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Oral Fructanase Administration Reduces Gastrointestinal Symptom Severity after Acute Inulin Challenge in Healthy Adults

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A B S T R A C T

Background: Fructanase, an enzyme that hydrolyzes dietary fructans to fructose in vitro, may reduce gastrointestinal (GI) microbial fermentation in vivo by breaking down fructans before transit to the colon.

Objectives: This study evaluated the effects of a microbial fructanase on GI symptoms and intestinal fermentation in males and females after inulin-type fructan ingestion.

Methods: A randomized, double-blind, crossover study design was used with 30 healthy adults [mean (standard deviation) age: 38.6 (7.3) y and body mass index: 24.5 (3.0) kg/m^2] who consumed 25 g inulin mixed into 40 g oatmeal with either 1 capsule containing fructanase or placebo maltodextrin. GI symptoms and fatigue were assessed using visual analog scales at baseline and postprandially for 24 h. Breath hydrogen and methane concentrations were measured postprandially hourly for 8 h. A Wilcoxon signed-rank test was used to compare paired differences between fructanase and placebo conditions.

Results: The maximum 0 to 8 h overall abdominal symptom score was not statistically significant ($P = 0.13$) between groups. Compared with placebo, fructanase coadministration with inulin reduced abdominal pain ($P = 0.044$) and fatigue ($P < 0.001$). Rank-based repeated-measures analysis showed that fructanase reduced burping ($P = 0.040$) during the 0 to 8 h period. Over the 8 to 24 h period, fructanase reduced overall abdominal symptoms ($P = 0.030$), bloating ($P = 0.011$), abdominal pain ($P = 0.019$), and flatulence ($P = 0.044$). Breath hydrogen and methane outcomes did not differ significantly between groups.

Conclusions: Fructanase coadministration with inulin reduced GI symptoms in healthy adults, suggesting that it may be a useful dietary supplement for fructan sensitivity. Further trials in a cohort with GI symptoms such as irritable bowel syndrome are warranted.

This trial was registered at clinicaltrials.gov as NCT06628869 (https://clinicaltrials.gov/study/NCT06628869).

Keywords: dietary fiber, enzyme, FODMAP, food sensitivity, food intolerance

Introduction

Food sensitivity, or food intolerance, describes a persistent, nonimmunological gastrointestinal (GI) response to foods that are otherwise broadly well tolerated [1]. Dietary components associated with food sensitivity include gluten, histamine, fats, and fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) [1,2]. Clinical features of food sensitivity include GI symptoms such as abdominal bloating, burping, flatulence, indigestion, diarrhea, and constipation. Self-reported food sensitivity is estimated to affect ≤45% of the general population [3–6], and ≤80% of individuals with disorders of gut–brain interaction (DGBI) such as irritable bowel syndrome (IBS) [3,4,7–10].

Fructans are a FODMAP component that occur naturally in many grains, vegetables, and fruits, and include inulin—a prebiotic dietary fiber added as an ingredient to some foods. Chemically, fructans are polymers of fructose connected by

Abbreviations: CI, confidence interval; C_{max}, maximum concentration; DGBI, disorders of gut–brain interaction; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; FOS, fructooligosaccharides; GI, gastrointestinal; IBS, irritable bowel syndrome; INU, inulinase activity unit; iAUC, incremental area under the curve; mSI-SQS, modified single-item sleep quality scale; NDIN, New Dietary Ingredient Notification; ppm, parts per million; SI-SCS, single-item stool consistency scale; T_{max}, time to maximum; VAS, visual analog scale.

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chemical bonds that resist human digestive enzyme hydrolysis [11]. Long-chain fructans, such as inulin, typically have a degree of polymerization >10, whereas shorter fructans are defined as fructooligosaccharides (FOS) with a monosaccharide chain length of 2 to 10 [12]. Both long- and short-chain fructans transit intact to the proximal colon, where they undergo rapid fermentation by intestinal microbes, as evidenced by breath hydrogen testing after acute FOS or inulin ingestion [13–18]. It is this microbial fermentation-associated intestinal gas production that likely leads to abdominal bloating, distention, and pain after fructan consumption in susceptible individuals [16]. This fermentation of fructan, in combination with visceral hypersensitivity and the nocebo effect, results in symptoms in individuals with IBS [15,18–24].

One approach to limit GI symptoms associated with food sensitivities is to reduce intake of foods containing FODMAP [13,25,26]. Dietary fiber is a major component of FODMAP, so inherent consequences of this exclusionary strategy may be a reduction in dietary fiber intake and lower intestinal abundance of beneficial commensal microbes and derived beneficial metabolites [27–29]. Given the established health benefits of prebiotic FOS and inulin [30], new approaches alternative to FODMAP restriction diets could facilitate fiber intake and the associated freedom and comfort with tolerable, nonrestrictive diets. One such approach is microbial enzyme supplementation to facilitate hydrolysis of FODMAP, which has already been shown to be effective with β-galactosidase (i.e., lactase) or α-galactosidase in individuals with lactose or galactooligosaccharide sensitivity, respectively [31–34]. Specific to fructans such as inulin, fructanase (i.e., inulinase, fructan hydrolase, β-fructosidase, and β-fructofuranosidase) is a logical choice of supplemental enzyme for its fructolytic activity and longstanding, safe use in food processing applications. In vitro orogastric digestion simulations have previously shown that a food-grade, microbial fructanase from *Aspergillus tubingensis* effectively hydrolyzes fructans from several dietary substrates [35]. This same fructanase was also shown to be safe and tolerable in healthy adults after twice-daily supplementation for 4 wk at a total daily dose of 2000 inulinase activity units (INU) [36]. The objective of this randomized, double-blind, placebo-controlled crossover trial was to evaluate the effects of coadministration of a 350 INU dose of fructanase with 25 g of inulin on GI symptom severity by visual analog scale (VAS) and indirect intestinal microbial fermentation by breath hydrogen and methane analyses. We hypothesized that fructanase coadministration with inulin would reduce postprandial GI symptom severity and breath hydrogen and methane concentrations.

