

Efficacy and Safety of GutGard® in Managing Gastroesophageal Reflux-Related Symptoms: A Phase III, Single-Centre, Double-Blind, Randomized Placebo-Controlled Trial

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Keywords

Liquorice · *Glycyrrhiza glabra* · GutGard® · Efficacy · Safety · Randomized clinical trial

Abstract

Introduction: Liquorice (*Glycyrrhiza glabra*) is a traditional herbal remedy with various pharmacological activities mainly used for digestive and respiratory ailments. GutGard® is a flavonoid-rich, deglycyrrhizinated liquorice root extract and is standardized to glabridin ($\geq 3.5\%$ w/w), and others viz., glabrol, eicosanyl caffeate, docosyl caffeate, and total flavonoids ($\geq 10\%$ w/w) with glycyrrhizin ($\leq 3.0\%$ w/w) as glycyrrhizin causes electrolyte imbalance, hypertension, and water retention. Hence, the objective of the current study was to assess the efficacy, safety, and tolerability of GutGard® in managing gastroesophageal reflux (GER)-related symptoms when compared to placebo. **Methods:** It was a double-blind, parallel group, randomized, placebo-controlled trial with participants randomized in a 1:1 ratio to either the placebo group or GutGard® group. The duration of the interventions/treatment was for 28 days and the follow-up visits were done at day 7, day 14, day 28, and day 35. A telephonic follow-up was also done on day 21. The primary outcome measures studied was the change in the Gastroesophageal Reflux Disease-Health-Related Quality of Life and the Gastroesophageal Reflux Disease

Symptom Assessment Scale. **Results:** We screened a total of $n = 296$ participants and enrolled $n = 200$ participants and obtained written, informed consent from them. Participants in the GutGard® group reported a significantly better quality of life at the end of the intervention period ($p = 0.014$). They also reported earlier resolution of symptoms of GER as against the placebo group, especially the symptoms of heartburn ($p = 0.017$ on day 14 and $p = 0.005$ on day 28) and regurgitation ($p = 0.025$ on day 7, $p = 0.029$ on day 14, and $p = 0.022$ on day 28). **Conclusions:** The GutGard® group showed better and earlier resolution (within 2 weeks) of symptoms of GER as against the placebo group, especially heartburn and regurgitation.

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Wirksamkeit und Sicherheit von GutGard® zur Behandlung der Symptome von gastroösophagealem Reflux: Eine monozentrische, doppelblinde, randomisierte, placebokontrollierte Studie der Phase III

Schlüsselwörter

Süßholz · *Glycyrrhiza glabra* · GutGard® · Wirksamkeit · Sicherheit · Randomisierte klinische Studie

Zusammenfassung

Einleitung: Süßholz (*Glycyrrhiza glabra*) ist ein traditionelles pflanzliches Heilmittel mit vielfältiger pharmakologischer Aktivität, das hauptsächlich bei Leiden des Verdauungstrakts und der Atemwege eingesetzt wird. GutGard® ist ein flavonoidreicher, deglycyrrhizinierter Süßholzwurzelextrakt und ist standardisiert auf Glabridin ($\geq 3,5$ % Gew./Gew.) und andere, nämlich Glabrol, Eicosanylkafeate, Docosylkafeate und Gesamtflavonoide (≥ 10 % Gew./Gew.), mit Glycyrrhizin ($\leq 3,0$ % Gew./Gew.) da Glycyrrhizin Elektrolytungleichgewicht, Bluthochdruck und Wassereinlagerung verursacht. Das Ziel dieser Studie war die Beurteilung der Wirksamkeit, Sicherheit und Verträglichkeit von GutGard® zur Behandlung der Symptome von gastroösophagealem Reflux (GER) im Vergleich zu Placebo. **Methoden:** Es handelte sich um eine doppelblinde, randomisierte, placebokontrollierte Parallelgruppenstudie, in der die Teilnehmenden per Randomisierung im Verhältnis 1:1 der Placebo- oder der GutGard®-Gruppe zugeteilt wurden. Die Dauer der Interventionen/Behandlung betrug 28 Tage; Beobachtungstermine erfolgten an Tag 7, Tag 14, Tag 28 und Tag 35. Eine telefonische Beobachtung erfolgte außerdem an Tag 21. Die primären Endpunkte der Studie waren die Veränderungen der Ergebnisse des GERD-HRQL-Fragebogens (Gastroesophageal Reflux Disease – Health Related Quality of Life) und der GSAS (Gastroesophageal Reflux Disease Symptom Assessment Scale). **Ergebnisse:** Insgesamt $n = 296$ Personen nahmen am Screening teil, davon nahmen wir $n = 200$ in die Studie auf und holten ihre schriftliche Einwilligungserklärung nach Aufklärung ein. Die Teilnehmenden in der GutGard®-Gruppe berichteten am Ende des Interventionszeitraums über eine signifikant höhere Lebensqualität ($p = 0.014$). Sie berichteten auch über ein schnelleres Abklingen der GER-Symptome im Vergleich zur Placebogruppe, insbesondere im Hinblick auf die Symptome Sodbrennen ($p = 0.017$ an Tag 14 und $p = 0.005$ an Tag 28) und Regurgitation ($p = 0.025$ an Tag 7, $p = 0.029$ an Tag 14 und $p = 0.022$ an Tag 28). **Schlussfolgerungen:** Die GutGard®-Gruppe zeigte schnelleren und stärkeren Rückgang (innerhalb von zwei Wochen) der GER-Symptome als die Placebogruppe, insbesondere im Hinblick auf Sodbrennen und Regurgitation.

