ± 0.8	7.1 ± 0.9	0.0 ± 0.3	0.606	7.2 ± 0.6	7.1 ± 0.6	−0.1 ± 0.3	0.075	0.102
	Albumin (g dL^{-1})	4.1 ± 0.5	4.0 ± 0.5	−0.1 ± 0.4	0.273	4.2 ± 0.5	4.1 ± 0.6	−0.1 ± 0.6	0.340	0.884
	Total cholesterol (mg dL^{-1})	150.5 ± 28.1	153.8 ± 23.3	3.2 ± 19.5	0.298	153.2 ± 24.2	149.8 ± 21.7	−3.3 ± 12.8	0.110	0.079
	Triglyceride (mg dL^{-1})	108.2 ± 21.9	105.7 ± 15.3	−2.5 ± 21.0	0.457	107.6 ± 18.0	106.7 ± 16.2	−0.9 ± 11.3	0.611	0.676
	HDL-C (mg dL^{-1})	48.9 ± 8.6	49.1 ± 8.6	0.1 ± 3.3	0.809	48.4 ± 9.7	48.0 ± 9.7	−0.4 ± 4.4	0.580	0.556
	LDL-C (mg dL^{-1})	83.2 ± 26.0	83.6 ± 26.0	0.4 ± 6.8	0.706	81.8 ± 31.2	80.9 ± 28.7	−0.8 ± 15.1	0.734	0.641
	BUN (mg dL^{-1})	13.6 ± 3.5	14.0 ± 3.9	0.4 ± 2.4	0.310	14.2 ± 3.7	13.6 ± 3.8	−0.6 ± 2.7	0.182	0.093
	Creatinine (mg dL^{-1})	1.0 ± 0.1	0.9 ± 0.2	−0.0 ± 0.2	0.839	0.9 ± 0.2	0.9 ± 0.2	−0.0 ± 0.2	0.471	0.687
	Uric acid	5.2 ± 1.3	5.3 ± 1.4	0.1 ± 0.8	0.456	5.3 ± 2.4	5.0 ± 1.4	−0.3 ± 2.2	0.338	0.250
	Glucose (mg dL^{-1})	96.5 ± 21.6	98.3 ± 21.6	1.7 ± 14.8	0.464	98.8 ± 20.4	102.2 ± 21.1	3.4 ± 10.7	0.053	0.568
Urinalysis	pH	5.9 ± 0.5	6.0 ± 0.4	0.1 ± 0.5	0.086	6.2 ± 0.3	6.1 ± 0.4	−0.1 ± 0.5	0.481	0.081
	Specific gravity	1.0 ± 0.0	1.0 ± 0.0	−0.0 ± 0.0	0.772	1.0 ± 0.0	1.0 ± 0.0	−0.0 ± 0.0	0.895	0.769

Values are presented as mean ± SD. [a] Analyzed using a paired t-test between the baseline and 12 weeks within each group (weeks 0 *vs.* 12). [b] Analyzed using an independent t-test for the change values between the groups (GGE03 *vs.* placebo).

safety of ginger.[80] Steaming, a thermal processing method, has been shown to alter the phytochemical profile of ginger, enhancing its bioavailability and biological activity. Steamed ginger extract is known to have higher GD content than ginger extract.[40] GD is known to have antioxidant and anti-inflammatory activities.[66] Therefore, the gastric health improvement effect of GGE03 might be due to the increase of GD through the steaming process.

Placebo is important for maintaining blinding. Thus, controlling the placebo effect is critical in RCT clinical trials.[81] According to previous studies, the placebo response rate in FD subjects ranged from 37.2% to 42.2%.[82,83] A placebo effect is thought to be influenced by psychological, neurobiological, and natural mechanisms.[84] In this study, to overcome the placebo effect, a double-blind method and subject education at each visit were used to encourage management of expectations, thus reducing the placebo response.[85] In addition, the placebo was made of ingredients that did not affect the efficacy. It was provided in the same appearance and amount. In this study, the GGE03 group demonstrated a significantly greater improvement in FD symptoms compared to the placebo group. While the placebo group exhibited only limited changes, the GGE03 group showed substantial and meaningful symptom relief. This highlights the effectiveness of unique active compounds in GGE03 in alleviating FD symptoms, suggesting that GGE03 is a more efficient treatment option than placebo.

