

Standardized *Perilla frutescens* extract improves acute postprandial meal-induced Gastrointestinal discomfort: Randomized control trial

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Research Article

Keywords: GI discomfort, phenolic compounds, bloating, burping, *Perilla frutescens*, Benegut®, human study

Posted Date: September 3rd, 2025

DOI: <https://doi.org/10.21203/rs.3.rs-6886069/v1>

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Additional Declarations: Competing interest reported. Biotesys (CRO) was paid by Amino Up and Vital Solutions (now a part of Fytexia Group) to perform and report the scientific work that formed the basis of this publication. C.R., J.M. and J.C are employed by Fytexia; KH is employed by AminoUP and SBW is employed by Vital Solutions. Fytexia is involved in the research and development, and marketing and sales of (poly)phenol extract-based ingredients for food and nutraceutical industries and supported the study. Amino UP is the producer of the raw ingredient *Perilla frutescens* extract. Therefore, Fytexia, Vital Solutions and Amino UP has a commercial interest in this publication. Vital Solutions approved the final trial protocol prior to its implementation but was not involved in the study implementation and data collection.

Abstract

Gastrointestinal (GI) discomforts affect a large population all over the world. Acute symptom relief without side effects is an attractive option. *Perilla frutescens* is an herb rich in phytochemicals that is traditionally used for anti-inflammatory and anti-allergenic effects. In this acute study we elucidate the effects of Benegut®, a proprietary *Perilla frutescens* extract, on relief of postprandial GI discomfort on 30 (22 women, 8 men) healthy participants in the age group of ≥ 25 and ≤ 70 years. Participants were included in the study if they obtained an overall GI discomfort score of 5 out of 10 on a VAS questionnaire post a high caloric meal on the screening visit. Participants attended two other visits where they either consumed 300 mg of Benegut® or placebo after the same high caloric meal as the screening. During these visits subjects rated their discomfort symptoms at defined time points (0, 5, 15, 30, 45, 60 and 90 min). We observed that $iAUC_{0-90 \text{ min}}$ overall GI discomfort significantly improved in the Benegut® group (3073 ± 1255) compared to placebo (3742 ± 1611) and screening (4286 ± 1131). Bloating, burping and feeling of fullness significantly improved with *Perilla frutescens* supplementation compared to screening. Overall Benegut® provided an acute symptom relief for GI discomfort post high caloric meal consumption.

Clinical trial Gov registration number: NCT05603416

INTRODUCTION

Gastrointestinal (GI) discomfort affects a wide range of population and impairs quality of life. GI discomfort symptoms are recurrent in nature and are characterized by heartburn/epigastric pain, postprandial fullness, bloating and burping(1). Generally, these symptoms are also accompanied by nausea and abdominal cramps/spasms. This cluster of symptoms without an underlying pathophysiology is known as functional GI disorders. GI symptoms are predominantly meal-related symptoms as they get aggravated after meal consumption(2). The prevalence of bloating based on population studies are estimated between 16–30%(3).