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Introduction

Glycyrrhiza glabra (Family: Leguminosae) commonly known as liquorice (licorice) has long history of use globally as a food and medicinal plant. In traditional systems of medicine, in countries like India, China, and Europe, liquorice is used for gastrointestinal and respiratory ailments. A number of biologically active compounds have been isolated from liquorice. There are about 300 flavonoids and

20 triterpenoids [1]. Glycyrrhizin, a triterpenoid saponin is known to cause hypokalemia, hypertension, and water retention on long-term usage. Hence, most of the liquorice products contain low levels of glycyrrhizin to avoid side effects. GutGard® is a unique herbal extract of *G. glabra* standardized to $>3.5\%$ glabridin and $>10\%$ total flavonoids with very low levels of glycyrrhizin. The enriched flavonoids content in the GutGard® has unique benefits on functioning of the gut [2]. GutGard® demonstrated enhanced gut motility, gut integrity, gut immunity, and significant antiulcer activity in preclinical studies [3, 4]. Accordingly, in a randomized controlled clinical trial in participants with functional dyspepsia, GutGard® showed a significant decrease in total symptom scores of upper abdominal fullness, upper abdominal pain, heartburn, regurgitation, nausea, and vomiting (as measured by a 7-point Likert scale) on day 15 and day 30, respectively [5].

Several factors can influence the symptoms of gastroesophageal reflux (GER), including delayed gastric emptying, impaired lower oesophageal sphincter function, and related conditions. But the primary treatment approach mainly involves acid-suppressing therapies [6]. However, the negative effects of long-term acid suppression include increased risk of pneumonia, osteoporosis, micronutrient malabsorption, gut bacterial overgrowth, oesophageal candidiasis, and food allergy [7]. Hence, it was postulated that GutGard® could be a beneficial alternative in reducing the heartburn severity based on its effects on motility, antioxidant, and anti-inflammatory activity without altering acid secretion; thus, the current study was proposed to investigate the efficacy and safety of GutGard® in the management of GER symptoms, majorly heartburn and regurgitation in comparison to a placebo.

Materials and Methods

Study Design and Setting

It was a double-blind, parallel group, randomized, placebo-controlled trial conducted in a tertiary care teaching hospital between the time period October 11, 2019 and May 24, 2022. The trial was temporarily paused during the first wave of Coronavirus Disease of 2019 (COVID-19) pandemic for approximately a period of 6 months starting March 2020. The manuscript was prepared following the Consolidated Standards of Reporting Trials (CONSORT) guidelines to ensure transparent and completing reporting of the clinical trial (online suppl. Table 1; for all online suppl. material, see <https://doi.org/10.1159/000543367>).

Participant Eligibility Criteria

Healthy adults aged 18–60 years, experiencing GER symptoms for at least 1 month, with a minimum of two symptomatic days in the week before randomization,

confirmed by the treating physician to have GER-related symptoms, not using proton pump inhibitors and were willing to stop all other medications/supplements prescribed for GER were eligible. The exclusion criteria included red flag symptoms of dyspepsia (such as anaemia, difficulty swallowing, weight loss, persistent vomiting, gastrointestinal bleeding, or an epigastric mass); severe GERD symptoms affecting daily life (heartburn and regurgitation scores >3 on the Gastroesophageal Reflux Disease-Health-Related Quality of Life [GERD-HRQL]); pregnancy or breastfeeding; unwillingness to use contraception; allergies to medications or supplements; uncontrolled diabetes; abnormal liver or kidney function; HIV or hepatitis B/C infections; and inability to follow the study protocol.

Recruitment Strategy

Participants with GER symptoms were identified from institute's general/gastroenterology outpatient department. Additionally, a contract research organization assisted in identifying potential participants from the community through a house-to-house survey who were then referred to a physician for confirmation of diagnosis and eligibility criteria. The contract research organization played no other role other than the assisting in the recruitment.