FD is a chronic disease. Thus, treatment should be safe for long-term use. However, the most common medications for FD treatment can cause various side effects, such as increased risks of intestinal infection, small intestinal bacterial overgrowth, iron and vitamin B12 component malabsorption, and atrophic gastritis.[86,87] To evaluate the safety of GGE03 in this study, AEs, CBC analysis, blood chemistry analysis, and urinalysis were performed. There were no significant differences in any safety biomarkers between the two groups. All biomarkers were within their normal ranges, showing no clinically meaningful changes. Therefore, it was confirmed that 12 weeks of GGE03 intake was safe in humans. Ginger is "generally recognized as safe" (GRAS) by the US Food and Drug Administration (FDA). It is a safe ingredient with few reported interactions between ginger and drugs.[45,88,89] In a clinical study[41] with an RCT design targeting mild knee osteoarthritis, after GGE03 (480 mg day^{-1}) was administered for 12 weeks, safety markers showed no significant changes, similar to the results of this study. In addition, a clinical study[42] has reported that consuming steamed ginger ethanol extract (200 mg day^{-1}) for 12 weeks is safe in obese subjects, consistently confirming the safety of ginger. Therefore, GGE03 intake can help reduce drug dependence and improve symptoms for FD treatment without side effects.

This study has a few limitations. First, the enrollment and evaluation of subjects using a self-reported questionnaire might have resulted in biased study findings.[90] These questionnaires allow one to subjectively evaluate one's symptoms or conditions. However, the accuracy of the results might be reduced due to issues such as social desirability bias and recall bias. In addition, subjects may underestimate or overestimate their conditions, which may reduce the reliability of results. To reduce such bias, objective biomarkers should also be measured in expanded clinical studies.[11] Second, the short study period might be insufficient to assess long-term effects or persistence due to follow-up observations. FD is considered a chronic disease. Its symptoms vary widely over a long period of time.[58] In addition, its symptoms may relapse if the intervention is discontinued, making longer follow-up observations necessary.[11] Thus, expanded clinical studies with longer follow-up periods are needed. Third, the effect of GGE03 on *H. pylori* was not analyzed. It is known that *H. pylori* eradication can improve the symptoms of FD.[91] Therefore, future studies need to analyze the effect of GGE03 on *H. pylori*. Moreover, although all participants were diagnosed with FD according to the Rome IV criteria, baseline data on individual symptom frequencies were not collected. This absence of symptom-specific information is a limitation that should be considered in future studies.

Nevertheless, our study represents the first clinical trial with an RCT design to evaluate the efficacy and safety of GGE03 in FD subjects. This study provides novel clinical evidence demonstrating that GGE03 significantly improves gastric health by alleviating FD symptoms and enhancing quality of life, reinforcing its potential as a health functional food for gastric health promotion.

5. Conclusions

This is the first 12-week, randomized, double-blind, placebo-controlled clinical trial conducted to evaluate the efficacy and safety of GGE03 for gastric health in FD subjects. The intake of GGE03 significantly improved GSRS scores (total and subscores) and SF-36 sub-scales compared to the placebo group, demonstrating its broad-spectrum efficacy in alleviating multiple FD-related symptoms. It enhanced gastric health and quality of life without side effects. Therefore, this study provides sufficient clinical evidence that GGE03 can be used as a health functional food for improving gastric health.

Author contributions

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Conflicts of interest

The authors declare no conflicts of interest. The funder was not involved in the study design, collection, analysis, and

interpretation of data, the writing of this article or the decision to submit it for publication.

Data availability

The data presented in this study are available within the article.