Physiological factors such as excess acid secretion, delayed gastric emptying, visceral hypersensitivity, disordered communication between gut-brain, as well as psychological factors such as stress and depression are involved in the development of GI disorders. GI discomforts are widely reported in patients with undiagnosed *Helicobacter pylori* gastritis or in subjects with irritable bowel syndrome(4). Due to the multifactorial nature of this condition, monotherapy might not be apt for all patients. Thus, symptom relief is regarded as the primary treatment option in these cases. Proton pump inhibitors (PPI) are widely used as first line therapy for GI discomfort. However long-term use of PPI poses health risks(5). Traditional and natural ingredients offer an interesting option for the management of GI discomforts in primary intervention. Products derived from plant sources such as Iberogast, motilone has been widely used for the treatment of GI discomforts (6). *Perilla frutescens* L Britton is an annual aromatic herbaceous plant that belongs to the species of *Perilla* in the mint family Lamiaceae. In China, cultivated taxa of *perilla* are divided into five varieties: var. *frutescens*, var. *arguta*, var. *crispa*, var. *auriculato-dentata* and var. *acuta*. The edible parts of the plant are the leaves, stems and the seeds that have been used whole in Asian cooking (sauces, soups, as spices) or as extracts for medicinal reason depending on the variety. The leaves of *Perilla frutescens* L. Britton contain many phytochemical compounds that can be classified either as hydrophilic (phenolic acids, flavonoids, anthocyanins) or hydrophobic (lipophilic) (7). The flavonoids include vicenin-2 (apigenin-6,8-di-C-glycoside) and rosmarinic acid. Preclinical studies have shown the antioxidant ability of *Perilla* leaf extracts and inhibitory effects on producing proinflammatory cytokines (8, 9). Although predominant of the effects of *Perilla* extracts are from in vivo or in vitro studies, few human clinical studies have shown proven therapeutic effects such as antiallergic, antioxidant, prokinetic and anti-aging related cognitive effects (10–13). Furthermore, *Perilla* leaf

extract and its patented component Vicenin-2 has shown to display antispasmodic effect which could potentially aid in relieving gastrointestinal discomfort. This hypothesis was further tested in a pilot trial. Benegut® the standardized *Perilla* leaf extract, displayed chronic beneficial effects on GI discomfort relief in a human pilot clinical trial.

In this scope, a proprietary standardized extract of *Perilla frutescens* (L.) Britton, Benegut® with a phytochemical composition of phenolic acids, mainly rosmarinic acid and a flavonoid fraction was investigated. The characterisation of the product has been published earlier(14). Benegut® has previously displayed chronic beneficial effects on GI discomfort relief in a human pilot clinical trial and has also displayed antispasmodic effects in an *in vitro* mechanistic study. This study aims to determine whether Benegut® can alleviate overall GI discomfort in a post-meal acute set up. Secondary outcomes include evaluating changes in individual GI discomfort symptoms postprandially after a high caloric meal.

METHODS AND MATERIALS

Study population

Healthy volunteers (male and female) in the age of ≥ 25 and ≤ 70 years and BMI of 19–30 kg/m² without clinically diagnosed diseases with relevant effect on gastrointestinal system were included in the study. After informed consent, subjects were screened for their eligibility to take part in the study. Exclusion criteria included subjects who were diagnosed for any medical condition or under prescription medications for digestive symptoms. Further exclusion criteria are mentioned in the supplementary information. Lifestyle, nutritional and sporting habits were assessed during screening. Subjects were instructed to keep their normal nutritional, sporting and lifestyle habits. The clinical study was performed at the study site of BioTeSys GmbH in Esslingen, Germany. The protocol was approved by the Institutional Review Board (IRB) of Landesärztekammer Baden-Württemberg (Ethical committee number: F-2022-093). Study was conducted in accordance with Good Clinical Practice and was registered in clinicaltrials.gov (NCT05603416, <https://clinicaltrials.gov/study/NCT05603416>) registered on October 21, 2022.

Study product and study design

Study product was composed of Filler sorbitol (ad 100%), Benegut® (15.0%, 300 mg per portion), aroma (1.5%), release agent magnesium salts of fatty acids (0.16%), sweetener steviol glycosides (0.15%). Benegut®, a proprietary extract of *Perilla frutescens* (Amino Up Co., Ltd., Japan), is standardized on a special flavonoid fraction, on vicenin 2 and on rosmarinic acid, determined by HPLC (14). Placebo contained maltodextrin with the same excipients as the study product. Both the products were provided as direct dissolve preparation in sticks and ingested orally directly after end of high caloric meal as single dose.