Interventions

GutGard[®] is a flavonoid-rich, deglycyrrhizinated liquorice root extract and is standardized to glabridin ($\geq 3.5\%$ w/w), and others viz., glabrol, eicosanyl caffeate, docosyl caffeate, and total flavonoids ($\geq 10\%$ w/w) with glycyrrhizin ($\leq 3.0\%$ w/w). The key flavonoids include glabridin, liquiritigenin, isoliquiritigenin, and various chalcones [5]. It complies with global quality standards for content of pesticides, heavy metals, microbiology and aflatoxins as given in US Pharmacopeia and the Ayurvedic Pharmacopoeia of India. Manufacturing aligns with Indian regulatory protocols. The investigational product (IP), GutGard[®], provided in capsules, contained 75 mg *G. glabra* extract with excipients. It was dispensed twice daily during the study period once on the day of randomization and again on day 14 in bottles containing 35 capsules sufficient for 2 weeks of dosing along with few extra capsules. Placebo capsules mirrored the appearance and contained only the excipients. GutGard[®] dosage followed prior trials [5]. Participants took it twice daily for 4 weeks post-meals. Prescribing physicians were trained in clinical pharmacology and regulatory trials. Along with them, a gastroenterologist and an Ayurvedic physician oversaw safety. Rescue medication was Famotidine 20 mg orally, not exceeding two tablets every 12 h. Compliance was verified through pill counting at the final visit.

Outcome Measures

Primary outcome measures included the GERD-HRQL scores at baseline and day 28, and Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS) symptom severity scores at baseline, day 7, day 14, day 28, and day 35 compared to the placebo group. Secondary measures encompassed the frequency of GER-related symptoms based on GSAS, rescue medication use, treatment adherence, change in quality of life (QoL) score as assessed by the Global Assessment Questionnaire, proportion of participants with rebound effects (requirement of at least 1 day of rescue medication or ≥ 2 days of mild symptoms), gastric emptying as assessed by solid meal scintigraphy, abnormal liquid meal scintigraphy, and the occurrence of adverse drug reactions such as nausea, vomiting, diarrhoea, abdominal pain, arthralgia, myalgia, rash, pruritus, allergy, abnormal liver or renal function tests or any other new-onset complaints adjudicated to be casually related to the study medication.

Validated Scales Used in the Study

The GERD-HRQL scale contains QoL questions, nine pertaining to heartburn and six pertaining to regurgitation and the participant is asked to assess QoL on a 6-point Likert scale ranging from 0 (no symptoms) to 5 (incapacitated to do daily activities) [8]. The scale was translated in local languages (Hindi and Marathi) and back translated by professional translators following which a cognitive debriefing was done in five native speakers for each of the languages.

The GSAS scale [9] is a validated scale that evaluates GER-related symptoms in the following domains, namely:

- (a) Number of symptoms: total number of symptoms endorsed as present by the participant. The score may range from 0 (no symptoms) to 15 (all symptoms present).
- (b) Frequency: sum of responses (on how frequently on a given day they experience a particular symptom) across all items divided by the total number of symptoms ($n = 15$).
- (c) Severity: sum of responses (on Likert scale) across all items divided by the total number of symptoms ($n = 15$).
- (d) Distress: sum of responses (on Likert scale) across all items divided by the total number of non-missing symptoms.

This scale has been used to evaluate the efficacy of drugs such as omeprazole in reducing GER symptoms [10]. This scale was also translated in local languages (Hindi and Marathi) and back translated by professional translators following which a cognitive debriefing was done in five native speakers for each of the languages. While administration, the participants were first asked if

they experienced the symptom (yes/no) during the past 2 weeks. Frequency was assessed by asking the participant to indicate “how many times in the past week did you have this symptom?” Severity of each symptom was assessed on a 4-point scale ranging from 0 (not at all) to 3 (very much).

The QoL scale (Global Assessment Questionnaire) was also translated in local languages (Hindi and Marathi) and back translated by professional translators. It is a five-point questionnaire evaluating the participant perspectives on the usefulness of the study medication [11].

Sample Size

Sample size estimation for the current study was based on an earlier phase II trial involving 50 participants with functional dyspepsia, randomized to receive GutGard® 150 mg/day or placebo [5]. Assumptions from this trial included mean (SD) total symptom scores at day 30 for GutGard® (14.76 [3.72]) and placebo (20.44 [4.08]), with an alpha error of 5% and power of 90%. The formula suggested a minimum of 10 participants in each arm, but due to differences in study population and small sample size in the phase II trial, a decision was made to include a minimum of 100 participants in each arm (total $N = 200$).

Randomization Sequence Allocation, Allocation Concealment, and Blinding

Computer-generated randomization with a fixed block size of four assigned participants to GutGard® 150 mg/day or placebo in a 1:1 ratio. The on-site pharmacists, knowledgeable about treatment groups, created the randomization sequence, overseen by an independent clinical pharmacologist. Allocation concealment used sequentially numbered opaque sealed envelopes, opened only after confirming participant eligibility. Both participants and researchers remained unaware of the allocation, and strict measures prevented communication or contamination between the blinded and unblinded teams, aligning with established practices in prior and ongoing clinical trials at the site.

