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Efficacy of a prebiotic formulation for treatment of functional constipation and associated gastrointestinal symptoms in adults: A randomised controlled trial

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ABSTRACT

Objectives: Functional constipation is the result of a complex interplay between the gastrointestinal tract, the gut microbiome, the nervous system, along with diet and lifestyle factors. This study aimed to evaluate the efficacy of a prebiotic formulation containing plant-based extracts rich in dietary fibre and polyphenols in the management of functional constipation and associated gastrointestinal symptoms.
Design: This 3-week randomised controlled study assessed the effect of a prebiotic formulation (6 g powder taken in water twice daily), by comparison with a capsule designed to have minimal effect on gastrointestinal function, on indicators of bowel health in healthy adults with low fibre intake and meeting the Rome IV criteria for functional constipation.
Methods: Participants were informed that they may receive one of two products, either a powder or a capsule, both of which contained prebiotics. The primary outcome was change in frequency of complete spontaneous bowel movements. Secondary outcomes assessed were gastrointestinal symptoms, quality of life and mood using the PAC-SYM, PAC-QoL, and DASS-21. Safety and tolerability were also assessed.
Results: There was a significant improvement in bowel movements ($p < 0.001$) and improved stool consistency ($p < 0.01$) in participants taking the prebiotic powder formulation compared to those taking the capsule. Accompanying this was a significant reduction in overall gastrointestinal symptoms ($p < 0.001$) including abdominal ($p < 0.001$), rectal ($p = 0.004$) and stool ($p = 0.002$) symptoms, and a significant improvement in quality of life (p 0.001). There was a significant reduction in mean score for depression, anxiety, and stress for participants in both groups, which indicated a significant improvement in mood during the study that was unrelated to bowel function.
Conclusions: The results showed that the prebiotic powder formulation taken twice per day for 21 days was effective in reducing clinical symptoms of functional constipation in individuals reporting a low fibre intake.

1. Background

Constipation, the infrequent and difficult passage of stools, is often accompanied by abdominal symptoms such as bloating, discomfort and pain, and has a negative effect on quality of life. It is often considered a symptom of poor gastrointestinal health. The clinical evaluation of the potential underlying causes of constipation includes assessment for mechanical and motility disorders, metabolic/endocrine and neurological disorders, myopathic disorders, psychological disorders, and medications. The exclusion of a known primary medical condition results in a diagnosis of functional constipation [1,2]. The Rome IV diagnostic criteria for functional constipation requires that two or more of the following are experienced: straining; lumpy or hard stools; sensation of incomplete evacuation; sensation of anorectal obstruction/blockage; requiring manual manoeuvres to facilitate defecations, and fewer than 3 motions per week for at least the last 3 months [1].

Functional constipation is likely to be influenced by various combinations of lifestyle factors (diet, obesity, exercise, water intake);

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psychological factors (anxiety, stress, trauma, childhood conditioning); and more recently, there is emerging evidence for the possible involvement of an altered gut microbiota [3]. A primary recommendation for the management of functional constipation is to increase the intake of dietary fibre [4]. The mechanism of action of dietary fibre is known to be functional in nature, promoting bulking of the stool and water retention and improving stool transit time [5]. There are additional benefits of specific plant-based dietary fibres including supporting metabolic health, antioxidant and anti-inflammatory effects and modulation of the gut microbiota [6]. There are a number of specific dietary fibres that have clinical evidence for improving functional bowel health, including psyllium [7–9], inulin [10,11], arabinogalactan [12], partially hydrolysed guar gum (PHGG) [13], and acacia gum [14]. Slippery elm (*Ulmus rubra*) and pectin oligosaccharides have been used in traditional medicines for supporting gastrointestinal health although not specifically indicated for constipation [15].

