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Herbal formula improves upper and lower gastrointestinal symptoms and gut health in Australian adults with digestive disorders

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ABSTRACT

Gastrointestinal (GI) problems affect half of Western populations. Symptoms can vary from frequent reflux to irritable bowel syndrome. The Nutrition Care (NC) Gut Relief Formula contains a combination of herbs and nutrients including curcumin, *Aloe vera*, slippery elm, guar gum, pectin, peppermint oil, and glutamine shown to benefit the GI system. The 16-week pre-post study tested the hypothesis that the NC Gut Relief Formula would be tolerable and effective in improving GI symptoms and gut health in adults with digestive disorders. A total of 43 participants completed the study. After a control phase, participants took 5 g/d and then 10 g/d of the formula for 4 weeks. GI symptoms and GI health were assessed by a series of validated questionnaires, for example, Leeds Dyspepsia Questionnaire, Bristol Stool Chart, Birmingham IBS Symptom Questionnaire, and by intestinal permeability and gut microbiota profile. The NC Gut Relief Formula significantly improved the frequency and severity of upper and lower GI symptoms by 60%-80%, including indigestion, heartburn, nausea, constipation or diarrhea, abdominal pain, and troublesome flatulence, and significantly improved physical functioning, energy levels, mood, and sleep by 60%-80%. All participants with normal stool, 90% with hard stool, and 66% with soft stool recovered from intestinal permeability, evident by normal lactulose to mannitol ratios. The NC Gut Relief Formula generally improved microbial profile, with a marked increase in *Lactobacillus*, *Clostridium*, and *Faecalibacterium prausnitzii*. Almost half of the participants with upper GI symptoms taking proton pump inhibitors for heartburn no longer required proton pump inhibitors at the end of the study. A third of participants were able to reintroduce food triggers, such as fermentable oligosaccharides, disaccharides, monosaccharides, and polyols garlic, onion, and beans, or reflux-causing acidic/spicy foods, for example, citrus, tomato, and caffeine, in their diet after 3 months without symptom aggravation. The NC Gut Relief Formula significantly improved GI symptoms and associated quality of life over 3

Abbreviations: FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GERD, gastroesophageal reflux disorder; GI, gastrointestinal; IBS, irritable bowel syndrome; L/M ratio, lactulose to mannitol ratio; NIIM, National Institute of Integrative Medicine; NC, Nutrition Care; PPI, proton pump inhibitor; QoL, quality of life.

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months while reducing intestinal permeability, improving the microbial profile, reducing the need for reflux medication, and enabling the consumption of previous food triggers.

1. Introduction

Gastrointestinal (GI) problems affect half of adults in Western populations [1] and can manifest as frequent reflux, dyspepsia, heartburn, stomach pain or cramping, bloating, diarrhea or constipation, and conditions such as inflammatory bowel disease. The chronic occurrence of troublesome reflux at least twice a week manifests as gastroesophageal reflux disorder (GERD). GERD has a high prevalence of 10%-20% prevalence in Western countries [2], including Australia [3,4]. In some cases, GERD can lead to complications that include esophageal stricture, a narrowing or tightening of the esophagus that causes swallowing difficulties, and esophageal cancer [5]. Commonly prescribed medications for reflux include proton pump inhibitors (PPIs). However, long-term use of these PPIs can lead to a range of adverse effects, including withdrawal symptoms, nutritional deficiencies (specifically, vitamin B12 and magnesium), rebound acid hypersecretion, acute interstitial nephritis, gastric cancer, adverse effects with concomitant medication, bone fractures, enteric infections, and pneumonia [6,7]. *Helicobacter pylori* infections play a role in GI conditions such as gastritis, peptic ulcer disease, and gastric cancer; however, *H pylori* infection is inversely correlated to GERD [8,9].

Functional disorders of the lower GI tract account for about 40% of all referrals to gastroenterologists and include irritable bowel syndrome (IBS) with a worldwide prevalence of 12% [10]. Symptoms include abdominal pain and altered bowel habits and can be due to food intolerance, for example, lactose and fructose.

In addition to bulking agents and laxatives, patients with persistent IBS may be prescribed medication, including antidiarrheal, antispasmodic, and antidepressants, to decrease gut sensitivity. Prescription medications, however, can lead to adverse effects such as increased bloating, abdominal discomfort, dehydration, electrolyte disturbances, headache, dizziness, nausea, and dry mouth [11]. In more severe cases, prolonged medication use can result in adverse events, such as somnolence (sleepiness/drowsiness), hypotension, or ischemic colitis [11].

Alternative treatments with less adverse effects are needed. Several herbs have shown benefits for upper and lower GI problems, including reflux, GERD, and IBS. For example, curcumin has anti-inflammatory properties and has been shown to reduce symptoms of IBS in an 8-week trial [12]. In an in vitro cell culture study to simulate acid exposure experienced by GERD patients, curcumin prevented the expression of inflammatory cytokines (IL6, IL8, NF-κbeta) [13]. A meta-analysis of 16 clinical trials involving 651 patients found that peppermint oil significantly reduced the symptoms of IBS ($P < .005$) [14], and a meta-analysis of 4 trials involving 392 patients found that GI symptoms were reduced by 57% [15]. Although peppermint oil can exacerbate symptoms in GERD due to its relaxing effect of the lower esophageal sphincter [16], it has shown benefits by reducing acid regurgitation and improving other manifestations in patients with reflux less severe than GERD [17].

Aloe vera juice containing polysaccharides (50 mg/d) were as effective in reducing GERD symptoms as medications (PPI: omeprazole or histamine H2 antagonist: ranitidine) in a 4-week randomized controlled trial of patients (n = 79) with GERD [18]. The demulcent *Ulmus rubra* (slippery elm) has been traditionally used for its anti-inflammatory and mucous membrane soothing properties in conditions such as sore throats and coughs to digestive disturbances since the early 1900s. A recent study using a mixture of dried powdered slippery elm bark, lactulose, oat bran, and licorice root (C-IBS formula) significantly improved both bowel habit and IBS symptoms in patients with constipation predominant IBS [19]. Pectin, a nonfermentable, gel-forming fiber, has a bulking and prebiotic effect and has been shown to improve IBS symptoms [20] similarly to psyllium and guar gum [21-24]. Guar gum increased *Lactobacillus* and *Bifidobacterium* in IBS patients and improved quality of life (QoL) in IBS patients [25].

In other studies on nutrients, glutamine has been shown to help with gut repair by tightening the epithelial junctions in the intestinal walls, thereby aiding in the healing process of leaky gut, and also helps mouth ulcers to heal faster [26,27]. Furthermore, combinations of nutrients show some benefits on gut inflammation. For example, in an animal study, quercetin and vitamin E (α-tocopherol) lowered esophageal inflammation and decreased acid and pepsin production in the stomach of rats [28].

In the current study a single-arm pre-post study of 16 weeks' duration, we tested the hypothesis that the herbal Nutrition Care (NC) Gut Relief Formula—containing curcumin, *A vera*, slippery elm, guar gum, peppermint oil, and glutamine—would be tolerable and effective in improving GI symptoms and gut health in Australian adults with digestive disorders. Our specific objectives were to assess the effect of the herbal formula on GI symptoms, associated QoL, intestinal permeability, and the gut microbiome.

2. Methods and materials

2.1. Ethics statement

The study was approved by the National Health Medical Research Council (NHMRC) endorsed National Institute of Integrative Medicine (NIIM) Human Research Ethics Committee, and participants provided written informed consent. Trial registration: ANZCTRN12618000878279; registered 23 May 2018, https://www.anzctr.org.au/375140.

2.2. Study design and participants

The study was conducted as a single-arm pre-post study of 16 weeks' duration, with a 4-week run-in period as the control phase and a 12-week intervention period, which investigated

the tolerability of different dosages and effectiveness of the NC Gut Relief Formula on GI disturbances. We included adults with moderate GI disturbances of the upper and/or lower GI tract experiencing 1 or multiple symptoms at least once a week for at least 3 months. Symptoms included reflux, heartburn, regurgitation, nausea, bloating, abdominal pain, diarrhea, or constipation, and adults with diagnosed inflammatory bowel disease, such as IBS, were included. Adults excluded were those with GI symptoms due to pregnancy or cancer; diagnosed with serious chronic conditions, including celiac disease or cystic fibroses; those planning surgery or medication change during the study; and those with an intolerance or allergy to any of the ingredients in the NC Gut Relief Formula. We encouraged participants to cease their regular pre- and probiotics intake before commencing the study. We recruited through the NIIM clinic newsletter, NIIM Web site, flyers, Facebook, public lectures, and NIIM physicians.