Study Procedures

After obtaining consent during screening, participants underwent a general physical examination, and approximately 15 mL of blood was collected for routine tests (biochemistry, haematology, random blood sugar, and blood-borne virus screen). Urine was also collected for microscopy and dipstick in all participants and for urine pregnancy test for women of reproductive age group. An electrocardiogram was also obtained to rule out myocardial ischaemia. Normal results led to scheduling the baseline solid meal scintigraphy test and liquid meal scintigraphy (only in those with abnormal

solid meal scintigraphy). Other procedures of the baseline visit such as assessing the GSAS and GERD-HRQL, randomization, and dispensing of IP were done on the day of the last baseline scintigraphy scan. Randomization was planned within 14 days from the date of consent. A telephonic follow-up was done on day 7 to reevaluate GSAS and monitor for adverse events (AEs)/serious adverse events (SAEs). On day 14, GSAS assessment, AE/SAE assessment, evaluation of the number of rescue medications used, IP bottle collection and pill count, new IP bottle dispensing and collection of 5 mL blood to estimate serum creatinine and electrolytes level were performed. Day 21 was a telephone follow-up to ascertain AEs. On day 28, the following assessments were made: GSAS, GERD-HRQL, QoL (global assessment questionnaire), number of AE/SAEs; number of rescue medications used, IP bottle collection and pill count, collection of 10 mL blood for routine haematology and biochemistry, collection of urine for routine microscopy and dipstick, and solid meal scintigraphy. Whoever needed a liquid meal scintigraphy at baseline, underwent scintigraphy scan 1 (solid/liquid meal) on day 27 ± 2 and scintigraphy scan 2 (solid/liquid meal) on day 28 ± 2 . The sequence of the scintigraphy scans at post-intervention was allowed to be interchanged based on mutual convenience. After stopping the intervention on day 28, the participants were called back on day 35 to assess for rebound symptoms, GSAS, and number of rescue medications used. Those with persistent symptoms on day 35 received an 8-week course of tab. Pantoprazole 40 mg. Follow-up visits from day 7 onwards had a window period of ± 2 days. A schematic diagram of the study procedures is given in online supplementary Figure 1, and a summary is given in online supplementary Table 2.

Solid Meal Scintigraphy Procedure

The test was conducted on participants with an empty stomach (fasting for at least 4 h). They ingested a radio-labelled idli meal consisting of four idlis with 18.5–37 MBq (0.5–1 mCi) of ^{99m}Tc -sulphur colloid, 75 g of rice idli mixture, and 5 g of butter over 15 min. Sips of water were provided to clear the mouth. Images, in at least 64–64-pixel format, were captured using a general-purpose or low-energy high-resolution collimator. Planar images of the anterior and posterior views, covering the distal oesophagus, stomach, and proximal small bowel, were captured for 1 min immediately after meal ingestion. The images were analysed using a specific region of interest over the stomach at different time intervals to determine the percentage of retention at 1 and 2 h. The normal range was based on the pre-existing standardization done for the representative population [12, 13].

Liquid Meal Scintigraphy Procedure

The test, conducted on participants with an empty stomach (fasting for a minimum of 4 h), involved the consumption of radio-labelled orange juice (18.5–37 MBq or 0.5–1 mCi of ^{99m}Tc -sulphur with 200 mL of orange juice) over 5 min. Images, at least 64–64 pixels in format, were captured using a general-purpose or low-energy high-resolution collimator. Anterior and posterior planar images, including the distal oesophagus, stomach, and proximal small bowel, were obtained for 1 min immediately after juice ingestion. Continuous dynamic imaging with 1 min/frame was acquired in anterior and posterior projections up to 30 min, followed by subsequent static images at 1 h. The time to half ($T_{1/2}$) was calculated by plotting a time activity curve using region of interest over stomach. The normal range was based on the pre-existing standardization done for the representative population [14].

COVID-19 Pandemic-Related Amendments

Initially, the study planned to assess lower oesophageal sphincter pressure and 24 h gastric pH monitoring in 10% of participants. However, due to the onset of the COVID-19 pandemic, non-COVID non-emergency in-patient admissions were restricted at the site during the entire study period, and the hospital was permitted by the local government only to admit patients diagnosed with COVID-19. Consequently, these outcome measures were dropped, and the protocol was amended as these assessments required 36 h in-patient admission. New recruitments were temporarily paused for about 6 months from March 2020. During this pause, follow-up for three participants continued via telephone visits, with data collected except for blood-related assessments and scintigraphy.

Patient and Public Involvement

Patients or the public were not involved in developing the research question, study design, recruitment, reporting, or dissemination plans. Eligible individuals were included, but participants did not receive personal notifications of study findings. However, they can request and access the results. Outcomes will also be shared through a scientific publication based on the collected data.

Data Management and Quality Assurance

Research study doctors at the site recorded participant data in a specialized case record form. Data entry was done using Microsoft Excel (Publisher: Microsoft Corporation, Redmond, WA, USA, 2016). Monitors not involved in data collection or entry conducted 100% source data verification, ensuring authenticity, accuracy, and completeness. Analysis was performed using Sta-

tistical Product and Service Solutions (SPSS) for Windows, Version 20.0 (Publisher: IBM Corp., Armonk, NY, USA, 2011).

Statistical Analysis Plan

A modified intention-to-treat analysis was performed for both efficacy and safety. For analysing efficacy, data of all randomized participants including those who were lost to follow-up until the time they were in the study were used, and for analysing safety, data of all participants who at least took one dose of the interventional product was used. No imputations were done to treat missing values and the statistical significance was set at $p < 0.05$.