Methods

Trial protocol

This clinical trial was approved on 23 October, 2024 by the Sterling Institutional Review Board (IRB no. 12384). This single-site study was conducted between 4 November, 2024 and 16 December, 2024 at Biofortis Research in accordance with the protocol and consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation Good Clinical Practice guidelines. All participants gave written informed consent before participation and were free to withdraw from the study at any time. The trial was registered at clinicaltrials.gov (NCT06628869).

Participants

Participants were generally healthy aged 20 to 50-y with a BMI of 18.5 to 29.9 kg/m^2 with no history of major illness or clinically important GI condition (e.g., organic GI disease, DGBI, history of bariatric surgery, or food allergies/intolerances). Additional exclusion criteria included recent history (≤12 mo) of tobacco/nicotine use, females currently pregnant or unwilling to use contraception, recent antibiotic use (≤3 mo), recent use (≤2 wk) of medications or products known to influence GI function (e.g., histamine-2 receptor agonists, probiotic supplements, etc.), or known allergies to any of the study product ingredients. The screening visit included a medical history review with a board-certified physician in internal medicine, review of current medication/supplement use, assessment of height, weight, BMI, vital signs, and review of inclusion/exclusion criteria to determine eligibility.

Study products

During the fructanase period, participants consumed a serving of oatmeal with inulin (Orafti GR; Beneo) and a capsule containing OPTIZIOME Fructanase obtained from *Aspergillus tubingensis* (BIO-CAT, Inc.). During the placebo period, oatmeal containing 25 g of inulin was coadministered with a capsule containing maltodextrin.

Nutritional information, including FODMAP composition of oatmeal and inulin, is expressed on an as-is (fresh weight) basis (Table 1). To determine the baseline FODMAP and simple sugar profile of the commercial oatmeal vehicle (Quaker Gluten Free Quick 1-Minute Oats), a representative composite sample was analyzed by the Department of Gastroenterology and Translational Nutrition at Monash University (Lab Code: 14701728). Free monosaccharides and polyols (fructose, glucose, sorbitol, and mannitol) were quantified using HPLC coupled with evaporative light scattering detection. Oligosaccharides (raffinose, stachyose, and lactose) were determined by ultra-HPLC with evaporative light scattering detection using the Megazyme Raffinose/Sucrose/Glucose Assay Kit (Kit no. K-RAFGL; Megazyme International). Total fructans were quantified enzymatically and spectrophotometrically using the Megazyme Fructan Assay Kit (Kit no. K-FRUC; Megazyme International) via colorimetric detection with p-hydroxybenzoic acid hydrazide, conforming to the Association of Official Analytical Chemists (AOAC) Official Method 999.03 and the American Association of Cereal Chemists (AACC) Method 32.32. The macronutrient and sugar specifications of the native chicory root inulin (Orafti GR; specified dry matter of 97% ± 2%) were obtained from manufacturer quality control batch records quantified via high-performance anion-exchange chromatography with pulsed amperometric detection according to AOAC Official Method 997.08.

OPTIZIOME Fructanase (BIO-CAT, Inc) is a non–genetically engineered, wild-type fructanase preparation comprising filtered enzyme concentrate obtained from *Aspergillus tubingensis* (reclassified from *Aspergillus niger* in 2022) and tapioca maltodextrin. This fructanase preparation is standardized by

TABLE 1
Oatmeal and inulin nutritional information

Nutrient[1]	Oatmeal (40 g)[2]	OraftiGR Inulin (25 g)[3]	Maltodextrin[4]
Energy (kcal)	150	53	0
Total fat (g)	3	0	0
Total carbohydrate (g)	27	24.25	25
Total FODMAP (g)	0.23	24.25	0
Oligosaccharides (g)	0.21	22.25	0
Monosaccharides and disaccharides (g)	0.02	2.00	0
Polyols (g)	0.00	0	0
Protein (g)	5	0	0

Abbreviations: AOAC, Association of Official Analytical Chemists; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GOS, Galactooligosaccharides; HPAEC-PAD, high-performance anion-exchange chromatography with pulsed amperometric detection; HPLC-ELSD, HPLC coupled with evaporative light scattering detection; UHPLC-ELSD, ultra-HPLC with evaporative light scattering detection.
[1] Nutrition information is expressed on an "as-is" (fresh weight) basis.
[2] Oatmeal FODMAP and simple sugar values represent a representative composite sample analyzed by the Department of Gastroenterology and Translational Nutrition, Monash University (Lab Code: 14701728). Fructose, glucose, and polyols were analyzed via HPLC-ELSD; GOS was analyzed via UHPLC-ELSD; total fructans were analyzed via enzymatic-spectrophotometric assay (AOAC Method 999.03).
[3] Inulin specifications are derived from manufacturer quality control data analyzed via HPAEC-PAD (AOAC Official Method 997.08).
[4] Maltodextrin specifications are derived from manufacturer quality control data.

fructanase activity unit (INU), whereby 1 INU is defined as the amount of enzyme that liberates reducing sugars, such as fructose, from inulin at a rate of 1 mmol/min at pH 4.5 and 40°C. Each fructanase capsule was formulated to contain 350 INU (Lot No. INPHF09, BIO-CAT, Inc.). The New Dietary Ingredient Notification (NDIN) for OPTIZIOME Fructanase was submitted to the United States Food and Drug Administration and was received without objection, establishing a regulatory daily safe consumption limit of ≤2400 INU/d (NDIN no. 1303). Placebo capsules were manufactured with 400 mg tapioca maltodextrin. Both products were manufactured as opaque, white, size 1 capsules made from hydroxypropyl methylcellulose (Arizona Custom Blends Manufacturing, LLC) and titanium dioxide (E171), and were identical in appearance.