2.3. Study supplement

The NC Gut Relief Formula is a multi-ingredient herbal and nutritional powdered formula. Ingredients and bioactive compounds are provided in Table 1. The NC Gut Relief Formula was originally formulated as a food-grade product, containing complex herbal extracts and raw materials, selected on traditional and scientific evidence, and has been listed with the Therapeutic Goods Administration as a supplement since 2007. Herbal compounds in the formula have been tested for authenticity, quality, and purity as per British and US Pharmacopeia Monograph standards.

2.4. Allocation and compliance

After a 4 week run-in control phase, participants were allocated 5 g daily of the NC Gut Relief Formula powder for 4 weeks (month 1) followed by 10 g/d (month 2) to be taken mixed in water and/or food, and the patient's preferred dose (0/5/10 g/d) in the third month. The powder was provided in sachets, and participants were instructed to have the powder mixed with water (cold or warm) or with food. Participants were advised not to alter their general diet, medication, and exercise regimen throughout the trial. Compliance was assessed by questionnaire and by sachet count at the end of each visit.

2.5. Assessments/outcome measures

2.5.1. Questionnaires

A series of questionnaires was administered at all appointments (0, 4, 8, 12, and 16 weeks). At baseline, we assessed demographics, medication, diet, food triggers, and exercise regimen and followed up regarding any changes throughout the study. Assessment of upper GI symptoms such as dyspepsia and reflux and its impact on the QoL was done by the Leeds Short-Form Dyspepsia Questionnaire [29], GERD-Q [30], GERD-QoL [31], and the GERD-HRQL [32].

2.5.1.1. *Leeds Dyspepsia Questionnaire*. The validated Short-Form Leeds Dyspepsia Questionnaire assesses the frequency and severity of 4 dyspepsia symptoms—indigestion, heartburn, regurgitation, and nausea—on 5-point Likert scales (0-4 points). Data were analyzed as composite scores, with the highest score of 32 (4 points × 2 criteria (frequency/severity) × 4 symptoms).

2.5.1.2. *GERD-Q questionnaire*. The GERD-Q questionnaire consisted of 6 questions and 4 × 4-point Likert scales (0-3) assessing the frequency and severity of symptoms during the previous week (7 days). The GERD-Q was originally developed to distinguish GERD from less severe reflux and has high accuracy, sensitivity (65%), and specificity (71%) comparable to gastroenterological diagnostics, with a symptoms score of ≥8 indicative of GERD [30]. In our study, we used an adjusted unidirectional scoring system, with higher scores being consistent with higher frequency

Table 1 – Ingredient composition of each 5 g (1 sachet) of the NC Gut Relief Formula

Ingredients		Per 5-g sachet	
Curcuma longa rhizome as Cumerone		30.37 mg	
	Equiv. Curcumin		6.38 mg
Glutamine		2.5 g	
Quercetin		200 mg	
Glucosamine hydrochloride		500 mg	
	Equiv. Glucosamine		415.05 mg
A vera (inner leaf/gel without latex & rind)		2.5 mg	
	Equiv. *A vera* leaf fresh		500 mg
	Equiv. *Aloe* polysaccharides		187.5 mg
	Equiv. Aloin (as barbaloin)		0.02 μg
Ulmus rubra (slippery elm) bark powder		500 mg	
Guar gum		100 mg	
Pectin		100 mg	
Peppermint oil		3 mg	
Dibasic sodium diphosphate		260 mg	

Equiv, equivalent.

or severity of symptoms. The highest frequency score was 18 (3 points × 3 frequencies (days) × 6 questions), and the highest number of days with symptoms was 42 (7 days per week × 6 questions).

2.5.1.3. GERD-QoL questionnaire. The GERD-QoL is a 16-item questionnaire assessing the effect of GERD on 4 domains including impact on daily activities, diet, psychological well-being, and treatment effect. Each item is scored on a 5-point Likert scale [31]. The higher the score is, the more troublesome the symptoms. We used the scoring system described by Chan [31], as follows:

Daily Activity (DA) Score = (Q2 + Q4 + Q5 + Q8 + Q10 + Q11 + Q12 + Q13) *100/32.

Diet (DI) Score = (Q1 + Q6 + Q9) *100/12.

Psychological well-being (PW) Score = (Q15 + Q16) * 100/8.

Adjusted overall score = (DA + DI + PW)/3.

Treatment effect (TE) consisting of 3 questions in the GERD-Qol was only analyzed for participants taking medication (n = 11, PPI with upper GI symptoms).

Treatment effect (TE) Score = (Q3 + Q7+ Q14) *100/12, and overall score = (DA + DI + TE + PW)/4.

2.5.1.4. GERD-HRQL (health-related quality of life questionnaire) questionnaire. The GERD-HRQL is a 16-item questionnaire assessing the severity of heartburn and regurgitation and its impact on the QoL on a 6-point Likert scale (0-5), with higher scores indicative of greater negative impact [32]. For the assessment of lower GI symptoms, we administered the Bristol Stool Chart [33], the Birmingham IBS Symptom Questionnaire [34], and the IBS-QoL Questionnaire [35].

2.5.1.5. Birmingham IBS Symptom Questionnaire. The Birmingham IBS Symptom Questionnaire is a 14-item questionnaire assessing the frequency of lower GI symptoms during the last 4 weeks on a 5-point Likert scale (0-5), with higher numbers indicative of greater frequency [34].

2.5.1.6. The IBS-QoL Questionnaire. The IBS-QoL Questionnaire is a 30-item questionnaire with a 5-point Likert scale (1 = rarely to 5 = always) covering 10 domains over the past month, including emotional health, mental health, health belief, sleep, energy, physical functioning, diet, social role, and physical role [35]. In this study, we used an abridged version with 25 item not including 3 questions of sexual relations and 2 on work-related physical role. The higher the score is, the greater the negative effect of the lower GI symptoms on the QoL.

2.5.1.7. Bristol Stool Chart. The Bristol Stool Chart is a diagnostic scale that assigns a number (type 1-7) to samples of human feces based on its shape, color, and consistency [33]. Types 1-3 are constipation hard types, type 4 is the ideal type (like a sausage smooth and soft), and types 5-7 are diarrhea-type more watery loose types.

2.5.1.8. Other symptoms and pain questionnaire. We assessed the frequency and severity of 10 other noncolonic symptoms, including constant lethargy/fatigue, urinary urgency/ incontinence, mouth ulcers, rashes, nervousness, and palpitations, by a questionnaire [36] [37]. Pain was assessed by its severity, type, and location, and history using the pain 10-point visual analogue scale [38].

2.5.2. Helicobacter breath test

All participants underwent a *Helicobacter* breath test to test for *H pylori* infection as a potential confounding factor for upper GI symptoms. In positive cases, patients received antibiotic treatment before start of the study. Testing was done through Melbourne Pathology. Participants were required to have fasted for at least 6 hours with no food or fluid including water and to withhold all medications. On the day of the breath test, the participant was supplied with a special kit containing a urea and carbon 14–containing capsule. The patient had to blow into a special balloon for testing. In case of a positive result, participants were retested after 1 week of antibiotics before commencing the study.

2.5.3. Blood tests/inflammatory markers

Blood samples at baseline and 3 months were taken to assess cytokines tumor necrosis factor-α, interleukin (IL)-1β, IL-6, and IL-8, associated with IBS [39].

2.5.4. Intestinal permeability/leaky gut test

The intestinal permeability 6-hour urine test measures the ability of 2 differently sized nonmetabolized sugar molecules lactulose (larger molecular size) and mannitol (smaller molecular size) to permeate the intestinal mucosa. Secreted levels of a premeasured amount of lactulose and mannitol consumed were assessed at baseline (week 4) and at the end of the study (week 16) by an external pathology laboratory. Reference ranges are 0%-0.3% for lactulose recovery, 9.5%-25% for mannitol recovery, and 0-0.035 for lactulose to mannitol ratio (L/M) ratio. A high L/M ratio is indicative of increased paracellular permeability between the intestinal mucosal cells [40].