Baseline characteristics were summarized using descriptive statistics. Continuous data were summarized as mean (standard deviation) or median (interquartile range). Categorical data were summarized as frequency and percentage. The data were assessed for normal distribution using the Shapiro Wilk's test, and accordingly, between group-analysis for all outcome measures except safety was performed using the Mann-Whitney U test (if distribution was non-normal) or the independent sample t -test (if distribution was normal). An analysis using values adjusted with their respective baseline values were also performed to make final inferences. Adverse events were summarized as proportions and frequencies and were compared between the two groups using Fischer's exact test.

Results

A total of $n = 296$ participants were screened and a total of $N = 200$ participants ($n = 100$ in the GutGard® group and $n = 100$ in the placebo group) were enrolled and randomized. The participant flow diagram and the reasons for screen failure are given in online supplementary Figure 2. The overall mean (SD) age was 36.94 (7.03) years, and the minimum and maximum ages were 18 and 59 years, respectively. More than three-fourths of the participants were men. The baseline demographic and clinical parameters, group wise, have been summarized in online supplementary Table 3, and there were no significant differences between the two groups.

Analysis of GERD-HRQL

The adjusted analysis (Table 1) revealed that there was a significant reduction in the GutGard® group (as against the placebo group) with regards to the GERD-HRQL total scores on day 28 ($p = 0.014$). Heartburn when lying down ($p = 0.048$), heart burn while standing up ($p < 0.001$), heartburn after meals ($p = 0.012$), pain with swallowing ($p = 0.038$), taking medicines affecting daily activities ($p =$

Table 1. Gastroesophageal Reflux Disease-Health-Related Quality of Life total scores

Time point	GutGard®					Placebo					<i>p</i> value
	number analysed (n)	mean	SD	median	IQR (25th, 75th percentile)	number analysed (n)	mean	SD	median	IQR (25th, 75th percentile)	
Baseline	100	22.88	12.345	21.00	15.00, 29.00	100	19.93	10.431	19.50	11.00, 26.00	0.104
Day 28	78	3.83	5.901	1.00	0.00, 5.25	87	11.84	23.907	2.00	0.00, 9.00	0.305
Baseline adjusted day 28	78	-20.06	14.607	-19.00	-29.00, -11.00	87	-8.30	27.904	-14.00	-23.00, -9.00	0.014

SD, standard deviation; IQR, interquartile range.

0.040), regurgitation when standing up ($p = 0.008$), and regurgitation after meals ($p = 0.019$) had significantly decreased in the GutGard® group on day 28 (online suppl. Table 4).

Analysis of GSAS Scores

On baseline-adjusted analysis, there was a significant decrease in the overall frequency of symptoms, its severity, and patient distress since day 14 ($p = 0.004$, 0.022, and 0.010 on day 14 and $p = 0.003$, 0.006, and 0.048 on day 28, respectively) in the GutGard® group (as against the placebo group), although there was no significant decrease in the total number of symptoms present. On day 28, however, there was a trend towards a decrease in the total number of symptoms as well ($p = 0.093$). These results are summarized in Table 2.

The details of unadjusted and baseline-adjusted analysis with regards to individual symptom frequency are given in online supplementary Tables 5 and 6, respectively. In the baseline-adjusted analysis, there was a significant decrease in the GutGard® group (as against the placebo group) with regards to the symptom frequency of regurgitation and gurgling in stomach since day 7 ($p = 0.025$ and 0.023, respectively); heartburn since day 14 ($p = 0.017$); and flatulence ($p = 0.036$) and early satiety ($p = 0.024$) on day 28.

Similarly, the details of unadjusted and baseline-adjusted analysis with regards to the level of severity/distress/botheration caused by individual symptoms are given in online supplementary Tables 7 and 8, respectively. In the baseline-adjusted analysis, there was a significant decrease in the GutGard® group (as against the placebo group) with regards to the level of severity/distress/botheration caused by regurgitation since day 7 ($p = 0.010$); heartburn since day 14 ($p = 0.013$); and gurgling in stomach ($p = 0.014$) and early satiety ($p = 0.005$) on day 28.

Use of Rescue Medications and Adherence

There was no significant difference between the groups with regards to the use of rescue medications on D14 (Mann-Whitney $U = 7,855.00$; $n_1 = 88$, $n_2 = 97$; $p = 0.941$ two-tailed) and D28 (Mann-Whitney $U = 6,285.00$; $n_1 = 78$, $n_2 = 87$; $p = 0.331$ two-tailed). A total of 6 participants in the placebo group and 3 participants in the GutGard® group had an adherence rate of less than 80% ranging from 65.38% to 79.62%. There was no difference in the mean adherence rate between the two groups (placebo group = 95.10% and GutGard® group = 95.78%; $p = 0.552$).

QoL Assessment (Global Assessment Questionnaire)

The overall satisfaction was significantly higher ($p < 0.001$) in the GutGard® group (as compared to the placebo group) and many in the GutGard® group have found benefit in both day ($p = 0.003$) and night ($p = 0.003$), thereby making it recommendable to others with similar symptoms ($p = 0.002$). These results are summarized in Table 3.