The 350 INU dose was selected based on in vitro orogastric digestion simulations demonstrating that, although as little as 50 INU can substantially hydrolyze inulin, doses between 200 and 400 INU provide optimal, statistically significant increases in degradation compared with lower doses [35]. To maximize the probability of in vivo efficacy and align with current commercial usage rates, a dose of 350 INU was finalized. Furthermore, specific in vitro digestion simulations replicating the exact clinical challenge meal confirmed that 350 INU effectively degrades a 25 g inulin load when coadministered with the 40 g oatmeal vehicle under simulated physiological conditions (data not shown). The 350 INU dose used in this acute challenge is highly conservative, remaining well below both this regulatory ceiling of 2400 INU and the clinical safety ceiling of 2000 INU/d previously validated in a 4-wk human tolerability trial [36].

The capsules were consumed with a serving of 40 g of oatmeal containing 25 g of native chicory root inulin (Orafti GR, sourced from Beneo), with a degree of polymerization between 2 and 60 (mean ≥10), in 240 mL of water. Native inulin was selected as a control not only because of the wide use of inulin as an additive in a wide variety of processed foods, but also because its polydisperse spectrum of short and long fructose chains is representative of the natural complexity of whole foods while minimizing the interindividual variability seen with whole foods [37]. Tolerance studies suggest that mild-to-moderate symptoms generally do not become clinically evident until inulin intake reaches 10–15 g/d [19,20,38,39]. Alhasani et al. noted that acute intake of 20 g by healthy adults was well tolerated without any symptom scores being raised above 1 (mild). Meanwhile, Kruse et al. [40] gave healthy subjects 22 to 34 g of inulin per day, depending on energy needs, and noted general signs of abdominal discomfort, with flatulence and bloating being the most common symptoms. Thus, to maximize the occurrence of GI symptoms while limiting excessive discomfort, a 25 g inulin dose was chosen for this study.

Experimental design

This was a randomized, double-blind (participants and study personnel), placebo-controlled, crossover trial with 2 test visits to assess the efficacy of oral fructanase administration on reducing GI symptom severity after inulin challenge in healthy adults. A total of 30 participants were randomly assigned to either fructanase or placebo for the first visit and crossed to the alternate study product for the second visit after ≥7 d of washout. An overview of the experimental design is depicted in Figure 1. Test visits occurred the morning after an overnight fast (≥10 h; water only). After baseline/fasted assessments, participants consumed either the active or the placebo study product with a serving of 40 g oatmeal as a standardized breakfast, which was encouraged to be consumed within 10 min. Participants remained in the clinic for the next 8 h, during which they were instructed to remain rested (i.e., sitting still), without further dietary intake for 6 h, and complete study measurements at the timed intervals.

A VAS to record GI symptoms was followed by a breath sample for hydrogen and methane concentration measurements at baseline ($t = -15 \pm 5$ min) and every hour (±5 min) for the first 8 h after product consumption, whereby $t = 0$ was the time of product consumption. The morning after each test visit ($t = \sim$24 h), participants remotely recorded GI symptoms, stool consistency, and sleep quality using the GI symptom VAS (GI-VAS), Single-Item Stool Consistency Scale (SI-SCS), and modified single-item sleep quality scale (mSI-SQS), respectively.

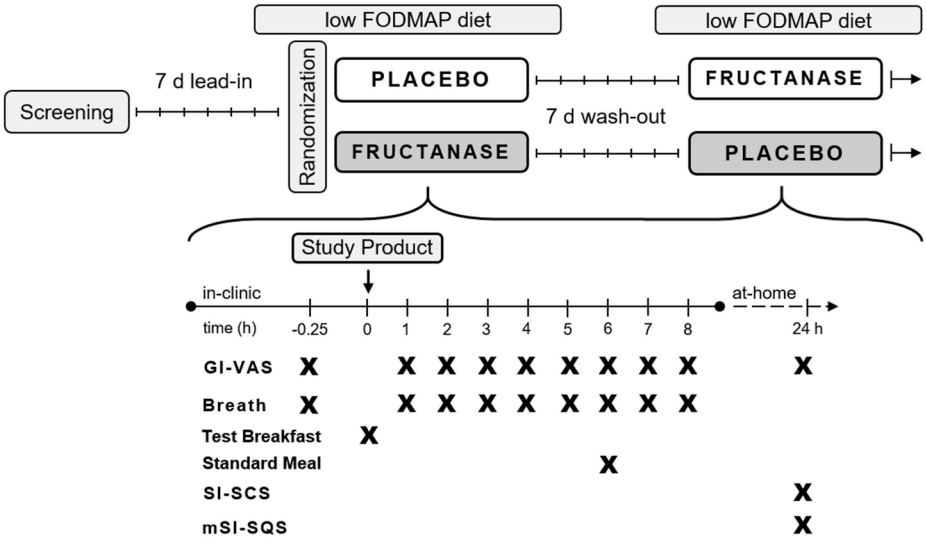

FIGURE 1. Experimental design. Fructanase or placebo was consumed with the test breakfast of 40 g oatmeal, 25 g inulin, and 240 mL water at $t = 0$ h. Gastrointestinal (GI) symptoms and breath hydrogen and methane were evaluated 8 h postprandially. GI symptoms, stool consistency, and sleep quality were also evaluated 24 h after consumption of study products. A standard, low-FODMAP meal was provided at $t = 6$ h. FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; mSI-SQS, modified single-item sleep quality scale; SI-SCS, single-item stool consistency scale; VAS, visual analog scale.

Finally, on the last day of the study, all participants were asked to guess their assigned product sequence.

Participants were instructed to abstain from supplements, beverages, or food products with digestive enzymes, prebiotic ingredients, live probiotics (e.g., yogurt, kombucha), or postbiotic ingredients throughout the study. Leading up to each test day, participants were instructed to abstain from alcohol consumption and vigorous exercise for 48 and 24 h, respectively. Participants were also asked to follow a low-FODMAP diet, as educated by a registered dietitian on staff, for 24 h before their test visits and throughout the observation period (i.e., test visit days and up to completion of 24 h postproduct questionnaires). To assist with compliance, low FODMAP, low-fiber meals (Supplemental Table 1) were provided for participants to consume the evening before each test visit and during each test visit at $t = 6$ h, immediately after GI-VAS completion and breath collection. Adverse events were assessed via open-ended questions at the end of each visit.