Vegetables and fruits are particularly rich in polyphenols (phenolic compounds), which have a broad range of beneficial actions including anti-inflammatory, antimicrobial and antioxidant activities [16]. Reviews of preclinical and clinical data of the effect of polyphenols on the gut microbiota attest to their prebiotic status, wherein increased dietary intake is associated with better health outcomes [17,18]. Lack of these dietary components is linked to poor gastrointestinal health and contributes to functional constipation and associated gastrointestinal symptoms [19]. *Theobroma cacao*, commonly known as cacao or the processed form cocoa, is particularly interesting in the context of bowel health as it is both a rich source of fibre (26–40 %) [20] and flavonoids, including but not limited to (−)-epicatechin, (+)-catechin and quercetin [21,22]. Research has identified that cocoa and cocoa-derived flavanols modify the inflammatory process [23] and since they are poorly absorbed in the intestine, may have a local anti-inflammatory effect within the gastrointestinal tract [24]. *Hylocereus polyrhizus*, commonly known as dragon fruit, has long been recognised as containing phenols, sterols, and flavonoids [25–28]. More recently, nutritional analysis confirmed dragon fruit's high nutritional value including dietary fibre (5 g/100 g) and total phenolics (55 mg/100 g), as well as being rich in essential minerals and vitamins [29]. Extracts of *T. cacao* and *H. polyrhizus* were combined with PHGG, acacia gum, pectin and *U. rubra* as sources of dietary fibre to create a formulation designed specifically for the treatment of functional constipation. Therefore, it was hypothesised that the formulation would increase bowel motions in individuals afflicted by functional constipation and alleviate associated gastrointestinal symptoms.

2. Methods

2.1. Trial design

This study was a 3-week, parallel-arm, controlled, randomized clinical trial evaluating the effects of a high dose prebiotic powder blend on functional constipation and associated symptoms. It was conducted at a single site in Brisbane, Australia between November 2020 and February 2021. The trial design was approved by the Ethics Committees of the National Institute of Integrative Medicine, Melbourne Australia (0075E 2020) and ratified by the University of Queensland, Brisbane, Australia (2020/HE002481). The trial was registered with the Australia New Zealand Clinical Trials Registry (ACTRN12620001247965).

The intervention was a prebiotic powder formulation supplied by Integria Healthcare Australia Pty Ltd containing (in a single 6 g serving): 3 g partially hydrolysed guar gum from the seed of *Cyamopsis tetragonolobus* (Sunfiber AG, Taiyo Kagaku, India), 1 g acacia gum from dried stem and branch exudates of *Acacia senegal* (Fibregum B, Nexira, France), 500 mg pectin as pH-modified citrus peel fibre (Standard HB-R 900, Herbstreit & Fox, Germany), 500 mg slippery elm bark (*Ulmus rubra*) (BI Nutraceuticals, USA), 500 mg red dragon fruit powder (*Hylocereus polyrhizus*) from methanol extract of the whole fruit (Shaanxi Jiahe Phytochemicals, China), and 500 mg organic cacao powder from *Theobroma cacao* seeds (Arrow Foods, USA). All components had a certificate of analysis. The powder was to be taken twice daily, by mixing the 6 g powder into 250 mL water.

A placebo that would match the prebiotic powder in form without affecting gastrointestinal function was judged as not possible to achieve. Maltodextrin, a soluble and digestible oligosaccharide, is generally used as placebo but in some studies it has been observed to improve bowel function (e.g. 13 g/day [30], 15 g/day [31]. Instead, a control was designed that would have minimal gastrointestinal effect: a 500 mg capsule containing maltodextrin (495 mg) and acacia gum (5 mg) taken once daily with 250 mL of water.

2.2. Inclusion and exclusion criteria

The study enrolled participants who were aged between 25 and 45 years, self-reporting functional constipation and meeting the Rome IV criteria for functional constipation which includes two or more of the following for the last three months: straining during more than 25 % of defecations; lumpy or hard stools (Bristol Stool Form Scale 1–2) in more than 25 % of defecations; sensation of incomplete evacuation for more than 25 % of defecations; sensation of anorectal obstruction/blockage for more than 25 % of defecations; manual manoeuvres to facilitate more than 25 % of defecations (e.g., digital evacuation, support of the pelvic floor); fewer than three complete spontaneous bowel motions (CSBM) per week; loose stools rarely present without the use of laxatives; insufficient criteria for irritable bowel syndrome. All participants self-reported they consumed on average less than 4 serves of vegetables, fruit and wholegrains combined per day. Individuals were not enrolled in the study if they did not meet the inclusion criteria; had a history of gastrointestinal disease, inflammatory bowel disease, or other functional gastrointestinal disorders including irritable bowel syndrome and gastroesophageal reflux disease; previous gastrointestinal surgery (intestinal resection, gastric bypass, colorectal surgery); or were experiencing dysphagia. They were also excluded if they had a potential secondary cause of constipation; systemic lupus erythematosus, cancer, thyroid disease, hepatic disease, or uncontrolled metabolic disease; or if they were taking medications affecting bowel function including antibiotics, antacids, proton pump inhibitors, stool softeners, laxatives, or fibre supplements at the time of recruitment or within the previous four weeks. Women who were pregnant or breastfeeding and those with a known allergy to any of the ingredients in the trial products were also excluded.