The study was performed as a double blind, randomized, placebo-controlled cross-over design with at least a 7-day washout phase between visits. Study was conducted between November 2022 to March 2023. Participants were stratified according to gender and were randomly allocated to the sequence of placebo followed by test product (or) test product followed by placebo. The randomization list was allocated with Randlist. This was a double blinding where the blinding was removed after the last patient out. After the screening/baseline visit, the consumption of the test meal was repeated twice in combination of intake of Benegut® (supplement) or placebo. During the screening phase a high caloric meal was served, to determine their individual portion causing GI discomfort. Briefly, they consumed cheeseburger, coleslaw, tortilla chips/nachos/tacos with cheese dip and salsa dip, ketchup/mayonnaise, chocolate muffin and lemonade, until the defined GI discomfort level was reached. As

previous meal could have a carryover impact on GI complaints, an easy to digest light meal was first provided in the lunch. The time of this last meal prior to the high caloric meal was also standardized with 5 hours. Subjects were advised to eat as much as they can and then rate their overall GI discomfort. Only subjects with minimum overall GI discomfort of 5 on a visual analog scale (VAS, 0-100mm) were enrolled. Only subjects experiencing such a cut-off value after the meal have been included. The amount of food consumed during the “overeating dinner” at screening visit was standardized for visit 1 and visit 2. The screening visit was considered as the baseline level of each participant as this involved symptom registration without placebo or the product.

The study products were ingested directly after the meal. The assessment of GI symptoms was done over a period of 90 min after intake of study products, during which subjects stayed under calm relaxing conditions. During this time, subjects were rating their overall GI-discomfort on a VAS at defined time points (0, 5, 15, 30, 45, 60 and 90 min). Additionally, the nature and severity of selected symptoms (feeling of fullness, burping, bloating, heartburn, rumbling, passage of gas, GI discomfort/cramps/pains, nausea, urge to defecate.) were assessed at the specified time points with a 6-point Likert scale. Participants also answered the questionnaire 10–15 minutes before the beginning of meal ingestion (-15 min). Questionnaire evaluating the bowel movement were also recorded at each visit. Safety at each visit was ensured by recording any adverse events in accordance with ICH/GCP.

Sample size

Based on the previous clinical study(14) a subjective alleviation of symptoms was reported in women for bloating and abdominal discomfort with -0.57 ± 0.63 and during placebo intervention of -0.19 ± 0.53 . Based on these data applying a matched pairs test approach and consideration of an alpha level of 0.05 and power of 0.8, an effect size of 0.65 was estimated for the a priori sample size determination using G*power 3.1.9.2. Based on the following input details - two tailed, effect size $d = 0.65$, alpha error problem: $\alpha = 0.05$, actual power: 80%, correlation between groups: 0.5 - a sample size of $n = 21$ subjects were estimated. As women are predominantly affected by gastrointestinal complaints (Guarner et al. 2008; Kim & Kim 2018), it was decided to perform the study with approximately 3:1 of women and men, respectively ($n = 22$ women and $n = 8$ men; total $n = 30$).

Statistical analysis

All the values are reported as mean and standard deviation. For the incremental AUC, baseline corrected (score prior to meal start) symptom scores were used. Differences amongst groups were evaluated with linear mixed model that accounts for repeated measures. Statistics were performed in R software (4.1.2). All randomized participants were included in the analysis.

RESULTS

Population characteristics

Study participant flow diagram is represented in Fig. 1. Baseline clinical characteristics are provided in Table 1. 30 participants (22 women and 8 men) with an average of 47.6 (SD 11.1) years and BMI of 25.2 (SD 3.3) Kg/m² participated and completed the study. Average calories consumed from the high calorific meal was 1551 Kcal (95% CI 1346–1756). Portion size was individually defined by subjects during the baseline visit. There were no significant differences in bowel movements during the three visits (data not shown).