Breath hydrogen and methane analysis

Before breath sampling, participants rinsed their mouths with 40 mL of 0.12% chlorhexidine solution for 30 s, after which breath was collected using a Quintron collection bag (QuinTron Instrument Company). Breath hydrogen and methane were measured by gas chromatography (Microlyzer Model SC; QuinTron Instrument Company). Hydrogen and methane concentrations were analyzed in duplicate using the BreathTracker SC analyzer (QuinTron Instrument Company) per the manufacturer's instructions. If the breath hydrogen concentration between the duplicates differed by $\geq$3 parts per million (ppm), a third measurement was performed. The final concentration reported was the average of the duplicates if only 2 measurements were obtained. If 3 measurements were obtained, the final concentration reported was the average of the 2 closest concentration measurements, or if this was not possible (i.e., measurements were equidistant), the average of all 3 measurements was reported. Secondary endpoints included incremental area under the curve (iAUC) (calculated by the linear trapezoid method), maximum concentration (C_{max}), and time to maximum (T_{max}) for breath hydrogen or methane.

Study questionnaires

GI Symptom VAS

The GI-VAS contained a series of questions regarding the severity of 8 GI symptoms occurring at the given moment [34,41]. These GI symptoms included overall abdominal symptoms, abdominal bloating, abdominal pain, flatulence, burping, stomach rumbling, nausea, and fatigue. These GI symptoms were measured using a 100 mm VAS scale ranging from "excellent, none at all" (score: 0) to "really awful, the worst it has been" (score: 100). Participants were instructed to rate themselves by marking the VAS at the point that was most appropriate to their feeling at that time. All 0 to 8 h VAS scores were baseline-adjusted, whereby the respective baseline ($t = -15$ min) score was subtracted from the score at each time point thereafter. The primary endpoint was the maximum overall abdominal symptoms VAS score over the 8 h postprandial period. Secondary endpoints included the maximum scores for all other GI-VAS symptoms for both 0 to 8 h and 8 to 24 h postprandial periods, and T_{max} GI-VAS 0 to 8 h scores. Total GI symptom 0 to 8 h burden was also a secondary endpoint, whereby symptom burden was the positive iAUC, calculated by the linear trapezoid method with baseline subtracted from postprandial time points.

Single-Item Stool Consistency Scale

The SI-SCS was used to rate stool consistency from 0 to 5 (0: no bowel movement, 1: significantly or 2: slightly more firm

than usual, 3: usual, 4: slightly or 5: significantly more loose than usual). The SI-SCS was used to capture participant-reported stool consistency if a bowel movement occurred in the ~24 h after study product consumption.

Modified Single-Item Sleep Quality Scale

The mSI-SQS was previously validated as a weekly questionnaire [42]. The mSI-SQS directs the participant to rate the overall quality of sleep for the prior night by marking an integer score from 0 to 10, according to the following 5 categories: 0 = terrible, 1 to 3 = poor, 4 to 6 = fair, 7 to 9 = good, and 10 = excellent. When rating their sleep quality, participants were instructed to consider the following core components of sleep quality: how many hours of sleep they had, how easily they fell asleep, how often they woke up during the night (except to go to the bathroom), how often they woke up earlier than they had to in the morning, and how refreshing their sleep was. The mSI-SQS was completed by each participant the morning after (t = 24 ± 1 h) consuming the assigned study product.

Statistical methods

The primary endpoint was the maximum overall abdominal symptoms GI-VAS score over the 8 h postprandial period. A sample of 26 participants was expected to provide 80% power (α = 0.05, 2-tailed) to detect a 0.58 effect size, estimated based on published data of the effects of α-galactosidase on GI symptoms [34]. A total of 30 participants were randomly assigned to allow for attrition. A randomization list was uploaded to the Medrio electronic case report form platform (Medrio Inc.). When a participant was determined to be eligible for the study, a randomization number and associated blinded intervention sequence were assigned to the participant through the randomization module of the Medrio platform.

Secondary endpoints included all other GI-VAS scores, breath hydrogen and methane concentrations, participant-reported sleep quality and stool quality, and participant-guessed product sequence. All statistical analyses were conducted using SAS for Windows (version 9.4; SAS Institute Inc.). Tests of significance were 2-sided and performed at the 0.05 significance level. Because of the normality violation for the GI-VAS maximum scores, positive iAUC, and T_{max}, as well as the sleep quality score, all group comparisons were performed with the Wilcoxon signed-rank test. A repeated-measures mixed model with rank transformation was used to evaluate the change in GI symptoms over time. The model contained fixed-effect terms for test condition, time point, and the time point by test condition interaction. Effects for the test sequence and the test period were also included. A random effect was included for the participant nested within test sequence, and the autoregressive [1] covariance structure was imposed upon the residuals for the repeated measures within a test. If the interaction term was at least marginally significant ($P \leq 0.10$), estimate/contrast statements were used to estimate the within-product change from baseline as well as the product differences in the change from baseline at each postprandial time point. A stepdown Bonferroni (Holm) adjustment was applied for multiple comparisons.

Stool consistency and sleep quality were each expressed as the proportion of participants with slightly-to-significantly more loose stools or good-to-excellent sleep, respectively, and the exact binomial confidence interval (CI) was calculated within each condition.

Breath hydrogen iAUC and C_{max} were analyzed with a mixed model containing fixed-effect terms for test condition, test sequence, and test period, with subject nested within test sequence as a random effect. Because of model violations, T_{max} and all outcomes for breath methane were analyzed with the Wilcoxon signed-rank test.

Results

Participant characteristics

A total of 30 participants were randomly assigned, and all completed the study protocol (defined as completion of study visits) in its entirety and were included in the final analyses (Supplemental Figure 1). One participant did not respond to poststudy visit 24-h questionnaires for the placebo condition. Missing data were not imputed, and only observed data were included in the statistical analysis. Participant baseline characteristics are shown in Table 2.