2.3. Trial randomisation and procedures

Trial participants were recruited from the public through social media advertising. Eligible participants attended the clinic for the baseline interview, where they provided written informed consent and were enrolled into the trial. Participants were informed that they may receive one of two products, either a powder or a capsule, both of which contained prebiotics. Participants were allocated randomly to the two arms of the study, in a 1:1 ratio, and provided with enough of the powder or capsules for the 3-week study along with instructions, food diary and blood test paperwork.

Participants attended the clinic at the beginning and end of the three-week treatment period. Prior to both visits participants completed a 3-day food diary and undertook a blood test. At these visits, medical history, blood pressure, weight, medication, and supplement use were recorded. Standardised validated questionnaires (PAC-SYM, PAC-QoL and DASS-21) [32–34] were administered to evaluate the degree of symptoms participants experienced and the effect on quality of life and depression, anxiety, and stress.

Participants were assessed remotely via telephone on days 7, 14 and 21 by a nutritionist unaware of treatment allocation. The assessment involved recording the participants self-reported frequency of complete

spontaneous bowel movements (CSBM) and stool consistency over the previous 7 days, as well as dosage adherence, and any adverse effects that occurred. Participants were considered compliant if they consumed 85 % or more of their allocated trial treatment.

2.4. Outcome measures

The primary outcome was change in number of CSBM per week over 21 days of treatment. Secondary outcomes were stool consistency and patient symptoms, quality of life, and mood. Stool consistency was assessed at baseline and on days 7, 14 and 21 using the visual tool, the Bristol Stool Chart, which ranks stool consistency on a scale ranging from 1 = very hard small pebbles, to 7 = entirely liquid [35]. Patient symptoms, quality of life, and mood were assessed at the beginning and end of the three-week treatment period. The Patient Assessment of Constipation – Symptoms (PAC-SYM) is a 12-item questionnaire that includes three symptom subscales: abdominal (four items); rectal (three items); and stool (five items). Items are scored on a 5–point scale, with scores ranging from 0 (symptom absent) to 4 (very severe) [32]. The Patient Assessment of Constipation – Quality of Life (PAC-QoL) questionnaire consists of 28 questions evaluating the impact of symptoms with responses from 0 (symptom absent) to 4 (very severe). It also includes four subscales; physical discomfort (4 items), psychosocial discomfort (8 items), worries and concerns (11 items), and treatment satisfaction (5 items) [33]. Mood was assessed using the Depression Anxiety and Stress Scale (DASS-21), which is a 21-item quantitative measure of distress in terms of depression, anxiety, and stress, with 7 questions in each category. A 4-point severity scale was used to rate each state during the past week, from 0 'did not apply to me at all' to 3 'applied to me all the time'. The answers were summed to provide individual scores for depression, stress, and anxiety that each have a range of 0–21, and these values were doubled for interpretation using the DASS-42 clinical severity ratings according to instructions in the DASS manual [34].

To aid interpretation of the findings, diet was assessed by a self-reported 3-day food diary prior to baseline and during days 18–21 for comparative diet analysis. The participants were asked to complete a chart with the headings: breakfast, mid-morning snacks/drinks, lunch, afternoon snacks/drinks, dinner, and supper as well as any additional fluids (drinks, water, alcohol etc). The diet diaries were assessed by the research team, and where needed, additional clarification sought (and noted in the diary). For uniformity, a nutritionist reviewed and entered data using FoodWorks 10 software for all the diaries [36].

The safety and tolerability of the study interventions were evaluated by assessing full blood counts and metabolic profile results at baseline and day 21, and self-reported adverse effect data collected at clinic interviews.

2.5. Statistics

Sample size was based on change in CSBM with the following assumptions: CSBM/week at baseline = mean of 2.5. An increase of 1 CSBM/week would be a change to 3.5 of the mean which constitutes the clinically important difference (SD = 0.6; 80 % power and 0.05 alpha). Response to the capsule was estimated to be an increase by 0.53 CSBM/week, with a clinically worthwhile difference estimated to be 0.47. Therefore, the sample size calculation was deemed to be 26 people per group. Allowing for 10 % dropout, 61 participants were enrolled.