Table 1
Baseline clinical characteristics of the study participants

Characteristic	Men	Women
Age (years)	46.4 (16.6)	48.1 (14.4)
BMI (Kg/m ²)	25.8 (2.3)	24.9 (3.7)
Blood pressure (mm Hg, Systolic/Diastolic)	126.3 (16.3)/	80.0 (10.7)

Tolerability and safety

Tolerability and safety were assessed by asking and recording all reported adverse events. Two adverse events were noted on the study days, which were already present when the subjects arrived to the study site. None of the adverse events were related to the study products.

Overall GI discomfort

Participants reported a similar lower levels of GI discomfort before the start (pre-test) of the high caloric meal in all the three visits. Overall GI was assessed on a VAS and the incremental area under the curve (iAUC) was calculated for overall GI discomfort from 0 to 90 min post intake of the study products. The primary endpoint iAUC_{0-90 min} for overall GI-discomfort (Table 2) was significantly decreased after intake of supplement (3073 ± 1255) in comparison to intake of placebo (3742 ± 1611) ($p = 0.0061$) with 66.7% of subjects having lower iAUC_{0-90 min} overall GI discomfort after intake of supplement in comparison to placebo. The maximum symptom score observed (denoted by Cmax) also reduced in supplement and placebo in comparison to baseline visit. When leaving the study site after 90 min, the overall GI discomfort was not returned to the baseline conditions.

Table 2

Incremental AUC (0-90min) of overall GI discomfort and individual symptoms with maximum symptom score (Cmax) and time at which maximum symptom score occurred (Tmax)

	Groups	No. of participants with symptom	iAUC	Cmax	Tmax
Overall GI Symptoms	Benegut	30	3073 ± 1255 *^a	49 ± 18*	23 ± 28*
	Placebo	30	3742 ± 1611	56 ± 21b	28 ± 27
	Screening	30	4286 ± 1131	65 ± 10	39 ± 37
Feeling of Fullness	Benegut	30	198 ± 95 *	3 ± 2*	7 ± 18
	Placebo	30	230 ± 107	4 ± 2	6 ± 18
	Screening	30	277 ± 99	4 ± 2	16 ± 25
Passage of gas	Benegut	26	101 ± 86	2 ± 2*	30 ± 26
	Placebo	28	108 ± 104	2 ± 2	30 ± 27
	Screening	29	134 ± 100	3 ± 2	41 ± 32
Bloating	Benegut	30	177 ± 113 *	3 ± 2	19 ± 27
	Placebo	30	206 ± 119	4 ± 2	18 ± 25
	Screening	30	241 ± 125	4 ± 2	24 ± 32
Abdominal Pain and cramps	Benegut	24	86 ± 95	2 ± 2	10 ± 21*
	Placebo	23	96 ± 119	2 ± 2	16 ± 25
	Screening	26	128 ± 101	3 ± 2	25 ± 29
Rumbling in stomach	Benegut	26	92 ± 104	2 ± 2	20 ± 27
	Placebo	26	94 ± 110	2 ± 2	29 ± 33
	Screening	30	104 ± 123	2 ± 2	28 ± 31
Burping	Benegut	30	130 ± 86 *	3 ± 2	20 ± 28
	Placebo	28	174 ± 110	3 ± 2	15 ± 26
	Screening	30	177 ± 101	3 ± 2	12 ± 24
Heart Burn	Benegut	15	28 ± 54	1 ± 1	10 ± 21
	Placebo	13	15 ± 62	1 ± 1b	12 ± 25
	Screening	15	39 ± 78	1 ± 2	19 ± 32
Nausea	Benegut	18	45 ± 68 *	1 ± 2*	10 ± 22
	Placebo	15	58 ± 77	2 ± 2	11 ± 23

* significant differences between Benegut and Screening; ^a significant differences between Benegut and Placebo; ^b significant differences between Placebo and Screening

	Screening	18	85 ± 106	2 ± 2	17 ± 31
Urge to defecate	Benegut	19	62 ± 93	2 ± 2	21 ± 29
	Placebo	17	70 ± 106	2 ± 2	27 ± 36
	Screening	23	90 ± 87	2 ± 2	36 ± 38
* significant differences between Benegut and Screening; ^a significant differences between Benegut and Placebo; ^b significant differences between Placebo and Screening					