GI symptoms

Compared with placebo, fructanase did not significantly affect the primary outcome—maximum 0 to 8 h postprandial overall abdominal symptoms [median difference (95% CI): 1 (0, 8); P = 0.13] (Table 3). A marginally significant difference [median difference (95% CI): 0.5 (0, 9); P = 0.051] between test conditions was detected for maximum postprandial abdominal pain, where lower scores were reported following fructanase. In addition, a significant difference [median difference (95% CI): 5 (0, 9); $P < 0.001$] was detected between test conditions for maximum postprandial fatigue, where lower scores were reported following fructanase (Table 3). There were no significant differences between test conditions for any other maximum postprandial GI-VAS scores. For positive iAUC 0 to 8 h GI-VAS scores, significant differences between test conditions were detected for abdominal pain [median difference (95% CI): 0.5 (0.0, 12.0); P = 0.044] and fatigue [median difference (95% CI): 7.8 (0.0, 31.0); $P < 0.001$], where the symptom burdens were lower following fructanase compared with placebo (Table 3). For T_{max} 0 to 8 h GI-VAS scores, a significant difference [median difference (95% CI): 0.0 (0, 1); P = 0.028] was detected between test conditions for flatulence, where the T_{max} was shorter following fructanase compared with placebo (Table 3). A marginally significant difference [median difference (95% CI): 0 (0, 2); P = 0.051] was detected between groups for burping,

TABLE 2
Baseline participant characteristics

Characteristics	(n = 30)[1]
Female	13 (43.3%)
Male	17 (56.7%)
Race	
Asian	2 (6.7%)
Black/African American	14 (46.7%)
>1 race	1 (3.3%)
White	13 (43.3%)
Age (y)	38.6 (7.3)
BMI (kg/m^2)	24.5 (3.0)
Systolic blood pressure (mm Hg)	108.8 (9.2)
Diastolic blood pressure (mm Hg)	65.4 (7.5)

[1] Values are count (%) or mean (SD).

TABLE 3
Postprandial gastrointestinal symptoms (0–8 h)

Symptom[1]	Max (mm)			p-iAUC (mm × h)			T_{max} (h)		
	Placebo	Fructanase	Difference	Placebo	Fructanase	Difference	Placebo	Fructanase	Difference
Overall abdominal	6.5 (0.0, 24.0)	3.0 (0.0, 10.0)	1 (0, 8)	13.0 (0.0, 44.0)	4.3 (0.0, 19.0)	2.8 (0.0, 15.5)	7.5 (6.0, 8.0)	7.0 (3.0, 8.0)	0 (0, 1)
Abdominal bloating	5.5 (2.0, 20.0)	3.0 (1.0, 16.0)	1 (0, 4)	9.0 (3.0, 43.5)	4.0 (1.0, 22.0)	1.8 (0.0, 6.5)	7.0 (7.0, 8.0)	7.0 (4.0, 8.0)	0 (−1, 1)
Abdominal pain	2.5 (0.0, 16.0)	0.5 (0.0, 9.0)	0.5 (0, 9)[2]	5.3 (0.0, 23.5)	0.3 (0.0, 11.0)	0.50 (0.0, 12.0)[3]	7.0 (5.0, 8.0)	8.0 (6.0, 8.0)	0 (0, 0)
Flatulence	11.0 (2.0, 32.0)	15.0 (3.0, 36.0)	0.5 (−2, 4)	15.8 (5.5, 61.0)	28.5 (1.5, 58.0)	0.0 (−22.0, 10.5)	8.0 (7.0, 8.0)	7.0 (5.0, 8.0)	0.0 (0, 1)[3]
Burping	1.0 (0.0, 21.0)	1.0 (0.0, 4.0)	0 (0, 1)	1.5 (0.0, 11.5)	0.8 (0.0, 9.0)	0.0 (−1.0, 3.0)	8.0 (6.0, 8.0)	6.5 (2.0, 8.0)	0 (0, 2)[2]
Stomach rumbling	8.5 (2.0, 26.0)	6.5 (0.0, 23.0)	0 (−2, 4)	22.5 (3.5, 47.5)	13.8 (0.0, 48.0)	1.3 (−4.0, 9.0)	6.5 (5.0, 8.0)	7.0 (4.0, 8.0)	0 (0, 0)
Nausea	1.0 (0.0, 3.0)	0.0 (0.0, 2.0)	0 (0, 1)	0.8 (0.0, 6.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	8.0 (6.0, 8.0)	8.0 (5.0, 8.0)	0 (0, 1)
Fatigue	6.5 (0.0, 21.0)	0.0 (0.0, 6.0)	5 (0, 9)[3]	11.5 (0.0, 60.5)	0.0 (0.0, 8.5)	7.8 (0.0, 31.0)[3]	5.0 (2.0, 8.0)	4.5 (1.0, 8.0)	0 (0, 3)

Abbreviations: CI, confidence interval; Max, maximum score above baseline; p-iAUC, incremental area under the curve above baseline; T_{max}, time to maximum score.
Group comparisons were performed with the Wilcoxon signed-rank test.
[1] $N = 30$ participants. Placebo and fructanase values are median (IQR). Paired difference values are median (distribution free 95% CI).
[2] Indicates $P < 0.1$ between groups.
[3] Indicates $P < 0.05$ between groups.

where the T_{max} was shorter following fructanase compared with placebo. Finally, a significant difference between treatments for maximum 8 to 24 h GI-VAS scores was detected for overall abdominal [median difference (95% CI): 0.0 (0.0, 9.0); $P = 0.030$], abdominal bloating [median difference (95% CI): 1.0 (0.0, 10.0); $P = 0.011$], abdominal pain [median difference (95% CI): 0.0 (0.0, 5.0); $P = 0.019$], and flatulence [median difference (95% CI): 1.0 (−1.0, 14.0); $P = 0.044$], where the symptom scores were lower following fructanase compared with placebo (Table 4). Because of the possible impacts of sex and BMI on GI disorders [43,44], post hoc subgroup analyses were performed, which showed that these significant differences between test conditions for maximum 8 to 24 h GI-VAS scores were only present among male participants (Supplemental Table 2) or those with a BMI of <25 (Supplemental Table 3).