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References

1 N. J. Talley, Functional Dyspepsia: Advances in Diagnosis and Therapy, *Gut Liver*, 2017, **11**, 349–357.
2 G. S. Sayuk and C. P. Gyawali, Functional dyspepsia: diagnostic and therapeutic approaches, *Drugs*, 2020, **80**, 1319–1336.
3 U. C. Ghoshal, R. Singh, F.-Y. Chang, X. Hou, B. C. Y. Wong and U. Kachintorn, Epidemiology of uninvestigated and functional dyspepsia in Asia: facts and fiction, *J. Neurogastroenterol. Motil.*, 2011, **17**, 235.
4 V. Stanghellini, F. K. Chan, W. L. Hasler, J. R. Malagelada, H. Suzuki, J. Tack and N. J. Talley, Gastroduodenal disorders, *Gastroenterology*, 2016, **150**, 1380–1392.
5 V. Ivashkin, I. Mayev, A. Sheptulin, T. Lapina, A. Trukhmanov, I. Kartavenko, V. Kiprianis and O. Okhlobystina, Diagnosis and treatment of the functional dyspepsia: clinical guidelines of the Russian Gastroenterological Association, *Russ. J. Gastroenterol. Hepatol. Coloproctol.*, 2017, **27**, 50–61.
6 L. Wauters, R. Dickman, V. Drug, A. Mulak, J. Serra, P. Enck, J. Tack and the ESNM FD consensus group, United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on functional dyspepsia, *United Eur. Gastroenterol. J.*, 2021, **9**, 307.
7 B. Lacy, K. Weiser, A. Kennedy, M. Crowell and N. Talley, Functional dyspepsia: the economic impact to patients, *Aliment. Pharmacol. Ther.*, 2013, **38**, 170–177.
8 D. J. Gracie, P. Bercik, D. G. Morgan, C. Bolino, M. I. Pintos-Sanchez, P. Moayyedi and A. C. Ford, No increase in prevalence of somatization in functional vs organic dyspepsia: a cross–sectional survey, *Neurogastroenterol. Motil.*, 2015, **27**, 1024–1031.
9 I. Aziz, O. S. Palsson, H. Törnblom, A. D. Sperber, W. E. Whitehead and M. Simrén, Epidemiology, clinical characteristics, and associations for symptom-based Rome IV functional dyspepsia in adults in the USA, Canada, and the UK: a cross-sectional population-based study, *Lancet Gastroenterol. Hepatol.*, 2018, **3**, 252–262.
10 T. Esterita, S. Dewi, F. G. Suryatenggara and G. Glenardi, Association of functional dyspepsia with depression and anxiety: a systematic review, *J. Gastrointest. Liver Dis.*, 2021, **30**, 259–266.
11 S. M. Shin, S. J. Youn, Y. Choi, B. M. Kim, N. Y. Lee, H. J. Oh, H. S. Kwon and H. Ko, Fermented Gold Kiwi for Improved Gastric Health: Evaluation of Efficacy and Safety in a Randomised, Double-Blind, Placebo-Controlled Trial, *Nutrients*, 2024, **16**, 2670.
12 K. H. Oh, Y. Nam, J. H. Jeong, I. K. Kim and U. D. Sohn, The effect of DA-9701 on 5-hydroxytryptamine-induced contraction of feline esophageal smooth muscle cells, *Molecules*, 2014, **19**, 5135–5149.
13 L. E. Mazzoleni, G. B. Sander, C. F. de Magalhães Francesconi, F. Mazzoleni, D. M. Uchoa, L. R. De Bona, T. C. Milbradt, P. S. Von Reisswitz, O. Berwanger and M. Bressel, Helicobacter pylori eradication in functional dyspepsia: HEROES trial, *Arch. Intern. Med.*, 2011, **171**, 1929–1936.
14 P. Moayyedi, B. C. Delaney, N. Vakil, D. Forman and N. J. Talley, The efficacy of proton pump inhibitors in non-ulcer dyspepsia: a systematic review and economic analysis, *Gastroenterology*, 2004, **127**, 1329–1337.
15 J. Tack, P. Janssen, T. Masaoka, R. Farré and L. Van Oudenhove, Efficacy of buspirone, a fundus-relaxing drug, in patients with functional dyspepsia, *Clin. Gastroenterol. Hepatol.*, 2012, **10**, 1239–1245.
16 E. M. Quigley, Prokinetics in the management of functional gastrointestinal disorders, *J. Neurogastroenterol. Motil.*, 2015, **21**, 330.
17 P. Moayyedi and J. Mason, Clinical and economic consequences of dyspepsia in the community, *Gut*, 2002, **50**, iv10–iv12.
18 K. Mala, J. Thomas, D. S. Syam, B. Maliakel and I. Krishnakumar, Safety and Efficacy of Ferula asafoetida in Functional Dyspepsia: A Randomized, Double–Blinded, Placebo–Controlled Study, *Evidence-Based Complementary Altern. Med.*, 2018, **2018**, 4813601.
19 J. P. Bartley and A. L. Jacobs, Effects of drying on flavour compounds in Australian–grown ginger (Zingiber officinale), *J. Sci. Food Agric.*, 2000, **80**, 209–215.
20 B. Fuhrman, M. Rosenblat, T. Hayek, R. Coleman and M. Aviram, Ginger extract consumption reduces plasma cholesterol, inhibits LDL oxidation and attenuates development of atherosclerosis in atherosclerotic, apolipoprotein E-deficient mice, *J. Nutr.*, 2000, **130**, 1124–1131.
21 E. Langner, S. Greifenberg and J. Gruenwald, Ginger: history and use, *Adv. Ther.*, 1998, **15**, 25–44.
22 B. White, Ginger: an overview, *Am. Fam. Physician*, 2007, **75**, 1689–1691.
23 H. S. El-Abhar, L. N. A. Hammad and H. S. A. Gawad, Modulating effect of ginger extract on rats with ulcerative colitis, *J. Ethnopharmacol.*, 2008, **118**, 367–372.