2.5.5. Gut microbiome-stool test

The GI Effects Stool Profile Test (Genova, Asheville, NC, USA; https://www.gdx.net/product/gi-effects-comprehensive-stool-test) provides a comprehensive profile of commensal bacterial species in colony-forming units per gram of stool by polymerase chain reaction DNA analysis. Polymerase chain reaction DNA–based analysis offers a more accurate result than standard culturing technologies. We calculated relative abundance/microbial richness. The research assistant provided enrolled patients with a test kit from Genova via Nutripath (Ashburton, Victoria, Australia) at their first appointment for baseline testing (week 4 before the intervention) and before their final appointment (week 16).

2.6. Statistical analyses

A sample size of 50 participants was calculated to detect a difference of 9% (SD = 10%) in lactulose recovery (reference range 0%-0.3%) before and after the intervention period with 80% power and 95% confidence and to account for 20% dropout or nonattendance at all appointments. Analyses were performed using SPSS (PASW version 26; IBM, Armonk, NY, USA), and statistical significance was set at $P < .05$. In this

single-arm study, the differences in continuous variables within groups (pre- and postintervention) were analyzed with repeated-measures Student t test at 4, 8, and 12 compared to baseline weeks for questionnaires and with the Student t test for outcome measures with 2 time points at 12 weeks and baseline (stool, urine, and blood tests) for continuous variables. Categorical variables were analyzed by χ^2 and Fisher exact test for small numbers. The run-in phase between week 0 and 4 served as control, and analyses were undertaken for all questionnaires.

3. Results

3.1. *Participants*

The trial was conducted at the NIIM in Melbourne, Australia, between May 2018 and January 2019. A total of 66 participants were screened for eligibility; 50 patients were enrolled in the trial, with 2 testing positive for *H pylori* infection, resuming the trial after completing a 1-week antibiotics course, and testing negative for *H pylori* in the retest. A total of 7 participants withdrew from the trial, including 3 patients due to illness unrelated to the trial, 2 participants reported severe constipation or bloating after taking the formula in the first month of the intervention, and 2 participants were lost to follow-up. Forty-two (n = 42) of the total of 43 participants completing the trial reported lower GI symptoms, and 75% also reported experiencing less upper GI symptoms (n = 32). Most participants were female (76%) with a mean age of 50 years. Questionnaire assessments were completed by all participants at all time points (n = 43); intestinal permeability assessed at 2 time points, weeks 4 and 16, was completed by all but 1 participant (n = 42); and the stool analysis was completed at both time points by 86% (n = 37). Fig. 1 provides the study flowchart. Compliance was very good, with all participants consuming the 5-g/d dose in month 1 and 90% consuming 10 g/d in month 2. The preferred daily dose of the NC Gut Relief Formula was 5 g for n = 13 and 10 g for n = 28, and 2 participants chose 0 g in month 3 due to disliking the taste and texture of the formula.

Tolerability and acceptability were generally high, with 45% liking the taste; 37% were neutral; and 7% disliked the taste. Almost all (93%) found it easy to take the formula, with most mixing the powder with warm water as recommended. All of the participants completing the trial reported no bothersome adverse effects. At the beginning of the trial, a third of participants with upper GI symptoms including reflux and heartburn (34%, 11/32) regularly took prescription medications including PPIs to relieve their symptoms, for example, Somac (Nycomed GmbH, Konstanz, Germany), Nexium (AstraZeneca UK Ltd, Luton, UK), Zantac (Aspen Pharmacare, St Leonards, NSW, Australia), and Pariet (Eisai GmbH, Frankfurt am Main, Germany). Almost a quarter (24%, 10/42) of

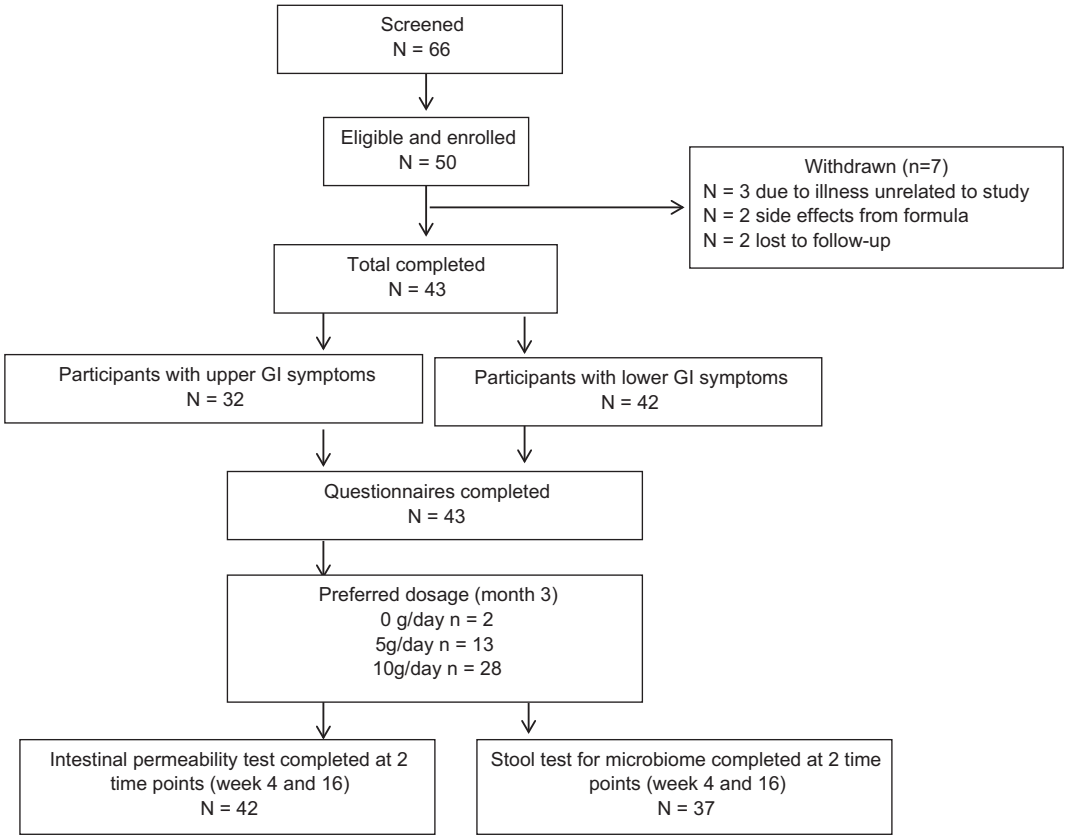

Fig. 1 – Study flowchart of participants.

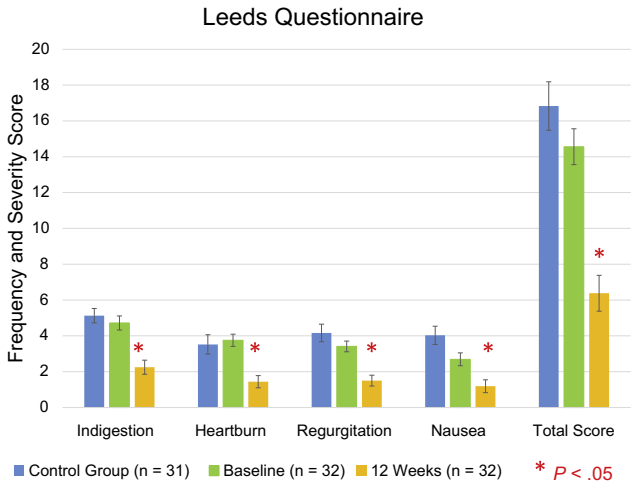

Fig. 2 – Frequency and severity of upper GI symptoms by Leeds Dyspepsia Questionnaire.Values are means ± SE scores at 3 time points. Higher scores are linked with greater severity and frequency. Highest composite score is 32. Lower scores are associated with improvement.

participants with lower GI symptoms regularly took laxatives to relief constipation.

3.2. *Assessment of GI symptoms by questionnaire*

Analysis of questionnaire data in the control phase confirmed no significant differences in GI symptoms in week 4 (baseline and start of intervention) compared with week 0 (enrolment) (control data displayed in figures, not shown in tables).