Breath hydrogen and methane

The iAUC, C_{max}, and T_{max} for breath hydrogen and methane are presented in Table 5. After the ingestion of the 25 g inulin and 40 g oatmeal challenge, breath hydrogen concentrations rose significantly from baseline across all participants, reaching a C_{max} of ~100 ppm at 7 h postconsumption. Although substantial colonic fermentation was evident, there were no significant differences ($P > 0.05$) between test conditions for any of the breath hydrogen or methane measurements (Figure 2).

Single-item stool consistency scale score

No bowel movements were reported by 9 of 29 (31%) participants following placebo and by 8 of 30 (26.7%) following fructanase within 24 h of the in-clinic consumption of study products. Slightly-to-significantly more loose (soft) stool than usual (i.e., scored either 4 or 5) was reported by 8 of 29 [27.5% (95% CI: 12.7, 47.2%)] participants following placebo, and by 5 of 30 [16.6% (95% CI: 5.6, 34.7%)] following fructanase. The mean difference (0.2, 95% CI: −0.18, 0.62) in stool consistency score between test conditions among those reporting any bowel movement was not statistically significant.

TABLE 4
Postprandial maximum gastrointestinal symptoms (8–24 h)

Symptom	Maximum score (mm)[1]		
	Placebo	Fructanase	Difference
Overall abdominal	7.0 (1.0, 14.0)	3.5 (0.0, 8.0)	0.0 (0.0, 9.0)[2]
Abdominal bloating	6.0 (0.0, 14.0)	1.5 (0.0, 7.0)	1.0 (0.0, 10.0)[2]
Abdominal pain	1.0 (0.0, 6.0)	0.0 (0.0, 2.0)	0.0 (0.0, 5.0)[2]
Flatulence	15.0 (3.0, 32.0)	8.0 (0.0, 56.0)	1.0 (−1.0, 14.0)[2]
Burping	1.0 (0.0, 4.0)	1.0 (0.0, 3.0)	0 (−1.0, 0)
Stomach rumbling	4.0 (0.0, 9.0)	1.0 (0.0, 7.0)	0 (0, 4.0)
Nausea	0 (0, 1.0)	0 (0, 12.0)	0 (0, 0)
Fatigue	2.0 (0, 5.0)	0 (0, 64.0)	0 (0, 2.0)

[1] $N = 30$ participants. Placebo and fructanase values are median (IQR). Paired difference values are median (distribution free 95% confidence interval). Group comparisons were performed with the Wilcoxon signed-rank test.
[2] Indicates $P < 0.05$ between groups.

TABLE 5
Postprandial breath hydrogen and methane (0–8 h)

Breath[1]	iAUC (ppm × h)			C_{max} (ppm)			T_{max} (h)		
	Placebo	Fructanase	Difference	Placebo	Fructanase	Difference	Placebo	Fructanase	Difference
Hydrogen	444.9 (371.8, 517.9)	389.2 (316.2, 462.2)	55.7 (−11.8, 123.0)	116.72 (98.47, 134.96)	107.14 (88.90, 125.38)	9.58 (−8.06, 27.21)	7.0 (6.0, 8.0)	6.0 (6.0, 7.0)	0 (0, 1.0)
Methane	44.3 (36.3, 193.0)	39.6 (34.5, 108.0)	4.0 (−0.3, 9.8)	8.5 (7.0, 28.0)	7.8 (6.0, 19.0)	0 (0, 1.42)	6.0 (5.0, 7.0)	6.5 (6.0, 8.0)	−0.5 (−1, 0)[2]

Abbreviations: CI, confidence interval; C_{max}, maximum concentration; iAUC, incremental area under the curve; T_{max}, time to maximum concentration.
[1] $N = 30$ participants. Group comparisons were performed with a mixed model for the incremental AUC and C_{max} for hydrogen; therefore, the model-derived mean (95% CI) is presented for the test condition and the mean (95% CI) for the difference. The Wilcoxon signed-rank test was used for comparisons for methane and T_{max}; therefore, the median (IQR) is presented for the test condition and the median (distribution free 95% CI) for the difference.
[2] Indicates $P < 0.1$ between groups.

FIGURE 2. Postprandial breath hydrogen (0–8 h) and methane concentrations. $N = 30$ participants.

Modified single-item sleep quality scale score

No significant difference was detected between test conditions in the sleep quality score during the night after placebo or fructanase consumption [median difference (95% CI) 0.0 (−1.0, 0.0); $P = 0.91$]. Following placebo, 25 of 29 (86.2%) participants reported good-to-excellent sleep (score 7–10), whereas 23 of 30 (76.7%) participants reported good-to-excellent sleep following fructanase.

Exit survey and safety

When asked to guess their product sequence upon study exit, 71.43% and 66.67% correctly guessed that they were randomly assigned to either fructanase or placebo first, respectively (data not shown). Two adverse events were reported, where only 1 was considered to be moderate (abdominal bloating). The moderate abdominal bloating occurred during the placebo period and was deemed probably related to the study test condition under blinded review.

Discussion

To our knowledge, this is the first clinical trial describing the efficacy of fructanase in relieving inulin-induced GI symptoms in healthy adults. Although the primary outcome of maximum 0 to 8 h postprandial overall abdominal GI symptoms was unaffected by co-ingestion of fructanase (350 INU) with 25 g inulin, specific indices such as abdominal pain and fatigue were experienced to a significantly lower degree, and the onset of flatulence was delayed compared with placebo. Furthermore, in the 8 to 24 h postclinic period, fructanase significantly reduced overall abdominal symptoms, abdominal pain, bloating, and flatulence in the 8 to 24 h postclinic period, particularly in males and individuals with a BMI <25.