Individual GI discomfort symptoms

Nine individual GI symptoms were measured during three visits. Similar to overall GI discomfort, $iAUC_{0-90\text{ min}}$ was calculated for each of the symptom. Feeling of fullness, bloating and burping were the three main prevalent symptoms. Heart burn, nausea and urge to defecate were the less prevalent symptoms. The $iAUC_{0-90\text{ min}}$ of feeling of fullness, bloating, burping and nausea significantly reduced in the supplement group compared to the baseline visit (Table 1). Even though there were no statistical significance in other symptoms, supplement had a lower $iAUC_{0-90\text{ min}}$ compared to screening and placebo. The number of participants experiencing each symptom at each visit is given in Table 1.

Additionally, we also evaluated the differences between symptoms at the end of study (90th minute) represented as Fig. 2. While $iAUC$ gave the overall symptom experience, the evaluation of symptoms at end of postprandial period showed if the participants attained symptom relief at the end of the observation. We noticed that abdominal pain and cramps, bloating were the two symptoms that were significantly different from placebo and baseline at 90th minute.

DISCUSSION

Upper GI discomfort is common after a high caloric meal. Previous studies have shown that high caloric meal consumption can significantly induce bloating, feeling of fullness and nausea(15, 16). We observed a similar trend in our study where during all the three visits, feeling of fullness, bloating and burping were the main symptoms noted. With supplementation of *Perilla frutescens* extract we noted that these individual symptoms improved in comparison to baseline and overall postprandial GI discomfort was improved in comparison to baseline and placebo. The polyphenolic mixture of rosmarinic acid and the flavonoid fraction in *Perilla frutescens* extract are expected to contribute to the alleviation of the symptoms that were observed in this study.

Predominant of the studies in the area of symptom relief for GI discomforts are based on probiotics and postbiotics. Although these solutions have shown promising results, these studies involve a chronic treatment period. Thus, there is a need for product development for acute symptom relief. *Perilla frutescens* extract, in a previous clinical trial, has displayed GI discomfort relief effects on a chronic set up. Thus, the current study strengthens the previous one by offering proof on acute symptom relief. The aetiology of GI discomfort is multifactorial. We suggest that during chronic consumption of *Perilla frutescens* extract, the effect might be mediated via changes in gut microbiota and improvement of barrier function. Intestinal barrier dysfunction leading to increased infiltration of mast cells have been noted in cases of functional dyspepsia (17). Mast cells lead to proinflammatory cytokine release causing an acute inflammation potentially interfering with enteric nerve functions and increased visceral sensitivity (18). Interestingly, *Perilla frutescens* extract has shown to improve the intestinal

barrier function measured with trans epithelial electrical resistance in cell culture model(19). Rosmarinic acid and apigenin components of *Perilla frutescens* extract has demonstrated beneficial gut barrier function in several preclinical models(20, 21). In dextran sulphate sodium induced colitis mice, apigenin has demonstrated to enhance the expressions of important gut barrier markers such as ZO-1, occludin, claudin-1, and claudin-3(22).

Whilst chronic effects are potentially modified via gut microbiota and intestinal barrier, acute effects might be mitigated by altering visceral sensitivity, smooth muscle contractions and post prandial gut hormones. Visceral sensitivity affected by acute inflammation, gut hormones and nutrients modulate the communication of nociceptive information from GI tract to the brain(1). This leads to improper gastric emptying and therefore bloating. Post prandial state involves regulation of various hormones some of which are suggested to be altered in subjects with gastrointestinal disorders. Subjects with functional dyspepsia have been noted to have higher plasma cholecystokin (CCK) and lower ghrelin compared to healthy controls(16). Interestingly apigenin found in seeds of *Perilla frutescens* has shown to inhibit food intake by acting on gut hormones(23).