24 Y. Masuda, H. Kikuzaki, M. Hisamoto and N. Nakatani, Antioxidant properties of gingerol related compounds from ginger, *BioFactors*, 2004, **21**, 293–296.
25 W. Si, Y. P. Chen, J. Zhang, Z.-Y. Chen and H. Y. Chung, Antioxidant activities of ginger extract and its constituents toward lipids, *Food Chem.*, 2018, **239**, 1117–1125.
26 A. H. El-Ghorab, M. Nauman, F. M. Anjum, S. Hussain and M. Nadeem, A comparative study on chemical composition and antioxidant activity of ginger (Zingiber officinale) and cumin (Cuminum cyminum), *J. Agric. Food Chem.*, 2010, **58**, 8231–8237.
27 C. G. Frondoza, A. Sohrabi, A. Polotsky, P. V. Phan, D. S. Hungerford and L. Lindmark, An in vitro screening assay for inhibitors of proinflammatory mediators in herbal extracts using human synoviocyte cultures, *In Vitro Cell. Dev. Biol.: Anim.*, 2004, **40**, 95–101.
28 H.-Y. Young, Y.-L. Luo, H.-Y. Cheng, W.-C. Hsieh, J.-C. Liao and W.-H. Peng, Analgesic and anti-inflammatory activities of [6]-gingerol, *J. Ethnopharmacol.*, 2005, **96**, 207–210.
29 R. Lantz, G. Chen, M. Sarihan, A. Solyom, S. Jolad and B. Timmermann, The effect of extracts from ginger rhizome on inflammatory mediator production, *Phytomedicine*, 2007, **14**, 123–128.
30 P. Minghetti, S. Sosa, F. Cilurzo, A. Casiraghi, E. Alberti, A. Tubaro, R. Della Loggia and L. Montanari, Evaluation of the topical anti-inflammatory activity of ginger dry extracts from solutions and plasters, *Planta Med.*, 2007, **73**, 1525–1530.
31 S. M. Nanjundaiah, H. N. M. Annaiah and S. M. Dharmesh, Gastroprotective Effect of Ginger Rhizome (Zingiber officinale) Extract: Role of Gallic Acid and Cinnamic Acid in H+, K+–ATPase/H. pylori Inhibition and Anti–Oxidative Mechanism, *Evidence-Based Complementary Altern. Med.*, 2011, **2011**, 249487.
32 R. Haniadka, E. Saldanha, V. Sunita, P. L. Palatty, R. Fayad and M. S. Baliga, A review of the gastroprotective effects of ginger (Zingiber officinale Roscoe), *Food Funct.*, 2013, **4**, 845–855.
33 M. L. Hu, C. K. Rayner, K. L. Wu, S. K. Chuah, W. C. Tai, Y. P. Chou, Y. C. Chiu, K. W. Chiu and T. H. Hu, Effect of ginger on gastric motility and symptoms of functional dyspepsia, *World J. Gastroenterol.*, 2011, **17**, 105–110.
34 Z. Wang, J. Hasegawa, X. Wang, A. Matsuda, T. Tokuda, N. Miura and T. Watanabe, Protective effects of ginger against aspirin-induced gastric ulcers in rats, *Yonago Acta Med.*, 2011, **54**, 11.
35 Y. Shukla and M. Singh, Cancer preventive properties of ginger: a brief review, *Food Chem. Toxicol.*, 2007, **45**, 683–690.
36 E. C. Chan, S. L. Yap, A. J. Lau, P. C. Leow, D. F. Toh and H. L. Koh, Ultra–performance liquid chromatography/time–of–flight mass spectrometry based metabolomics of raw and steamed Panax notoginseng, *Rapid Commun. Mass Spectrom.*, 2007, **21**, 519–528.
37 X.-L. Cheng, Q. Liu, Y.-B. Peng, L.-W. Qi and P. Li, Steamed ginger (Zingiber officinale): Changed chemical profile and increased anticancer potential, *Food Chem.*, 2011, **129**, 1785–1792.