Despite these statistically significant observations, the absolute symptom severity experienced across all groups was minimal, with most participants rating their maximum symptoms below 50 mm on the 100 mm VAS. Because this study used a healthy cohort without a DGBI, participants generally tolerated the 25 g inulin dose without the visceral hypersensitivity typically seen in patients with IBS. In support, physiological imaging demonstrates that healthy adults can accommodate the substantial colonic gas volumes produced by acute high doses of inulin (≤40 g) with minimal symptoms [16]. In contrast, similar gas loads in patients with IBS trigger severe pain due to colonic hypersensitivity to distension [15]. Consequently, the high intrinsic tolerance of our healthy cohort likely created a floor effect, limiting the measurable impact of fructanase on the primary endpoint of maximum overall abdominal symptoms (0–8 h). Thus, although these small shifts serve as promising proof-of-concept findings, determining true clinical effectiveness will require future trials in an inulin-sensitive or IBS cohort, where higher baseline symptom severity would allow for clinically meaningful absolute reductions.

Our results are similar to studies with other microbial FODMAP-specific enzymes such as lactase and α-galactosidase. Consumption of lactase obtained from *Kluyveromyces lactis* (6000 units) 5 min and 10 h before consumption of cow milk by 30 adults with lactose intolerance significantly reduced 0 to 8 h GI intolerance symptoms compared with placebo [33]. There was also a significant reduction in cumulative 0 to 4 h breath hydrogen excretion with either lactase dosing window compared with placebo. Similarly, α-galactosidase (300 or 1200 units) reduced GI symptoms in healthy adults consuming a meal with 420 g cooked beans, with the higher dose also reducing breath hydrogen [31]. α-Galactosidase also reduced GI symptoms related to high galactooligosaccharide meals in individuals with IBS [31,34]. These studies, like the current one, suggest that targeted enzyme supplementation can effectively address FODMAP-related symptoms by reducing intestinal fermentation.

Fructans are recognized as one of the most consistent FODMAPs to trigger symptoms in individuals with IBS [24]. A growing body of evidence supports the effectiveness of a low-FODMAP diet in managing IBS symptoms [25,45,46]. Fructans are widely present in numerous nutrient- and fiber-rich fruits, vegetables, and legumes, as well as common Western foods such as grains [47]. Furthermore, fructans, specifically inulin, are used as fat or sugar replacers, texture enhancers, sensory modulators, or prebiotics in a variety of food products, including yogurt, cheese, butter, ice cream, baked goods, and fruit juices [47]. Consequently, there are concerns regarding the potential for compromised diet quality in patients with IBS due to the restrictive nature of a low-FODMAP diet [48], as well as alterations in gut microbiota composition—notably a reduction in the growth of beneficial bacteria such as *Bifidobacterium* [28], a genus associated with putative immunomodulatory and anticancer properties [49]. Our findings suggest that fructanase supplementation may offer a targeted strategy to address specific fructan intolerance, such as in individuals with IBS, potentially without necessitating an overly restrictive diet.

We assessed breath hydrogen and methane as a noninvasive and indirect approximation of intestinal fermentation [50]. Our observation of marginally longer T_{max} breath methane with fructanase contrasts with studies demonstrating that shorter-chain FOS ferments more rapidly compared with long-chain inulin [51]. Because FOS possess a lower molecular weight than longer-chain inulins, they exert a greater osmotic effect in the small intestinal lumen and are subject to more rapid microbial fermentation; thus, FOS are generally more likely to induce rapid GI symptoms compared with long-chain inulin, which does not accelerate GI transit as readily [16,52,53]. Given that complete in vivo hydrolysis of fructans by fructanase supplementation is unlikely, the aim is to reduce the overall fructan load sufficiently to alleviate symptoms. Future studies are warranted to investigate the possibility of residual GI symptoms arising from the presence of shorter-chain FOS and excess fructose after co-ingestion with fructanase in this population.

The mechanism underlying fructan intolerance involves the incapacity of human digestive enzymes to hydrolyze the β-glycosidic linkages in these complex polysaccharides, leading to their delivery to the large intestine [54]. Bacterial fermentation of these undigested carbohydrates results in gas production (such as hydrogen), and individuals with DGBI can experience symptoms like bloating, borborygmi, flatulence, and cramps [15,54]. Physiological observations with pure liquid sugar solutions, which typically yield breath hydrogen peaks within 3 h [33,55], often do not reflect the GI transit and fermentation physiology that occurs when those carbohydrates are embedded within a solid food matrix [56]. Indeed, although inulin-only experimental drinks elevate breath hydrogen over a 6-h postprandial observation period in healthy adults [16,57], the breath hydrogen C_{max} in our study did not peak until ~7 h. The delayed ~100 ppm breath hydrogen C_{max} likely reflects the composite fermentation of both inulin and the oatmeal vehicle, driven by the much slower fermentation kinetics of complex inulin and the slower orocecal transit associated with the solid oatmeal test meal and the extended 6-h postprandial fast [34,56].

Published data suggest that 40 g of oatmeal (providing ~1.6–2.0 g of fermentable β-glucan) contributes an incremental ~15 to 25 ppm to the breath hydrogen response [58–60], adding to the ~68 to 74 ppm typically produced by 30 g of inulin alone [61]. Importantly, because the enzyme's substrate specificity targets fructosidic bonds, β-glucan fermentation would contribute equally to both study arms and does not confound the between-treatment comparisons. Finally, the reduction in breath hydrogen after fructanase co-ingestion did not reach statistical significance; a similar lack of significant attenuation is observed with α-galactosidase supplementation, in which breath hydrogen remained unaltered despite improvements in abdominal bloating following a complex galactooligosaccharide challenge [31,34]. As hypothesized by Tuck et al. [34], this phenomenon may occur because complex oligosaccharides exert prebiotic effects that increase the abundance of *Bifidobacterium* (a genus known to reduce overall hydrogen production) or because gases are produced locally but are not exhaled in sufficient quantities to alter breath measurements.