Results of Scintigraphy Scans and Rebound Effect

There was no difference between the groups with regards to gastric emptying for both solids and liquids (online suppl. Table 9). No clinically significant rebound effect was seen in GutGard® or placebo on day 35 after stopping intervention on day 28, and there were no significant differences between the groups in the adjusted analysis (online suppl. Table 10).

Adverse Events

There were no significant differences between the groups with regards to the frequency of occurrence of various AEs during the study period (Table 4). The causality assessment of each individual AE based on WHO's causality assessment scale is summarized in online supplementary Table 11. There were three moderate grade events all in the placebo group. The summary

Table 2. Gastroesophageal Reflux Disease Symptom Assessment Scale – outcome measures

Time point	Outcome measures	GutGard®			Placebo			p value				
		n	mean	SD	median	IQR (25th, 75th percentile)	n		mean	SD	median	IQR (25th, 75th percentile)
Baseline	Number of symptoms	100	8.82	2.739	9.00	7.00, 11.00	100	8.23	2.498	8.00	6.00, 10.00	0.076
	Frequency of symptoms		49.25	37.017	38.00	23.00, 59.50		42.49	30.765	35.00	21.25, 54.50	0.262
	Symptom Severity		0.9827	0.44370	0.93	0.67, 1.20		0.8807	0.37525	0.77	0.77, 0.62	0.096
	Distress		1.6825	0.53985	1.56	1.25, 2.00		1.6265	0.54315	1.50	1.17, 1.50	0.444
Baseline-unadjusted analysis												
Day 7	Number of symptoms	97	3.80	2.842	3.00	2.00, 6.00	97	3.54	2.962	3.00	1.00, 5.00	0.343
	Frequency of symptoms		15.62	25.554	9.00	3.00, 20.00		16.41	18.482	8.00	2.00, 29.00	0.810
	Symptom Severity		0.3278	0.28685	0.27	0.13, 0.47		0.3402	0.31291	0.27	0.13, 0.47	0.992
	Distress	83	1.3071	0.50822	1.00	1.00, 5.00	87	1.4642	0.66044	1.00	1.00, 1.88	0.296
Day 14	Number of symptoms	88	3.48	2.861	3.00	1.00, 5.00	90	3.48	2.877	3.00	2.00, 5.00	0.993
	Frequency of symptoms		12.47	15.908	7.00	2.00, 14.75		18.44	22.590	8.00	3.00, 31.25	0.219
	Symptom Severity		0.3034	0.26970	0.27	0.07, 0.40		0.3548	0.33143	0.27	0.12, 0.53	0.455
	Distress	87	1.2450	0.58097	1.00	1.00, 1.41	74	1.5092	0.61784	1.31	1.00, 2.00	0.006
Day 28	Number of symptoms	78	2.29	2.773	2.00	0.00, 3.25	87	2.31	2.319	2.00	0.00, 4.00	0.563
	Frequency of symptoms		8.81	16.746	3.00	0.00, 9.25		12.92	16.662	4.00	0.00, 23.00	0.112
	Symptom Severity		0.1752	0.21357	0.13	0.00, 0.27		0.2368	0.26874	0.13	0.00, 0.40	0.169
	Distress	48	1.2075	0.47677	1.00	1.00, 1.19	60	1.5308	0.71516	1.00	1.00, 2.00	0.011
Baseline-adjusted analysis												
Day 7	Number of symptoms	97	-4.94	3.657	-5.00	-7.00, -2.00	97	-4.69	3.340	-5.00	-7.00, -2.00	0.702
	Frequency of symptoms		-32.16	37.781	-26.00	-44.00, -11.50		-26.16	30.081	-21.00	-31.50, -11.00	0.078
	Symptom Severity		-0.6605	0.50700	-0.60	-0.90, -0.33		-0.5436	0.41581	-0.47	-0.80, -0.27	0.112
	Distress	83	-0.3721	0.74504	-0.38	-0.90, 0.00	87	-0.1749	0.70844	-0.07	-0.71, 0.33	0.050
Day 14	Number of symptoms	88	-5.28	3.359	-5.00	-8.00, -3.00	90	-4.66	3.604	-5.00	-7.00, -2.00	0.247
	Frequency of symptoms		-35.45	36.416	-28.50	-50.50, -15.00		-23.03	32.539	-19.00	-31.00, -5.75	0.004
	Symptom Severity		-0.6981	0.49575	-0.60	-1.07, -0.33		-0.5104	0.47163	-0.47	-0.80, -0.20	0.022
	Distress	77	-0.4754	0.81518	-0.50	-1.00, 0.00	74	-0.1366	0.74550	0.00	-0.70, 0.34	0.010
Day 28	Number of symptoms	78	-6.55	3.169	-7.00	-9.00, -4.75	87	-5.84	3.348	-5.00	-9.00, -3.00	0.093
	Frequency of symptoms		-40.96	37.468	-30.50	-53.75, -18.75		-28.32	29.800	-23.00	-35.00, -13.00	0.003
	Symptom Severity		-0.8427	0.48836	-0.80	-1.08, -0.47		-0.6322	0.42516	-0.60	-0.87, -0.33	0.006
	Distress	48	-0.4393	0.68880	-0.46	-0.94, 0.00	60	-0.1466	0.80982	-0.14	-0.74, 0.50	0.048
SD, standard deviation; IQR, interquartile range.												