Symptoms such as spasms and pain are induced by smooth muscle contractions in stomach and upper GI tract which are influenced by various pathways such release of acetylcholine, excess influx of calcium ions etc. Inhibition of these pathways could offer antispasmodic effect. Interestingly, rosmarinic acid and vicenin-2 have displayed inhibition of acetylcholine receptors in rat ileum, thus acting as anti-spasmodic agents(24). Rosmarinic acid from *Perilla frutescens* extract has also shown attenuation of atropine- and dopamine-induced inhibition of gastric emptying and gastrointestinal motility in animal model(25). Excess entry of calcium ions from extracellular fluid incites smooth muscle contractions. Cucumis melo seeds, which are rich in flavonoids, such as apigenin, luteolin, quercetin and rutin, has displayed antispasmodic, antiperistalsis actions by blocking calcium ion channels thus reducing calcium influx into smooth muscle cells. We expect a similar mode of action from the supplement, which needs to be evaluated in future mechanistic studies.

Studies focusing on treatment for GI discomfort and functional GI disorders are prone to placebo effects. Thus, also in the Placebo group overall GI was lower in compariso to screening, but not significant. As the study was powered and designed to evaluate the primary outcome, we did not see significance against placebo in iAUC of certain individual symptoms (burping, bloating and feeling of fullness). The key study limitation is that the study design involved evaluation of product intake after a high caloric meal, hence the discomfort relief cannot be generalized to normo-caloric situations. Future studies focusing on the triggers of GI discomforts and potential modes of action by *Perilla frutescens* extract would allow us to focus on individual symptoms as well. Overall, we conclude that Benegut® offers postprandial acute symptomatic relief for overall GI discomfort.

Abbreviations

GI Gastrointestinal, AUC area under curve, VAS visual analogue scale, CCK Cholecystokin

Declarations

Ethics approval: The protocol was approved by the Institutional Review Board (IRB) of Landesärztekammer Baden-Württemberg (Ethical committee number: F-2022-093). The study was conducted ethically, in accordance with the Declaration of Helsinki, and informed consent was obtained from all participants.

Consent for publication: Corresponding author and all authors provide their consent for consideration to publish this manuscript.

Acknowledgements: Not applicable

Author contributions

Conceptualization: SBW; Investigation CS, SBW; Methodology: CS, SBW; Data analysis: JM, CR; Data interpretation: JM, CR, KH, JC; Supervision: CR, JC, SBW, KH; Writing and review of draft: JM, CR, JC, SBW, KH

Availability of data and materials

The data presented in this study are available upon reasonable request from the corresponding author, due to privacy restriction.

Funding and conflict of interests

Biotesys (CRO) was paid by Amino Up and Vital Solutions (now a part of Fytexia Group) to perform and report the scientific work that formed the basis of this publication. C.R., J.M. and J.C are employed by Fytexia; KH is employed by AminoUP and SBW is employed by Vital Solutions. Fytexia is involved in the research and development, and marketing and sales of (poly)phenol extract-based ingredients for food and nutraceutical industries and supported the study. Amino UP is the producer of the raw ingredient *Perilla frutescens* extract. Therefore, Fytexia, Vital Solutions and Amino UP has a commercial interest in this publication. Vital Solutions approved the final trial protocol prior to its implementation but was not involved in the study implementation and data collection.