3.2.1. *Upper GI symptoms*

The NC Gut Relief Formula significantly improved the severity of the GI symptoms by 56%-62% and reduced their frequency by 64%, including indigestion, heartburn (burning sensation), regurgitation (acid reflux), and nausea, as assessed by the Leeds and GERD questionnaires ($P < .001$) [29,30] (Fig. 2). In addition, the NC Gut Relief Formula significantly improved the QoL in participants with upper GI symptoms, including daily activities by 59%, diet by 37%, psychological well-being/mood by 60%, and associated health-related QoL by 53%

Table 2 – Change of upper GI symptoms and QoL by questionnaire

Questionnaire	Measure	n	Baseline Mean ± SE	12 wk Mean ± SE	Difference Mean ± SE	Change in %	P value
a) Leeds	Indigestion	32	4.72 ± 0.45	2.25 ± 0.39	2.84 ± 0.35	–60%	P < 0 .001
	Heartburn	32	3.75 ± 0.48	1.44 ± 0.34	2.31 ± 0.35	–62%	P < 0 .001
	Regurgitation	32	3.41 ± 0.56	1.50 ± 0.30	1.91 ± 0.53	–56%	P = 0 .001
	Nausea	32	2.69 ± 0.51	1.19 ± 0.36	1.50 ± 0.40	–56%	P = 0 .002
	Total score	32	14.56 ± 1.61	6.38 ± 1.0	8.19 ± 1.20	–56%	P < 0 .001
b) GERD-Q	Frequency	32	5.84 ± 0.57	2.06 ± 0.35	3.78 ± 0.53	–64%	P < 0 .001
	Days	32	9.28 ± 1.19	2.80 ± 1.19	6.48 ± 1.07	–70%	P < 0 .001
c) GERD-QoL	Daily activity (DA)	32	42.77 ± 4.81	17.68 ± 3.60	25.09 ± 3.72	–59%	P < 0 .001
	Diet (DI)	32	52.08 ± 5.70	33.07 ± 6.27	19.01 ± 4.27	–36.5%	P < 0 .001
	Psych well-being (PW)	32	47.65 ± 6.31	19.14 ± 5.14	28.51 ± 5.62	–60%	P < .001
	Adjusted overall score [a]	32	47.50 ± 4.90	23.29 ± 4.45	24.21 ± 3.64	–51%	P < 0 .001
Subgroup on PPI	Treatment effect (TE)	11	56.06 ± 11.01	41.67 ± 8.84	14.39 ± 8.71	–25%	P = 0 .129 [c]
	Overall score [b] (subgroup on PPI)	11	76.04 ± 10.07	32.59 ± 6.60	43.44 ± 7.74	–57%	P < 0 .001 [c]
d) GERD-HQoL	Total score	32	18.50 ± 2.25	8.63 ± 1.62	9.88 ± 1.85	–53%	P < 0 .001
e) Pain	Upper GI pain	13	5.08 ± 0.69	2.62 ± 0.95	2.46 ± 1.33	–48%	P = 0 .088
	Lower GI pain	24	4.23 ± 0.54	1.97 ± 0.42	2.25 ± 0.59	–53%	P = 0 .001
	Other pain	24	5.08 ± 0.39	2.49 ± 0.43	2.59 ± 0.64	–51%	P < 0 .001

e) Pain: Only participants experiencing pain are included in the table. Some participants experienced several types of pain (eg, 3 types of pain [n = 5], upper and lower GI pain [n = 6], upper GI pain [n = 13]). Some participants did not report any pain.

[a] Adjusted overall score = (DA + DI + PW)/3.

[b] Overall score = (DA + DI + TE + PW)/4.

[c] Subgroup on PPI.

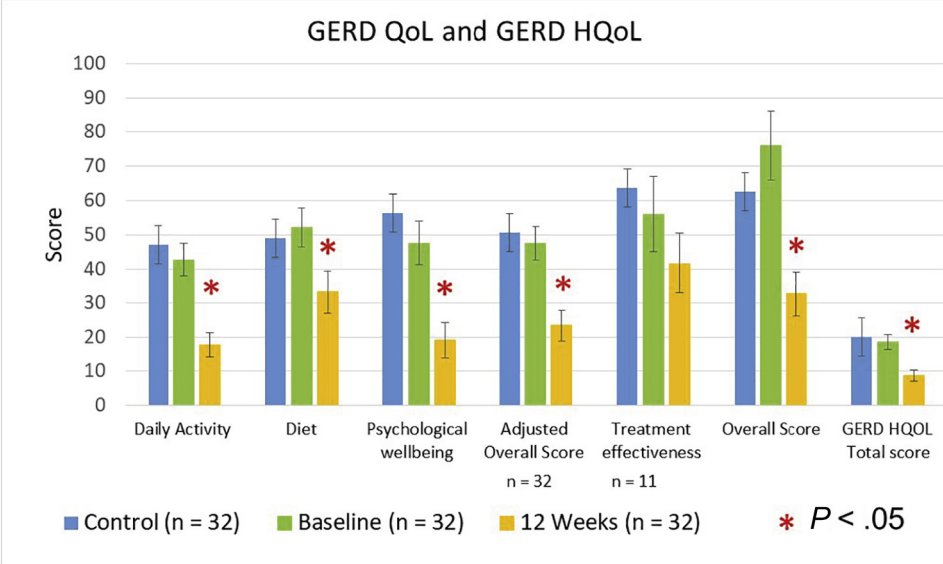

Fig. 3 – QoL associated with upper GI symptoms by GERD-QoL and GERD-HQoL.Values are means ± SE scores at 3 time points. Higher scores are linked with greater impact on QoL. Highest impact score is 75 for GERD-QoL and 50 for GERD-HQoL. Lower scores are associated with improvement.

($P < .001$). The influence of the NC Gut Relief Formula on the (treatment effect) was only assessed in those participants with regular PPI medication intake (n = 11). Although symptoms improved, the sample size was too small to reach statistical significance (Table 2 and Fig. 3).

3.2.2. *Lower GI symptoms*

3.2.2.1. *Birmingham IBS [34].* Three quarters of participants experienced a combination of GI symptoms at baseline, with the majority of 83% experiencing diarrhea and pain, and 77%

Table 3 – Change of lower GI symptoms and QoL by questionnaire

Questionnaire	Measure	n	Baseline Mean ± SE	12 wk Mean ± SE	Difference Mean ± SE	Change in %	P value
a) Birmingham IBS frequency (days)	Constipation	34	4.24 ± 0.75	2.97 ± 0.76	1.28 ± 0.60	–30%	P = .04
Subgroup with symptom	Diarrhea	37	5.94 ± 0.84	2.31 ± 0.47	3.62 ± 0.81	–61%	P < .001
	Abdominal pain	39	7.94 ± 0.88	2.14 ± 0.49	5.79 ± 0.79	73%	P < .001
	Troublesome flatulence	34	4.94 ± 0.37	1.38 ± 0.36	3.57 ± 0.52	–72%	P < .001
b) Birmingham IBS severity score	Constipation	34	6.88 ± 0.59	4.12 ± 0.70	2.76 ± 0.66	–40%	P < .001
Subgroup with symptom	Diarrhea	37	7.78 ± 0.72	4.43 ± 0.60	3.35 ± 0.62	–43%	P < .001
	Abdominal pain	39	7.97 ± 0.51	3.05 ± 0.46	4.92 ± 0.51	–62%	P < .001
	Troublesome flatulence	34	4.24 ± 0.13	1.79 ± 0.30	2.44 ± 0.35	–58%	P < .001
c) IBS-QoL	Emotional	42	9.41 ± 1.00	3.00 ± 0.78	6.40 ± 0.85	–68%	P < .001
	Mental health	42	9.07 ± 0.96	2.48 ± 0.74	6.60 ± 0.81	–73%	P < .001
	Sleep	42	4.09 ± 0.644	0.74 ± 0.33	3.36 ± 0.60	–82%	P < .001
	Energy	42	5.90 ± 0.55	1.79 ± 0.43	4.11 ± 0.53	–70%	P < .001
	Physical function	42	4.21 ± 0.74	1.38 ± 0.47	2.83 ± 0.73	–67%	P < .001
	Diet	42	7.52 ± 0.64	3.64 ± 0.56	3.88 ± 0.63	–51.5%	P < .001
	Social role	42	7.97 ± 0.76	3.40 ± 0.68	4.57 ± 0.67	–57%	P < .001
	Physical role	42	6.50 ± 1.00	2.00 ± 0.63	4.50 ± 0.79	–69%	P < .001
	Total score	42	51.95 ± 4.68	18.43 ± 4.13	33.52 ± 3.86	–64.5%	P < .001
d) Bristol Stool Chart	Optimal	10	4.50 ± 0.37	3.5 ± 0.4	1.0 ± 0.47	–22%	P = .063
(Type 1-7)	Soft (type 5-7)	12	4.75 ± 0.31	3.33 ± 0.23	1.42 ± 0.34	–30%	P < .001
	Hard (type 1-3)	21	3.19 ± 0.20	3.10 ± 0.40	0.095 ± 0.32	–3%	NS
e) Pain	Upper GI pain	12	5.08 ± 0.75	2.25 ± 0.95	1.80 ± 0.79	–35%	P = .065
VAS (1-10)	Lower GI pain	30	4.38 ± 0.49	1.58 ± 0.36	2.80 ± 0.56	–64%	P < .001
	Other pain	31	4.75 ± 0.39	2.81 ± 0.43	1.93 ± 0.63	–41%	P = .004

d) Bristol stool chart: optimal, type 4; types 1-3 are indicative of harder stool; types 5-7 are indicative of softer, watery stool.
e) Pain: Only participants experiencing pain are included in the table. Some participants experienced several types of pain. Some participants did not report any pain.
NS, not significant.