Beyond the vehicle itself, another notable limitation of the current study design is the 8-h observation window for breath hydrogen and methane testing. Native chicory inulin is a complex fructan that undergoes steady and prolonged fermentation in the distal colon [51,54]. In vitro fermentation models have demonstrated that although short-chain FOS are fermented rapidly within the first 4 h, the fermentation rate of long-chain inulin is

significantly higher during the 12- to 24-h period [19,51]. Clinical studies measuring 24-h breath hydrogen have similarly shown that substantial inulin fermentation continues well beyond the initial 6 to 8 h, often yielding total 24-h AUC values that are 4 to 10 times greater than the 0- to 6-h AUC alone [57]. Given the delayed 7-h breath hydrogen peak observed in our study, it is highly likely that the 8-h window missed the full extent of colonic gas production. Consequently, using an extended breath-testing window of ≤24 h, which can be easily facilitated with at-home breath collection bags [57,62], would be highly beneficial for future studies to accurately capture the full metabolic and symptomatic profiles of slowly fermented fibers. Furthermore, providing a second standardized, low-FODMAP meal during this observation period could facilitate the emptying of ileal contents into the ascending colon, thereby enhancing the visibility of fermentation while also minimizing background variability introduced by participants' habitual diets [57,63].

Nevertheless, our observed trend supports the possibility of reduced inulin fermentation due to fructanase-mediated hydrolysis. Recent in vitro simulations using liquid chromatography-mass spectrometry (LC-MS) have characterized the specific hydrolytic profile of the microbial fructanase used in this study [35]. Under simulated gastric digestion conditions, the enzyme was shown to completely hydrolyze all detectable inulin-type fructans with degrees of polymerization >3 within 2 h [35]. Although our current study did not evaluate the exact spectrum of chain lengths produced over an extended 24-h window, these prior LC-MS data indicate that the enzyme rapidly reduces complex inulin to very short oligosaccharides and terminal monosaccharides [35]. This rapid degradation significantly reduces the load of intact, highly fermentable long-chain polymers before they can reach the colon [35]. Importantly, both FOS and inulin are established prebiotics with bifidogenic effects [64], highlighting the potential of fructanase to mitigate symptoms in individuals with IBS while allowing them to benefit from these functional fibers.

Although our randomized crossover design inherently controlled for baseline interindividual variation, the demographic distribution of our cohort precluded a robust race-based interaction analysis. Genetic predispositions, such as lactase nonpersistence, are well-established demographic drivers of intolerance to disaccharides like lactose [65]. Although inulin is an oligosaccharide that is fermented by the gut microbiota rather than digested enzymatically by the host [13–18], its tolerance depends heavily on the baseline composition and metabolic capacity of the gut microbiota, which can vary significantly across racial and ethnic backgrounds [66]. Consequently, future adequately powered trials should specifically evaluate race and ethnicity as potential modifying factors in both baseline fructan tolerance and the mitigative efficacy of supplemental digestive enzymes.

Finally, our method for assessing stool consistency presented a methodological limitation. We acknowledge that the SI-SCS used in our study relies heavily on a subjective baseline, as participants must rate their stool against their own perception of normal. Because this can vary widely among individuals, future trials should instead use the Bristol Stool Form Scale. This tool, which employs a standardized visual picture key, is a more robust and validated objective measure for assessing stool form and consistency [67,68].

This study possesses several strengths, including the randomized, double-blind, placebo-controlled, crossover design, a controlled dietary protocol featuring a prestudy low-FODMAP diet and standardized observation period meals, and comprehensive objective and subjective outcome assessments. A notable limitation, however, is the use of isolated inulin powder rather than fructan-containing whole foods. In a real-life context, the habitual intake of fructans in the general population is ~3.51 g/d, and slightly higher at 4.01 g/d in individuals with disorders of gut–brain interaction [69]. Fructans are typically ingested within complex mixed meals containing other potential symptom-inducing components. For instance, wheat contributes most of the daily fructan intake but simultaneously contains gluten and α-amylase trypsin inhibitors [70]. Interestingly, a double-blind crossover challenge demonstrated that it is often the fructans in wheat, rather than the gluten, that primarily induce GI symptoms in patients with self-reported nonceliac gluten sensitivity [70]. Finally, the psychological expectancy of symptoms must be considered; recent findings illustrate that the mere expectation of consuming a trigger food can significantly exacerbate GI symptoms, highlighting the profound impact of the nocebo effect and gut–brain interactions [71].

In conclusion, this study provides promising initial evidence that fructanase supplementation can mitigate inulin-induced GI symptoms in healthy adults, albeit colonic fermentation (i.e., breath gas release) remained unaltered from placebo. These findings suggest a potential strategy for managing fructan intolerance. Future studies should optimize enzyme dose and timing strategies, evaluate the effectiveness of fructanase with real-world mixed meals, and confirm these findings in individuals with inulin sensitivity at baseline or in clinical populations such as those with IBS.

Author contributions

The authors' responsibilities were as follows – YQ, CJT, RL, CMC, SMG: contributed to conceptualization; VNK, AMS, YQ, CMC, SMG: contributed to investigation and project administration; TMB: contributed to data curation, formal analysis, validation, and visualization; EM, CFM, SMG: contributed to writing original draft; and all authors: contributed to the writing, review, and editing of the final manuscript and read and approved the final version.

Conflict of interest

At the time this study was conducted, YQ and SMG were employees of BIO-CAT, Inc., the company that funded the study and provided investigational products to the clinical trial site. BIO-CAT distributes OPTIZIOM Fructanase to dietary supplement manufacturers and stands to benefit financially from research on fructanase. BIO-CAT had a role in the study design, in the interpretation of data, in the writing of the manuscript, and in the decision to submit the article for publication, but did not participate in data collection. BIO-CAT holds relevant patents, United States Patent no. 5,445,957 and United States Patent no. 5,651,967. EM, CFM, TB, VNK, AMS, and CMC are employees of Biofortis, Inc., the company that BIO-CAT, Inc. contracted to conduct the clinical trial. All other authors report no conflicts of interest.

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Data availability

Data described in the manuscript, code book, and analytic code as well as protocol will be made available upon request pending application and approval of the corresponding author.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Perplexity AI Pro and Gemini 3.1 Pro in order to assist with literature search of relevant peer-reviewed articles and for language editing. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2026.101782.

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