38 J.-K. Shin, J. H. Park, K. S. Kim, T. H. Kang and H. S. Kim, Antiulcer Activity of Steamed Ginger Extract against Ethanol/HCl-Induced Gastric Mucosal Injury in Rats, *Molecules*, 2020, **25**, 4663.
39 M. Y. Song, D. Y. Lee, S. Y. Park, S. A. Seo, J. S. Hwang, S. H. Heo and E. H. Kim, Steamed Ginger Extract Exerts Anti-inflammatory Effects in Helicobacter pylori-infected Gastric Epithelial Cells through Inhibition of NF-κB, *J. Cancer Prev.*, 2021, **26**, 289–297.
40 Y. H. Nam, B. N. Hong, I. Rodriguez, M. S. Park, S. Y. Jeong, Y.-G. Lee, J. H. Shim, T. Yasmin, N. W. Kim and Y. T. Koo, Steamed ginger may enhance insulin secretion through KATP channel closure in pancreatic β-cells potentially by increasing 1-dehydro-6-gingerdione content, *Nutrients*, 2020, **12**, 324.
41 H. I. Baek, L. Shen, K. C. Ha, Y. K. Park, C. S. Kim, J. E. Kwon and S. J. Park, Effectiveness and safety of steamed ginger extract on mild osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial, *Food Funct.*, 2024, **15**, 9512–9523.
42 S.-H. Park, S.-J. Jung, E.-K. Choi, K.-C. Ha, H.-I. Baek, Y.-K. Park, K.-H. Han, S.-Y. Jeong, J.-H. Oh and Y.-S. Cha, The effects of steamed ginger ethanolic extract on weight and body fat loss: a randomized, double-blind, placebo-controlled clinical trial, *Food Sci. Biotechnol.*, 2020, **29**, 265–273.
43 H.-J. Kim, B. Kim, E.-G. Mun, S.-Y. Jeong and Y.-S. Cha, The antioxidant activity of steamed ginger and its protective effects on obesity induced by high-fat diet in C57BL/6J mice, *Nutr. Res. Pract.*, 2018, **12**, 503–511.
44 B. Kim, H.-J. Kim and Y.-S. Cha, The protective effects of steamed ginger on adipogenesis in 3T3-L1 cells and adiposity in diet-induced obese mice, *Nutr. Res. Pract.*, 2021, **15**, 279–293.
45 Y.-G. Lee, S. R. Lee, H. J. Baek, J. E. Kwon, N.-I. Baek, T. H. Kang, H. Kim and S. C. Kang, The Effects of Body Fat Reduction through the Metabolic Control of Steam-Processed Ginger Extract in High-Fat-Diet-Fed Mice, *Int. J. Mol. Sci.*, 2024, **25**, 2982.
46 G.-H. Lee, C. Peng, S.-Y. Jeong, S.-A. Park, H.-Y. Lee, T.-H. Hoang, J. Kim and H.-J. Chae, Ginger extract controls mTOR-SREBP1-ER stress-mitochondria dysfunction through AMPK activation in obesity model, *J. Funct. Foods*, 2021, **87**, 104628.
47 K. Lamas, L. Lindholm, H. Stenlund, B. Engström and C. Jacobsson, Effects of abdominal massage in management of constipation—A randomized controlled trial, *Int. J. Nurs. Stud.*, 2009, **46**, 759–767.
48 E. Dimenäs, H. Glise, B. Hallerbäck, H. Hernqvist, J. Svedlund and I. Wiklund, Well-being and gastrointestinal symptoms among patients referred to endoscopy owing to suspected duodenal ulcer, *Scand. J. Gastroenterol.*, 1995, **30**, 1046–1052.
49 Y. Choi, N. Kim, G. T. Noh, J. Y. Lee and D. H. Lee, The Efficacy and Safety of GCWB104 (Flos Lonicera Extract) in