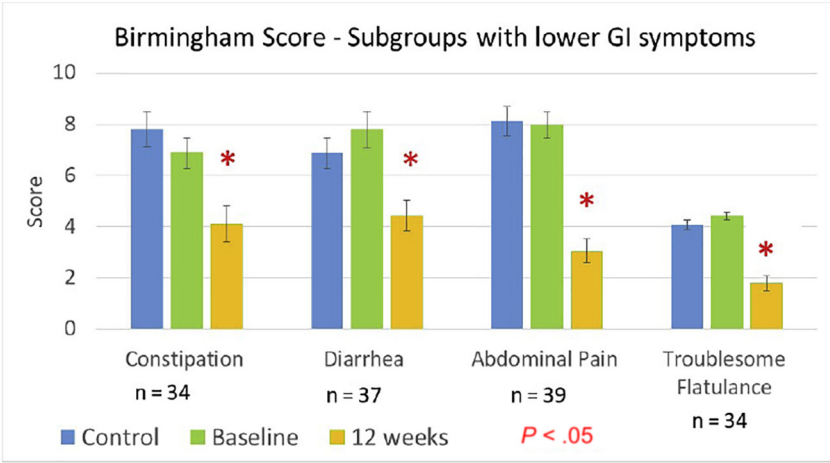

Fig. 4 – Frequency and severity and of lower GI symptoms by Birmingham IBS Symptom Score.Values are means ± SE scores at 3 time points. Higher scores are linked with greater severity and frequency. Highest score is 54. Lower scores are associated with improvement.

had constipation and pain. The NC Gut Relief Formula significantly reduced the frequency and severity by 40%-60% of lower GI symptoms such as constipation (40%), diarrhea (43%), abdominal pain (62%), and troublesome flatulence (58%) in participants with these symptoms at the beginning of the study ($P < .0001$) (Table 3 and Fig. 4).

3.2.2.2. *IBS-QoL [35].* The NC Gut Relief Formula significantly improved lower GI symptoms associated QoL by 50%-82% (mean 64.5%), including emotional and mental health and well-being, sleep (82%), energy, physical functioning, diet, and social interactions ($P < .001$) (Fig. 5).

3.2.2.3. *Bristol Stool Chart.* The NC Gut Relief Formula improved stool consistency toward the ideal type 4, both for participants with severe constipation and for those with watery loose stool. The number of participants with loose/diarrhea-like stools was significantly reduced because of bulking ingredients, such as pectin ($P < .001$) (Table 3 and Fig. 6). In addition, the NC Gut Relief Formula significantly improved stool frequency and regularity toward the ideal 1-2 times per day, from 58% of participants at baseline to 79% at the end of the 12-week intervention. Generally, 10 g/d of the formula was more constipating than 5 g/d.

3.2.3. *Pain and other symptoms*

Participants experiencing pain reported significantly less pain between 35% and 64% (mean 49%) after taking the NC Gut Relief Formula for 12 weeks ($P < .001$). Pain included upper and/or lower GI pain and other pain (Tables 2 and 3). Other GI-related symptoms, such as mouth ulcers, rashes, incontinence, constant fatigue, and nervousness, lessened during the study, with

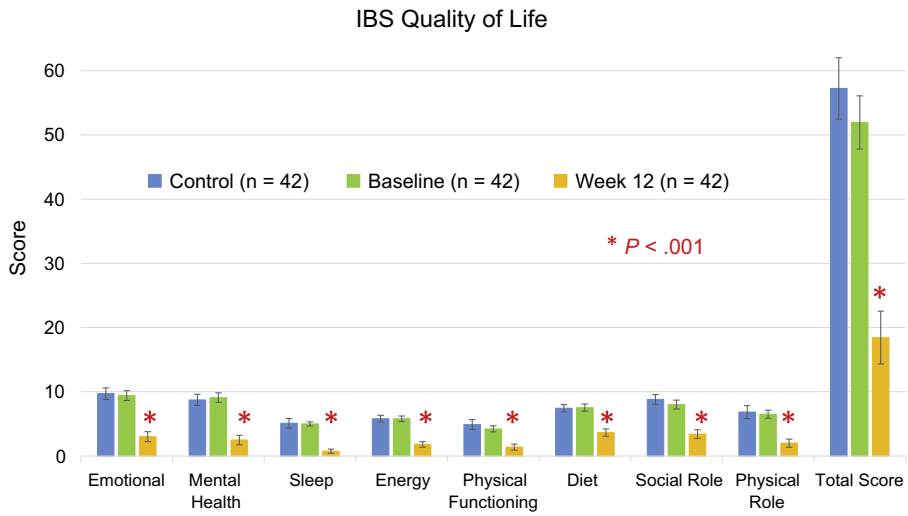

Fig. 5 – QoL associated with lower GI symptoms by IBS-QoL.Values are means ± SE scores at 3 time points. Higher scores are linked with greater impact on QoL. Highest impact score for IBS-QoL is 135. Lower scores are associated with improvement.

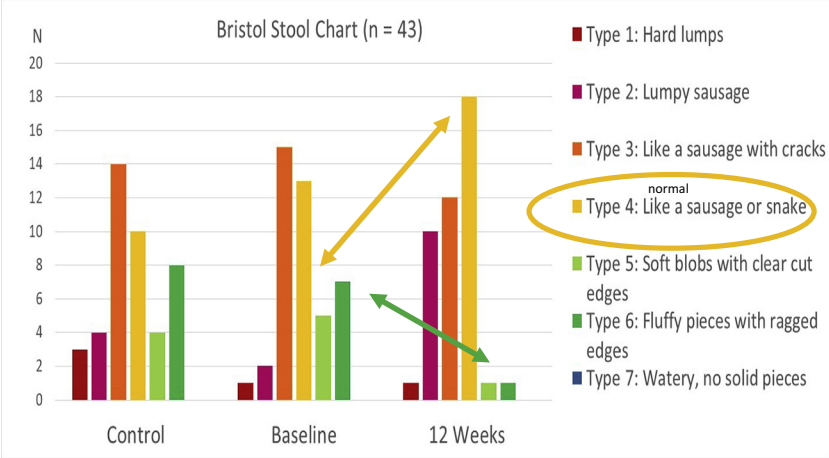

Fig. 6 – Bristol Stool Chart.Number of participants with stool type at 3 time points. Yellow = normal stool type 4, red color tones = harder stool types 1-3/constipation like, green color tones = watery stool types 5-7/diarrhea like. Stool types changed toward the normal type 4 (yellow bar), specifically for participants with loose stool (green bars) at 12 weeks.

fatigue being significantly lowered in 25% of participants, and 50% of participants reporting feeling nervous at the beginning of the study felt significantly less nervous after the 12-week intervention ($P < .05$) (data not shown).

3.3. *Inflammatory markers/cytokines*

Inflammatory markers in all participants were within or close to reference range. A larger sample would be required to study whether the NC Gut Relief Formula reduced or increased inflammation.

3.4. *Intestinal permeability/leaky gut*

All participants (n = 42) had intestinal permeability or leaky gut, evident by lactulose levels above the reference range in all participants, whereas about 80% (n = 35) had intestinal hyperpermeability (high lactulose and mannitol recovery). About half of the participants had an elevated L/M ratio, which suggested increased pore size of the gut mucosa, allowing larger, possibly antigenic molecules to enter the blood. The NC Gut Relief Formula significantly improved intestinal permeability, including lactulose recovery by 59%, mannitol recovery by 27%, and L/M ratio by 50% ($P < .001$).