Data was analysed with SPSS 26 (IBM, USA) software. Demographic parameters (age, weight, height, BMI, blood pressure) were analysed with unpaired t-tests. Differences between prebiotic powder and capsule groups in terms of CSBM/week was evaluated at four independent timepoints (baseline, day 7, 14, 21) using a repeat-measures ANOVA and t-tests. The Mann-Whitney U test was used to compare mean ranks of non-normally distributed change in CSBM/week between baseline and day 21 for the prebiotic powder and capsule groups. For all questionnaire assessments (PAC-SYM, PAC-QoL, DASS-21), change in group means from baseline to study completion were compared with paired t-tests. Safety data was analysed using unpaired t-tests. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1. Study group characteristics

There were 61 participants enrolled in the study; 31 participants allocated to take the prebiotic powder (male n = 3; female n = 28) and 30 participants to take the capsule (male n = 9; female n = 21). Participant age ranged from 25 to 45 years, with an average of 36 years for those taking the prebiotic powder and 38 years for the group taking the capsule. There were more female participants (n = 49) than male (n = 12) in the study, which is reflective of females being 85 % more likely to have constipation [37].

There were 3 incomplete data sets, all of whom were female participants taking the prebiotic powder. One participant withdrew due to adverse side effects, namely, increased bloating and flatulence, and the other two were lost to follow-up due to personal circumstances unrelated to the trial. Consequently, 58 participants completed the study (n = 46 female, n = 12 male) (Fig. S1).

3.2. Effect of the treatment on functional constipation

At screening, the participants self-reported passing no more than 3 stools per week on average over the past 3 months. In the week prior to commencing the treatment, 81 % experienced 3 or fewer CSBM. There were 11 participants (19 %) who passed 4 motions in the week prior to baseline (Fig. 1A). For participants allocated to the prebiotic powder group, the number of CSBM gradually increased each week through the trial (Fig. 1), with the average increasing from 2.8 at baseline to 4.9 CSBM/week at the end of the trial (Table 1). The group taking the capsule was similar at baseline with the average of 2.9 CSBM/week but this group reported little change over the study. The difference in mean CSBM/week was statistically significant even by the first week (Table 1).

Within those taking the prebiotic powder, 93 % (n = 26) of participants were classed as responders to treatment in that they reported an increase by at least 1 CSBM/week. There was wide variation in response to the treatment, with the median response being an increase of 1 CSBM/week (32 %), but some participants reporting an increase of up to 4 or 5 CSBM/week (Fig. 2). There were only two participants (7 %) who were considered non-responders to the treatment, defined as having had no increase in CSBM/week. For those taking the capsule, most participants (55 %) reported no change at end of treatment, with the remainder split between an increase by 1 CSBM/week (24 %) and decrease by 1 CSBM/week (21 %) (Fig. 2). The Mann-Whitney U test indicated a significant difference in change between groups ($p < 0.001$; mean rank powder = 42.27, capsule = 17.58).

3.3. Effect of the treatment on stool consistency

Participants self-assessed stool consistency using the Bristol Stool chart, reporting the numerical code as an integer from 1 to 7 for each CSBM. For each of the treatment weeks the sum of these numerical codes was divided by the sum of the number of CSBM. At baseline, both groups reported a similar average stool consistency of 2.8 and 2.7 respectively ($p = 0.847$), although the individual results varied considerably in both groups, from Type 1 to Type 6. There was a gradual shift in consistency towards a softer stool (3.3) in the group taking the prebiotic powder over the treatment period while the group taking the capsule remained unchanged (2.5) resulting in a significant difference in stool composition between groups ($p = 0.001$) for days 15–21.