Table 3. Quality of life at day 28

Quality of life [Likert scale: 0 – very satisfied; 1 – satisfied; 2 – somewhat satisfied; 3 – somewhat dissatisfied; 4 – dissatisfied; 5 – very dissatisfied]	GutGard®				Placebo				<i>p</i> value
	mean	SD	median	IQR (25th, 75th percentile)	mean	SD	median	IQR (25th, 75th percentile)	
Overall, how satisfied have you been with the study medication you have received for your heartburn during the past 2 weeks?	0.76	0.793	1.00	0.00, 1.00	1.54	1.421	1.00	1.00, 2.00	<0.001
How much have you benefited from the study medication you have received for your heartburn during the past 2 weeks?	1.81	1.058	2.00	1.00, 3.00	2.09	1.335	2.00	1.00, 3.00	0.519
Would you recommend the study medication you received for your heartburn to someone else with your condition?	0.04	0.194	0.00	0.00, 0.00	0.68	1.610	0.00	0.00, 0.00	0.002
Given your experience with other medications for your nighttime heartburn, would you say the study medication provided relief?	0.91	0.729	1.00	0.00, 1.00	1.59	1.443	1.00	1.00, 2.00	0.003
Given your experience with other medications for your daytime heartburn, would you say the study medication provided relief?	0.88	0.664	1.00	0.00, 1.00	1.57	1.468	1.00	1.00, 2.00	0.003
Total score (max. score 25)	4.40	2.202	5.00	3.00, 6.00	7.47	6.551	5.00	4.00, 7.00	0.007

SD, standard deviation; IQR, interquartile range. Number analysed: *n* = 100 each for GutGard® and placebo at baseline; and *n* = 78 and *n* = 87 for GutGard® and placebo at day 28, respectively.

Table 4. Adverse events – group-wise comparison

Adverse event	GutGard® (<i>n</i> = 97)		Placebo (<i>n</i> = 97)		<i>p</i> value
	frequency (<i>n</i>)	%	frequency (<i>n</i>)	%	
Diarrhoea	1	1.0	4	4.1	0.368
Vomiting	2	2.1	5	5.2	0.444
Abdominal pain	3	3.1	13	13.4	0.016
Headache	6	6.2	13	13.4	0.146
Arthralgia	0	0.0	4	4.1	0.121
Myalgia	2	2.1	8	8.2	0.100
Malaise	5	5.2	10	10.3	0.282
Itching	1	1.0	3	3.1	0.621
Rash	0	0.0	1	1.0	1.000
Fever	0	0.0	4	4.1	0.121
Hyperkalaemia	5	5.2	6	6.2	1.000
Hyponatremia	1	1.0	0	0.0	1.000

of individual laboratory parameters estimated is given in online supplementary Table 12. There were no differences between groups for any of the parameters at all timepoints. There were also no clinically significant

findings in urine analysis in any of the study participants at any time. No participants reported discontinuation of the study interventions because of AEs. There were no SAEs encountered in this study.

Protocol Deviations

There were a total of 12 minor protocol deviations that are unlikely to have affected data integrity or compromised participant safety (online suppl. Table 13). There were no major deviations that were reported.

Discussion

This study was a double-blind, parallel group, randomized, placebo-controlled trial with participants randomized in a 1:1 ratio to either the placebo group or GutGard® (150 mg/day) group with an aim to evaluate the safety and efficacy of GutGard® in patients with symptoms of GER majorly heartburn and regurgitation. The primary outcome measures were GERD-HRQL and GSAS score. The GutGard® group exhibited a notable decrease in GERD-HRQL total scores on day 28 compared to the placebo group ($p = 0.014$). Likewise, a significant reduction in the overall frequency of symptoms, their severity, and patient distress on the GSAS was observed in the GutGard® group since day 14 ($p = 0.004$, 0.022 , and 0.010 on day 14, and $p = 0.003$, 0.006 , and 0.048 on day 28, respectively). No significant differences were noted between the groups in terms of the frequency of various AEs throughout the study period.

Participants in the GutGard® group showed significant improvement in GERD-HRQL, particularly in heartburn and reflux components. These improvements were reflected in GSAS scores from day 14. Results were comparable to studies with PPI in GERD [10, 15]. However, some individual symptoms in the GSAS did not reach statistical significance with regards to frequency and the level of severity, likely due to their lower baseline frequency and severity.