After 12 weeks of intervention, 15% of participants achieved normal levels of lactulose recovery (χ^2: $P = .026$), and 32% of participants with elevated mannitol levels at the start achieved normal levels, raising the total of participants with normal levels from 18% to 50% (χ^2 test: $P < .05$). Ninety percent of all participants had normal L/M ratios from 53% at baseline (χ^2 test: $P < .001$) (Table 4 and Fig. 7). The dosage of the NC Gut Relief Formula (5 g or 10 g) did not change the outcome appreciably, and individuals on PPIs (n = 11) had a slightly smaller but still significantly positive improvement in intestinal permeability (data not shown).

We also analyzed leaky gut recovery by stool type. The NC Gut Relief Formula significantly improved lactulose recovery for 33% and mannitol recovery for 45% of participants with normal stool, and 14% (lactulose recovery) or 43% (mannitol recovery), respectively of participants with hard stool/constipation type

Table 4 – Intestinal permeability/leaky gut (n = 40) [a]

Measure	Baseline		12 wk		Difference	Change	*P* value
	n (%)	Mean ± SE	n (%)	Mean ± SE	Mean ± SE	%	
Lactulose recovery	40	1.33 ± 0.11	40	0.55 ± 0.05	0.78 ± 0.11	−59%	$P < .001$
Reference range (0%-0.3%)	0		6 (15%)			in 15%	
Above range (>0.3%)	40		34				χ^2 $P = .026$
Mannitol recovery	40	35.4 ± 2.14	40	26.0 ± 1.17	9.43 ± 2.0	−27%	$P < .001$
Reference range (9.5%-25%)	7 (18%)		20 (50%)			in 32%	
Above range (>25%)	33		20				χ^2 $P = .005$
L/M ratio	40	0.04 ± 0.004	40	0.03 ± 0.001	0.02 ± 0.004	−50%	$P < .0001$
Reference range (0-0.035)	21 (53%)		36 (90%)			in 36%	
Above range (>0.035)	19		4				χ^2 $P = .0009$

[a] n = 40, excluding n = 2 with 0-g/d dose of Gut Relief Formula for 2 months (weeks 4-12).

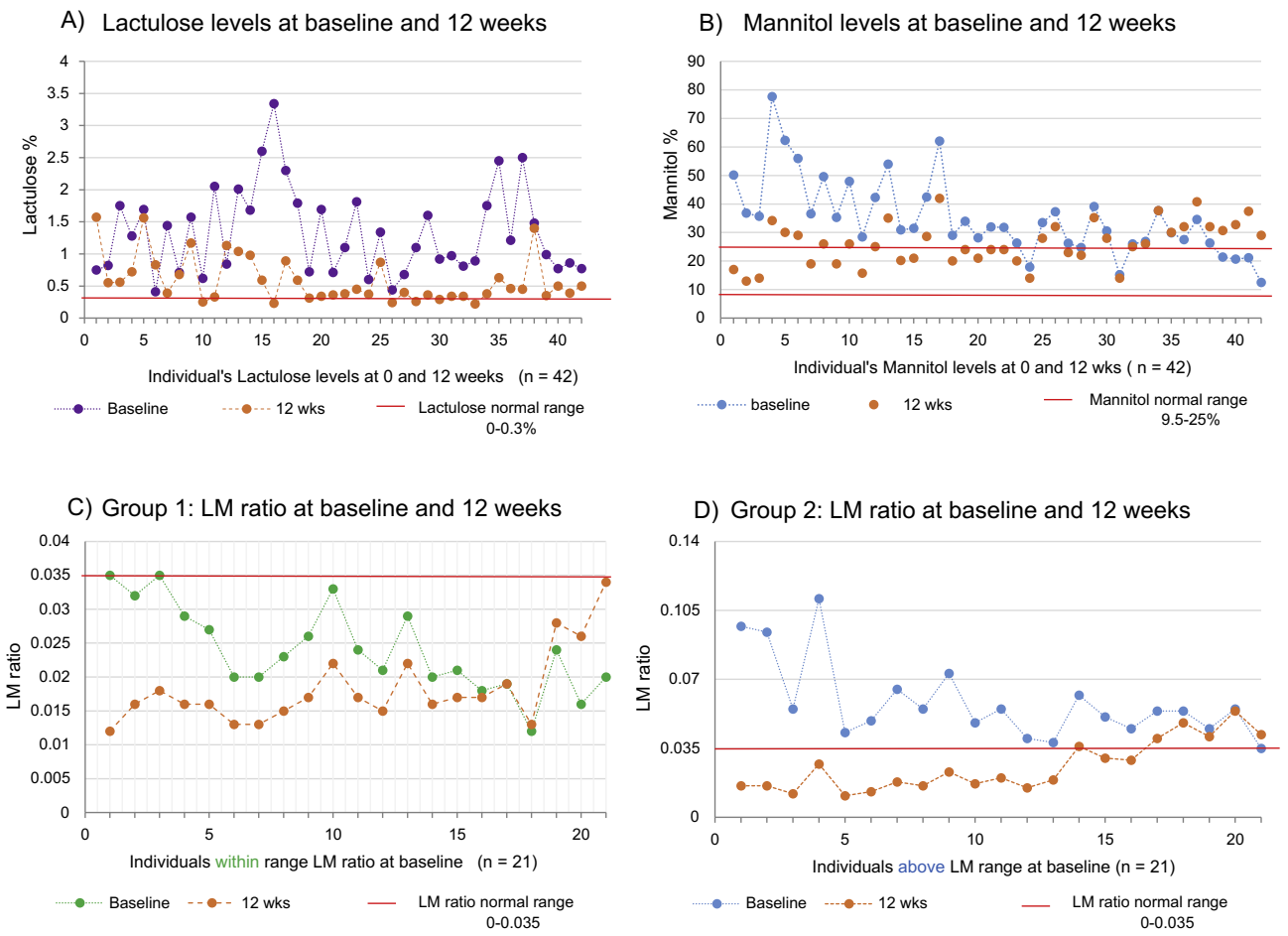

Fig. 7 – Intestinal permeability/leaky gut.Scatterplot of individual levels at baseline and at 12 weeks. (A) Lactulose levels, (B) Mannitol levels, (C and D) L/M ratio at baseline and 12 weeks by group, (C) group 1 = L/M ratio of individuals with L/M ratio within normal level at baseline, and (D) group 2 = L/M ratio above normal level at baseline.

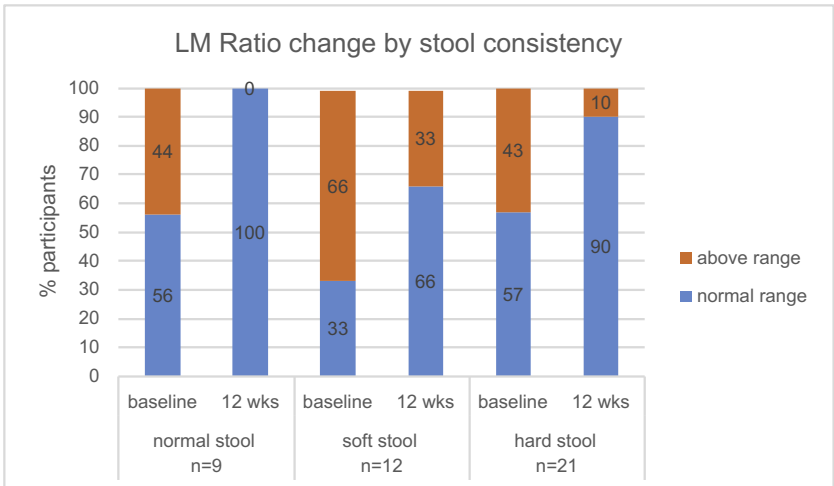

Fig. 8 – L/M ratio change by stool consistency.Percentage of participants within reference range (L/M ratio = 0-0.035, blue bar) and above the normal LM ratio range (>0.035, orange bar) at baseline and 12 weeks by stool consistency.

($P = .0001$), whereas there were no changes in the group with soft/diarrhea-type stool. A third of participants (33%) with soft stool had mannitol recovery values within the reference range at baseline and at 12 weeks. The NC Gut Relief Formula significantly improved L/M ratio for 44% of participants with normal stool, 33% of participants with soft/diarrhea-stool type, and 33% of participants with hard /constipation-type stool (all groups: $P = .0001$).