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Figures

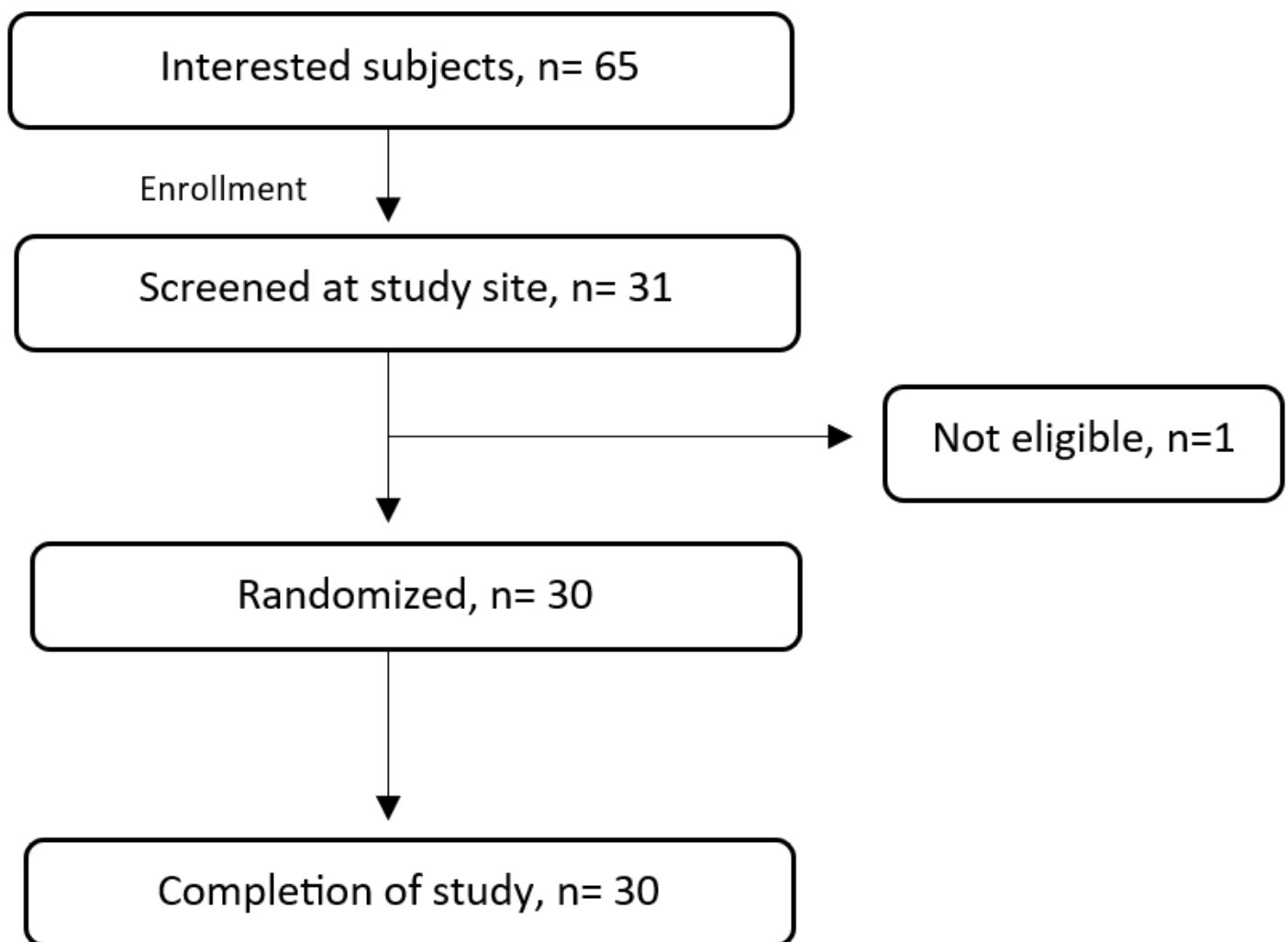


Figure 1

Participant flow diagram

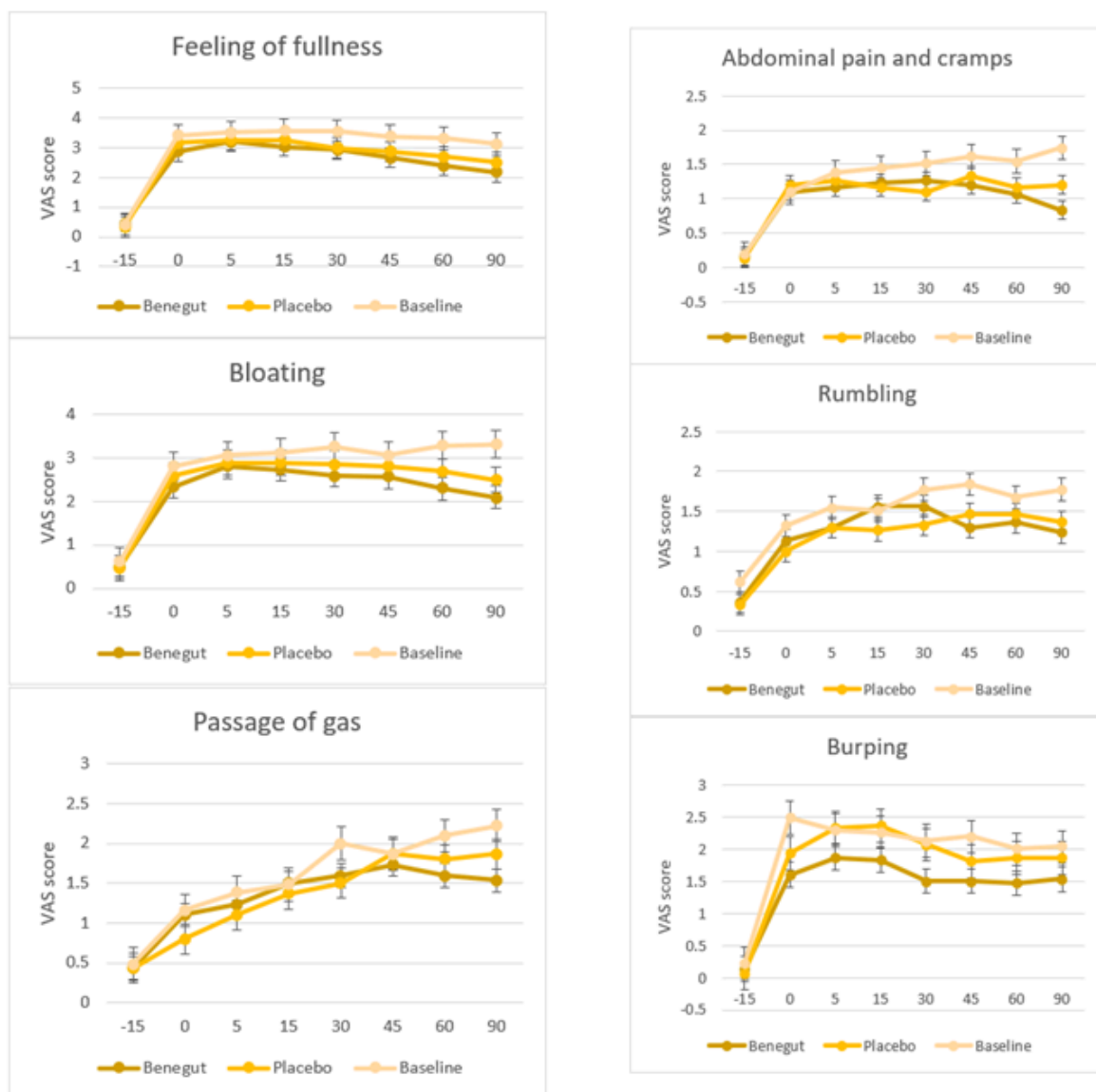


Figure 2

Curves representing the VAS score of symptoms at each time point represented by mean and SE for each group 1) Feeling of fullness 2) Bloating 3) Passage of gas 4) Abdominal pain and cramps 5) Rumbling in stomach 6) Burping 7) Heart burn 8) Nausea 9) Urge to defecate