Despite preclinical evidence suggesting a prokinetic effect [3], scintigraphy results showed no significant difference in gastric emptying between groups possibly because few participants had delayed/abnormal emptying at baseline. However, even approved prokinetics such as cisapride [16, 17], mosapride, and acotiamide [18, 19] did not have consistent effect in humans, although it showed in animal studies. Other proposed mechanisms include antiulcer, antioxidant activity with no pH increase [4], and protection of intestinal barrier integrity, thereby preventing leaky gut which is hypothesized to be one of the many factors in many chronic illnesses [2], suggesting a need for further studies on GutGard®'s pharmacodynamic effects in humans.

The current standard treatment for GER-related symptoms involves acid-suppressing agents, mainly PPIs. However, long-term PPI use is associated with notable side effects, including pneumonia, osteoporosis, and micronutrient malabsorption [7]. Moreover, some patients continue to experience consistent symptoms

despite PPI treatment [10]. GutGard® emerges as a potential natural alternative, especially for those not under control or requiring prolonged acid-suppressing agents. Advantages include no impact on nutrient absorption, as it does not increase gastric pH, and no rebound effect after treatment cessation as seen in this study, unlike PPIs or H₂ antagonists [20]. Being rich in flavonoids, it may support overall daily digestive health, possibly through microbiome modulation [2].

The strengths of the current study are that validated scales that were used to evaluate PPIs have been used to determine the efficacy. Further, the bias that concomitant medications could have caused were mitigated by a wash-out period before randomization. The limitations are that a few objective parameters such as the 24 h gastric pH monitoring and lower oesophageal sphincter pressure assessment that we had planned to evaluate in a subset of patients could not be executed due to the COVID-19 pandemic. GERD-HRQL and GSAS, although validated scales, involve some amount of subjectivity. Further, at the last follow-up, only 82.5% of all those randomized were available for the analysis. However, a post hoc power calculation using two independent sample *t*-test to assess difference between the two groups on the baseline adjusted mean GERD-HRQL and GSAS overall symptom severity score at day 28 with an alpha error of 5% was determined to be 93% and 83%, respectively. Also, the generalizability of the study results is limited to only those with mild-moderate GER-related symptoms. The difference in rescue medication use between groups was not significantly different probably because those with severe symptoms were excluded and those with mild-moderate symptoms are likely to have tolerated without the need for an additional medication. There was a significant difference in the number of people satisfied with GutGard® based on the QoL assessment but both groups mention similar perception with regards to benefit of the study intervention probably because of the social desirability bias. Lastly, the preclinical study findings on increased gut motility could not be translated in the clinical trials through the scintigraphy scans probably because the number of participants who had a delayed gastric emptying at baseline was small. Hence, studies specifically designed to probe the mechanism of action of GutGard® that translates to therapeutic benefit in humans should be undertaken in the future.

Conclusions

In summary, the GutGard® group reported a significantly better quality of life at the end of the intervention period as against the placebo group. They also showed better and earlier resolution of symptoms of GER as against the placebo group especially the symptoms of

heart burn and regurgitation which showed significantly better resolution even in 1 or 2 weeks of starting the intervention. There was no rebound effect noted in both the groups at 1-week post stopping the intervention. There was also no statistically significant difference in the occurrence of AEs between the two groups. Thus, GutGard® may be considered a promising option in the treatment of participants with symptoms of GER.

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Statement of Ethics

The study was conducted in accordance with all applicable national/international ethics and regulatory rules and guidelines. The study was approved by the Institutional Ethics Committee-1, Seth Gordhandas Sunderdas Medical College, and King Edward Memorial Hospital, Mumbai, India, before the commencement of the study (vide reference number EC/PHARMA – 05/2019 dated July 15, 19), and the study was also registered prospectively on September 23, 19 in the Clinical Trials Registry of India (CTRI/2019/09/021362). Written informed consent was also obtained from all participants before screening.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jeffrey Pradeep Raj: conceptualization, methodology, investigation, formal analysis, data curation, resources, software, validation, funding acquisition, writing – original draft, and project administration. Unnati Saxena, Mahesh Namdeo Belhekar, Harish Darak, and Ambika Mamde: data curation, investigation, and writing – review and editing. Shwetal Pawar: methodology, investigation, formal analysis, writing – review and editing, and supervision.

Data Availability Statement

Deidentified individual participant data are available with the corresponding author and will be shared upon reasonable request for future research/policy or guideline development. A preprint version of this article is available on ResearchGate [DOI: 10.13140/RG.2.2.27216.28161]. Reference: Raj JP, Saxena U, Belhekar MN, Mamde A, Darak H, Pawar SU. Efficacy and safety of GutGard® in managing gastro-esophageal reflux (GER)-related symptoms: A Phase III single-centre, double-blind, randomized, placebo-controlled trial [Preprint]. ResearchGate [DOI: 10.13140/RG.2.2.27216.28161], 26 September 2024. Available from: https://www.researchgate.net/publication/378585540_Efficacy_and_safety_of_GutGard_R_in_managing_gastro-esophageal_reflux_GER-related_symptoms_-_A_Phase_III_single-centre_double-blind_randomized_placebo-controlled_trial_GutGard_R_Manuscript_GutGard_R_M.

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