Functional Dyspepsia: A Single-Center, Randomized, Double-Blind, Placebo-Controlled Study, *Gut Liver*, 2020, **14**, 67–78.

50 L. Kleinman, R. Faull, R. Walker, G. V. R. Prasad, P. Ambuehl and U. Bahner, Gastointestinal-specific patient-reported outcome instruments differentiate between renal transplant patients with or without GI complications, *Transplant. Proc.*, 2005, **37**, 846–849.

51 A. L. Stewart and J. E. Ware, *Measuring functioning and well-being: the medical outcomes study approach*, Duke University Press, 1992.

52 S. Halder, G. Locke III, N. Talley, S. Fett, A. Zinsmeister and L. Melton III, Impact of functional gastrointestinal disorders on health–related quality of life: a population–based case–control study, *Aliment. Pharmacol. Ther.*, 2004, **19**, 233–242.

53 J. E. Ware Jr and C. D. Sherbourne, The MOS 36-ltem short-form health survey (SF-36): I. Conceptual framework and item selection, *Med. Care*, 1992, **30**, 473–483.

54 W. Je, *SF-36 health survey: manual and interpretation guide*, Health Institute, 1993.

55 J. A. Lewis, Statistical principles for clinical trials (ICH E9): an introductory note on an international guideline, *Stat. Med.*, 1999, **18**, 1903–1942.

56 J. Shin, T.-H. Oh, J.-Y. Kim, J.-J. Shim and J.-L. Lee, Efficacy and Safety of the Cudrania tricuspidata Extract on Functional Dyspepsia: A Randomized Double-Blind Placebo-Controlled Multicenter Study, *J. Clin. Med.*, 2021, **10**, 5323.

57 K. N. Harer and W. L. Hasler, Functional Dyspepsia: A Review of the Symptoms, Evaluation, and Treatment Options, *Gastroenterol. Hepatol.*, 2020, **16**, 66–74.

58 N. J. Talley and A. C. Ford, Functional dyspepsia, *N. Engl. J. Med.*, 2015, **373**, 1853–1863.

59 I. Masuy, L. Van Oudenhove and J. Tack, treatment options for functional dyspepsia, *Aliment. Pharmacol. Ther.*, 2019, **49**, 1134–1172.

60 Y.-P. Wang, C. C. Herndon and C.-L. Lu, Non-pharmacological approach in the management of functional dyspepsia, *J. Neurogastroenterol. Motil.*, 2020, **26**, 6.

61 A. Madisch, V. Andresen, P. Enck, J. Labenz, T. Frieling and M. Schemann, The diagnosis and treatment of functional dyspepsia, *Dtsch. Arztebl. Int.*, 2018, **115**, 222.