All participants (100%) with normal stool, 90% with hard stool, and 66% with soft stool had normal L/M ratio levels, indicating a recovery from leaky gut, after taking the NC Gut Relief Formula for 3 months (Fig. 8).

3.5. *Stool microbial profile*

Mean bacterial mass of commensal nonpathogenic good bacteria increased over time in all participants; specifically, the greatest increases were seen in lactobacilli by 29%, *Faecalibacterium prausnitzii* by 27%, and *Clostridia* species by 36%. Lactobacilli are known probiotics bacteria, *F prausnitzii* thrive on fiber such as pectin present in the NC Gut Relief Formula, and there are more than 100 nonpathogenic commensal *Clostridia* species in the human intestinal tract beneficial for immune function **(**Fig. 9A**).**

3.5.1. *Probiotics*

Mean bacterial mass of bifidobacteria decreased over time. Bifidobacteria and lactobacilli are standard probiotics. In this study, we asked participants to stop their probiotic intake before commencing the study at beginning of the control phase. Whereas the relative abundance of lactobacilli species increased in all participants (n = 37), the relative increase in bacterial mass was markedly higher in the group on probiotics before the study (n = 19) than the group not having taken any probiotic supplements (n = 18) (data not shown).

3.5.2. *Dosage*

Three quarters (77%, n = 20/26) of the participants with upper and lower symptoms chose to take 10 g of the NC Gut Relief Formula. A third (36%, n = 4/11) of the participants with only lower symptoms chose to take 10 g of the NC Gut Relief Formula, half (45%) chose 5 g, and n = 2 (20%) chose 0 g. This preference indicated that a larger dose of 10 g/d may be more beneficial for upper symptoms, whereas 5 g of the NC Gut Relief Formula may be sufficient to benefit lower symptoms.

The main microbial changes observed in the 5-g/d subgroup (n = 13) were an increase in *Clostridium* species, *F prausnitzii, Bacteroides vulgatus, Lactobacillus* species, and *Fusobacterium species*. The main changes in the 10-g/d subgroup (n = 28) were observed in *Clostridium* species and *F prausnitzii*, although to a lesser extent than in the 5-g subgroup, and in *Roseburia* species, not observed in the 5-g/d subgroup (data not shown).

In summary, less NC Gut Relief Formula (5 g/d) per day seems to result in more growth in a larger variety of bacterial species.

3.5.3. *Stool consistency*

Whereas the NC Gut Relief Formula generally improved microbial profile by increasing relative abundance/bacterial number in participants with normal or hard stool consistency, bacterial number decreased over time in those participants experiencing soft/diarrhea-type stool. We speculate that in the group with soft stool, because of the shorter transit time of food and NC Gut Relief Formula, bacteria have less time to feed and grow.

In addition to stool consistency, we analyzed microbial profile also by PPI use. Use of PPI appears to influence bacterial growth. Whereas the NC Gut Relief Formula generally improved microbial profile by increasing relative abundance/bacterial number in participants not taking PPIs (group no PPI, n = 29), bacterial number decreased over time in the group on PPI (n = 8) (Fig. 9B and C).

3.6. *Tolerability, dose, and food triggers*

Generally, the NC Gut Relief Formula was well tolerated. The formula seems to improve upper GI symptoms more quickly (after 2 months) than lower GI symptoms (after 3 months). The higher dose of 10 g/d of the formula was generally more constipating than 5 g/d, which was useful for participants suffering with loose stools but was regarded as contraindicative for participants with constipation/hard stools.

A large number of participants had to avoid certain trigger foods at the start of the study; however, participants were able to reintroduce trigger foods at the end of the study without provoking symptoms. Half of the participants (50%) with gluten and carbohydrate intolerance at start of the trial were able to reintroduce carbohydrate-rich foods, for example, white bread, into their diet. Half of those participants with fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) foods intolerance, such as garlic, onion, or beans; 40% of those with dairy intolerance; and 40% of those with intolerances to acidic or spicy foods, such as oranges, tomato, pineapple, and coffee, were able to consume food triggers and remained symptom-free.

Importantly, 40% of participants with upper symptoms requiring medication, such as PPIs and antacids (n = 5/11), were able to reduce or eliminate their medication at the end of the Gut Relief Study. A small number of participants with lower GI symptoms relying regularly on laxatives (2/10) were no longer requiring these at the end of the study.

4. Discussion

In summary, the NC Gut Relief Formula containing herbal ingredients with anti-inflammatory, analgesic, and prebiotic properties significantly improved upper and lower GI symptoms by 40%-60%. In our cohort of adults with severe reflux and/or IBS-like GI disturbances, symptoms included indigestion, heartburn, nausea, constipation or diarrhea, abdominal pain, troublesome flatulence, as well as fatigue and anxiety. With the improvements of symptom reduction, participants' QoL, physical functioning, mood, energy, and sleep improved significantly by 60%-80%. In addition, the pronounced intestinal permeability at the start of the study present in all participants improved for all and shifted significantly toward normal lactulose and mannitol levels. This indicated a healing gut mucosa in more than half of the