62 H. Kerdarian, S. Hassan, S. A. Mozaffarpur, H. Shirafkan and Z. Memariani, Effects of a Traditional Rose-Based Polyherbal Formula on Clinical Symptoms of Patients with Functional Dyspepsia: A Double-Blind Randomized Controlled Trial, *Tradit. Integr. Med.*, 2022, 20–39.

63 A. B. Sharangi and S. Das, Healing indigestion: A phytotherapeutic review, *Adv. Tradit. Med.*, 2022, **22**, 437–453.

64 Q. Q. Mao, X. Y. Xu, S. Y. Cao, R. Y. Gan, H. Corke, T. Beta and H. B. Li, Bioactive Compounds and Bioactivities of Ginger (Zingiber officinale Roscoe), *Foods*, 2019, **8**, 185.

65 H. Y. Lee, S. H. Park, M. Lee, H. J. Kim, S. Y. Ryu, N. D. Kim, B. Y. Hwang, J. T. Hong, S. B. Han and Y. Kim, 1−Dehydro–[10]–gingerdione from ginger inhibits IKKβ activity for NF–κB activation and suppresses NF–κB–regulated expression of inflammatory genes, *Br. J. Pharmacol.*, 2012, **167**, 128–140.

66 F. Li, V. Nitteranon, X. Tang, J. Liang, G. Zhang, K. L. Parkin and Q. Hu, In vitro antioxidant and anti-inflammatory activities of 1-dehydro-[6]-gingerdione, 6-shogaol, 6-dehydroshogaol and hexahydrocurcumin, *Food Chem.*, 2012, **135**, 332–337.

67 I. Bischoff-Kont and R. Fürst, Benefits of ginger and its constituent 6-shogaol in inhibiting inflammatory processes, *Pharmaceuticals*, 2021, **14**, 571.

68 D. Ang, N. J. Talley, M. Simrén, P. Janssen, G. Boeckxstaens and J. Tack, Endpoints used in functional dyspepsia drug therapy trials, *Aliment. Pharmacol. Ther.*, 2011, **33**, 634–649.

69 D. Khanna, R. D. Hays, A. B. Shreiner, G. Y. Melmed, L. Chang, P. P. Khanna, R. Bolus, C. Whitman, S. H. Paz and T. Hays, Responsiveness to change and minimally important differences of the patient-reported outcomes measurement information system gastrointestinal symptoms scales, *Dig. Dis. Sci.*, 2017, **62**, 1186–1192.

70 I. F. Hantoro, A. F. Syam, E. Mudjaddid, S. Setiati and M. Abdullah, Factors associated with health-related quality of life in patients with functional dyspepsia, *Health Qual. Life Outcomes*, 2018, **16**, 1–6.

71 H. Glise and I. Wiklund, Health–related quality of life and gastrointestinal disease, *J. Gastroenterol. Hepatol.*, 2002, **17**, S72–S84.

72 R. F. Yacavone, R. G. Locke III, D. T. Provenzale and G. M. Eisen, Quality of life measurement in gastroenterology: what is available?, *Am J Gastroenterol.*, 2001, **96**, 285–297.

73 M. Crichton, S. Marshall, W. Marx, E. Isenring, X. Vazquez-Campos, S. L. Dawson and A. Lohning, Effect of Ginger Root Powder on Gastrointestinal Bacteria Composition, Gastrointestinal Symptoms, Mental Health, Fatigue, and Quality of Life: A Double-Blind Placebo-Controlled Trial, *J. Nutr.*, 2023, **153**, 3193–3206.

74 B. F. Filipovic, T. Randjelovic, N. Kovacevic, N. Milinic, O. Markovic, M. Gajic and B. R. Filipovic, Laboratory parameters and nutritional status in patients with functional dyspepsia, *Eur. J. Intern. Med.*, 2011, **22**, 300–304.

75 M. Alizadeh-Naini, H. Yousefnejad and N. Hejazi, The beneficial health effects of Nigella sativa on Helicobacter pylori eradication, dyspepsia symptoms, and quality of life in infected patients: A pilot study, *Phytother. Res.*, 2020, **34**, 1367–1376.

76 S. Chrubasik, M. H. Pittler and B. D. Roufogalis, Zingiberis rhizoma: a comprehensive review on the ginger effect and efficacy profiles, *Phytomedicine*, 2005, **12**, 684–701.

77 B. H. Ali, G. Blunden, M. O. Tanira and A. Nemmar, Some phytochemical, pharmacological and toxicological properties of ginger (Zingiber officinale Roscoe): a review of recent research, *Food Chem. Toxicol.*, 2008, **46**, 409–420.

78 L. G. Aregawi, M. Shokrolahi, T. G. Gebremeskel and C. Zoltan, The Effect of Ginger Supplementation on the

Improvement of Dyspeptic Symptoms in Patients With Functional Dyspepsia, *Cureus*, 2023, **15**, e46061.

79 S. Lazzini, W. Polinelli, A. Riva, P. Morazzoni and E. Bombardelli, The effect of ginger (Zingiber officinalis) and artichoke (Cynara cardunculus) extract supplementation on gastric motility: a pilot randomized study in healthy volunteers, *Eur. Rev. Med. Pharmacol. Sci.*, 2016, **20**, 146–149.

80 J. S. Choi, Processed Gingers: Current and Prospective Use in Food, Cosmetic, and Pharmaceutical Industry, *Recent Pat. Food, Nutr. Agric.*, 2019, **10**, 20–26.

81 H. I. Baek, K. C. Ha, Y. K. Park, J. H. Lee, E. J. Kim, H. J. Ko and J. C. Joo, Anti-obesity effect of Neoagaro-oligosaccharides with overweight and obese subjects: a 16-week, randomized, double-blind, placebo-controlled clinical trial, *BMC Complementary Med. Ther.*, 2023, **23**, 368.

82 X. Jia, Y. He, L. Li and D. Xu, Pharmacological targeting of gastric mucosal barrier with traditional Chinese medications for repairing gastric mucosal injury, *Front. Pharmacol.*, 2023, **14**, 1091530.

83 P. Enck and S. Klosterhalfen, Placebo Responses and Placebo Effects in Functional Gastrointestinal Disorders, *Front. Psychiatry*, 2020, **11**, 797.

84 M. P. Jones and G. Holtmann, Placebo effects in functional dyspepsia: Causes and implications for clinical trials, *Neurogastroenterol. Motil.*, 2023, **35**, e14527.

85 S. H. Hafliethadottir, C. B. Juhl, S. M. Nielsen, M. Henriksen, I. A. Harris, H. Bliddal and R. Christensen, Placebo response and effect in randomized clinical trials: meta-research with focus on contextual effects, *Trials*, 2021, **22**, 493.

86 K. E. McColl, Effect of proton pump inhibitors on vitamins and iron, *Am. J. Gastroenterol.*, 2009, **104**(Suppl 2), S5–S9.

87 G. Bordbar, M. B. Miri, M. Omidi, S. Shoja and M. Akhavan, Comparison of a Novel Herbal Medicine and Omeprazole in the Treatment of Functional Dyspepsia: A Randomized Double-Blinded Clinical Trial, *Gastroenterol. Res. Pract.*, 2020, **2020**, 5152736.

88 J. Okonta, M. Uboh and W. Obonga, Herb-drug interaction: a case study of effect of ginger on the pharmacokinetic of metronidazole in rabbit, *Indian J. Pharm. Sci.*, 2008, **70**, 230.

89 M. S. Weidner and K. Sigwart, The safety of a ginger extract in the rat, *J. Ethnopharmacol.*, 2000, **73**, 513–520.

90 J. Shin, H. Ko, Y. H. Choi, I. Choi and Y. M. Song, Risk of comorbid cardiovascular disease in Korean long-term cancer survivors, *Eur. J. Cancer Care*, 2019, **28**, e13151.

91 L. J. Du, B. R. Chen, J. J. Kim, S. Kim, J. H. Shen and N. Dai, Helicobacter pylori eradication therapy for functional dyspepsia: Systematic review and meta-analysis, *World J. Gastroenterol.*, 2016, **22**, 3486–3495.