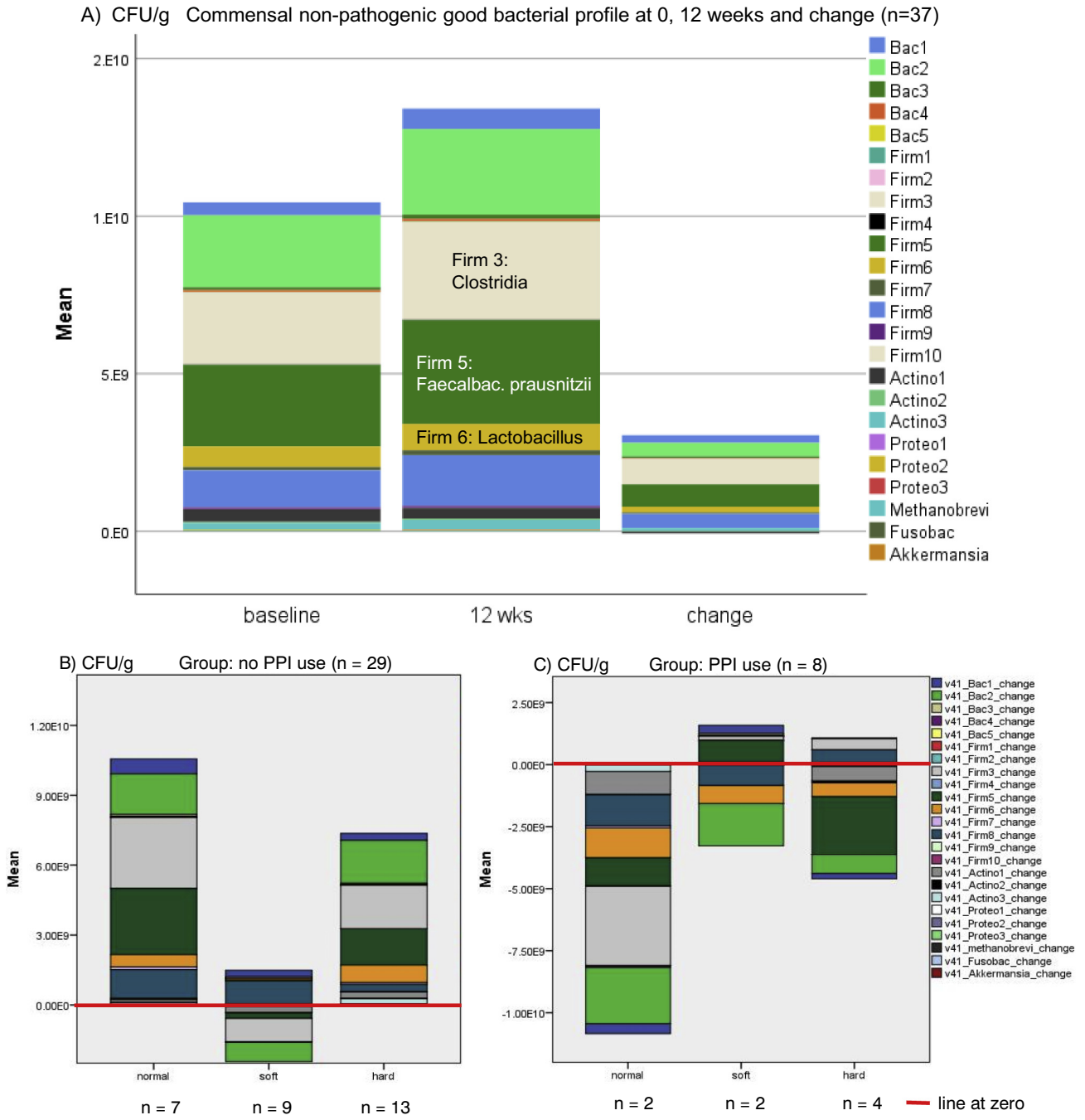

Fig. 9 – Microbial gut profile.CFU/g = colony-forming units per gram stool of (A) all participants at baseline, 12 weeks, and change after intervention; (B/C) microbial change by stool consistency and PPI medication use (no/yes). Bac, *Bacteroidetes*; Bac 1, *Bacteroidetes-Prevotella* group; Bac 2, *Bacteroides vulgatus*; Bac 3, *Barnesiella* spp; Bac 4, *Odoribacter* spp; Bac 5, *Prevotella* spp; Firm, *Firmicutes*; Firm 1, *Anaerotruncus colihominis*; Firm 2, *Butyrivibrio crossotus*; Firm 3, *Clostridium* spp; Firm 4, *Coprococcus eutactus*; Firm 5, *F prausnitzii*; Firm 6, *Lactobacillus* spp; Firm 7, *Pseudoflavonifractor* spp; Firm 8, *Roseburia* spp; Firm 9, *Ruminococcus* spp; Firm 10, *Veillonella* spp; Actino, *Actinobacteria*; Actino 1, *Bifidobacterium* spp; Actino 2, *B longum*; Actino 3, *Collinsella aerofaciens*; Proteo, *Proteobacteria*; Proteo 1, *Desulfovibrio piger*; Proteo 2, *Escherichia coli*; Proteo 3, *Oxalobacter formigenes*; Methanobrevi, *Methanobrevibacter smithii*; Fusobac, *Fusobacteriim* spp; Akkermansia, *Akkermansia muciniphila*; v41, change at 12 weeks compared to baseline.

participants (59%) by the end of the study. All participants with normal stool, 90% of those with hard stool, and 66% of those with soft stool recovered from intestinal permeability, evident by normal L/M ratios. Moreover, almost half of the participants with upper symptoms, including severe reflux and heartburn, had stopped their regular intake of PPIs by the end of the study. Coming off medication such as PPI reduces the risk of adverse effects and long-term complications [6,7].

The healing of the leaky gut provided participants a conduit to reintroduce former food triggers, specifically FODMAPs, acidic or spicy foods, dairy, or carbohydrate-rich food items. Half of the participants (50%) with FODMAP food-related GI problems were able to return to consuming FODMAP foods, such as garlic, onion, and beans, without triggering debilitating symptoms at the end of the study. Similarly, half (50%) of the participants saw improvements with carbohydrate-rich foods, 40% had improvements with dairy products, and 40% with primarily upper GI symptoms could consume acidic and spicy foods including citrus and tomato and remained symptom-free at the end of the study. Furthermore, our study provides evidence for the NC Gut Relief Formula to improve the gut microbiome by increasing the bacterial mass and diversity. In particular, we observed a marked increase in commensal *Clostridia* bacteria, consisting of more than 100 different nonpathogenic species, which are essential for improving immunity and protecting against allergies by activating innate immune genes in the intestinal epithelial cells [41]. *Lactobacillus* species were also markedly increased, specifically in participants who had regularly taken probiotics before the study, indicating that the prebiotics in the formula helped with the bacterial growth in the gut [42]. A third group of bacteria, which had markedly increased in our study population, was *F prausnitzii*, a species which particularly thrives on fiber such as pectin contained in the NC Gut Relief Formula [43].

The increased fiber intake in the form of nonfermentable, gel-forming pectin also provided a plausible mechanism for the improved stool consistency toward the normal type [43-45], assessed by the Bristol Stool Chart, in all participants and especially in the group with diarrhea-like loose stool consistencies. Generally, a higher daily dosage of 10 g/d compared to 5 g/d was preferred in this group, whereas those with constipation-prevalent IBS symptoms naturally preferred the lower dosing.

Our findings are consistent with the literature, whereby herbs and nutrients in the NC Gut Relief Formula, including curcumin, *Aloe vera*, slippery elm, guar gum, pectin, peppermint oil, and glutamine, have shown beneficial effects for the GI tract when taken individually [12,14,18-24,26,27,46]. Our study is the first to investigate the combination of these herbs and nutrients on the GI system.

The healing of the GI mucus membrane system and enrichment of the microbiome has been associated with several beneficial effects for the whole body, including immune function, brain function, mood, energy, and sleep [47,48]. A functional GI system will contribute to the absorption of essential nutrients, elimination of toxins, functioning of an active immune system, protection from pathogens, and production of essential neurochemicals and metabolites, such as serotonin, endorphins, and antimicrobials. There are many links between the enteric bacteria and the neural, endocrine, immune, and humoral systems [47,48]. Imbalances of the microbiome—or dysbiosis—have been linked to inflammatory GI disorders, depression, anxiety, and other neuropsychiatric conditions [47,48].

Previous studies primarily relied on validated questionnaires, including the Leeds Dyspepsia Questionnaire, GERD-Symptom-Q, GERD-QoL, and GERD-HQoL, to assess the severity and frequency of upper symptoms, including reflux, heartburn, nausea, indigestion, and their influence on daily activities, psychological well-being/mood, and diet. Additionally, questionnaires for the assessment of the severity and frequency of lower symptoms, including abdominal pain, bloating, diarrhea, and constipation, and their influence on the QoL included the IBS-Symptom-Q, IBS-QoL, and Bristol Stool Chart.

A small number of studies investigated the effect of specific nutrients or herbs on leaky gut or the gut microbiome. Administration of glutamine in burn injury patients resulted in significantly reduced intestinal permeability measured by the L/M test and in accelerated wound healing [49]. One study found guar gum to increase the growth of *Lactobacillus* and *Bifidus* species [25], and another study in autistic children with constipation and gut dysbiosis found guar gum to improve the intestinal microbiota profile [50]. Pectin delayed the loss of microbial diversity in ulcerative colitis patients after a fecal transplant [45].

In addition to the high compliance and completion rate, a strength of our study was that our findings by questionnaires were supported by the objective measures of the intestinal permeability test and the microbial stool test. We acknowledge the limitation of not incorporating a control group in the study. However, we believe that the single-arm pre-post design with a control run-in phase was more suited to the nature of the intervention. Firstly, it would not have been possible to design a placebo formula with the same texture, smell, and color of the herbal powder, therefore limiting the possibility of blinding. Secondly, differences between individuals were likely to be greater than within individuals in the microbial makeup and severity of leaky gut, therefore favoring the pre-post repeated-measures design, with individuals serving as their own control. A limitation of the study was the lack of 6 participants' stool samples. The small sample sizes in the subgroups (eg, PPI by stool consistency) limited generalizability of the findings. However, the subgroup studies provide new data for further hypothesis-driven research. Our study is the first to assess the synergistic effectiveness of the formula's ingredients. Further investigations on the effectiveness of the formula's individual components, such as the fiber pectin by way of a parallel controlled trial design are warranted.

In conclusion, we accept our hypothesis that the tested herbal formula was tolerable and effective in improving GI symptoms and gut health in adults with digestive disorders. The NC Gut Relief Formula containing curcumin, *Aloe vera*, slippery elm, guar gum, pectin, peppermint oil, and glutamine with anti-inflammatory, analgesic, and prebiotic properties significantly improved upper and lower GI symptoms in the study group over 3 months, manifesting in significant reductions in reflux, heartburn, abdominal pain, bloating, constipation, or diarrhea, dominant IBS symptoms. Improvement of GI symptoms in turn significantly improved the QoL, physical functioning, energy, mood, and sleep of study participants by 60%-80%.

Furthermore, the NC Gut Relief Formula significantly reduced intestinal permeability, enhanced the microbial profile, and reduced the need for reflux medication in 40% of participants who regularly took PPIs before the study. The healing of the mucus membrane in the gut enabled 40%-50% of participants to reintroduce potential food triggers such as FODMAPs, dairy, carbohydrate-rich foods, and/or acidic or spicy foods without relapse of GI symptoms.

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