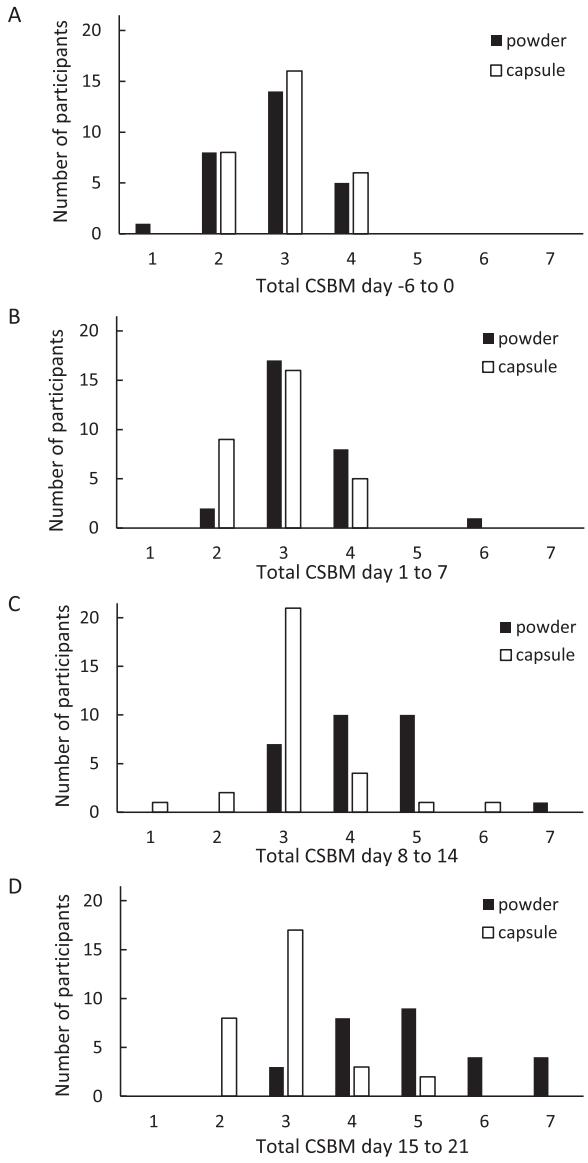

Fig. 1. Number of complete spontaneous bowel motions (CSBM) per week for participants who were randomized to the prebiotic powder formulation (n = 28) or capsule (n = 30) treatment. Number of CSBM were counted during the week prior to the intervention commencing (A), and then day 1–7 (B), day 8–14 (C), and day 15–21 (D) after commencing treatment.

Table 1
The mean and range in number of complete spontaneous bowel movements (CSBM) per week for participants who were randomized to take 6 g prebiotic powder twice daily or a capsule once a day for 21 days. Number of CSBM were counted during the week prior to the intervention commencing, and then day 1–7, day 8–14, and day 15–21 after commencing treatment. The mean and range are shown, with the probability (p) of the means being different according to paired t-tests.

Time	Prebiotic powder (n = 28)		Capsule (n = 30)		p
	mean	range	mean	range	
day −6 to 0	2.8	1–4	2.9	2–4	0.563
day 1 to 7	3.3	2–6	2.9	2–4	0.021
day 8 to 14	4.2	3–7	3.2	1–6	<0.001
day 15 to 21	4.9	3–7	3.0	2–5	<0.001

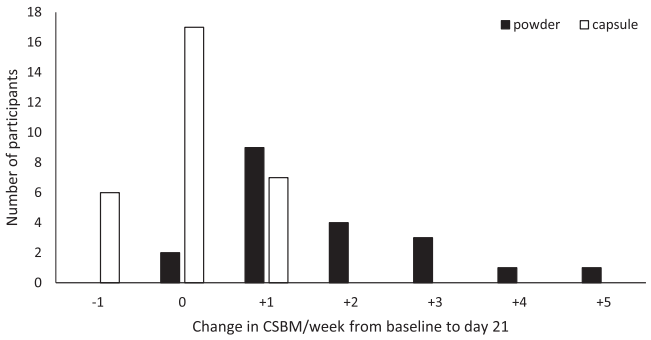

Fig. 2. Change in number of complete spontaneous bowel motions (CSBM) per week for participants who were randomized to the prebiotic powder formulation (n = 28) or capsule (n = 30) treatment. The number of CSBM counted during the week prior to the intervention commencing were subtracted from the number of CSBM counted during the third week (day 15–21) after commencing treatment.

3.4. Effect of the treatment on constipation-related symptoms (PAC-SYM)

There was no difference in the total PAC-SYM score between groups at baseline (p = 0.977) (Table 2). At day 21, there was a significant improvement in total symptom scores for the group taking the prebiotic powder formulation (reduced from 16.6 to 5.7), compared those taking the capsule (reduced from 18.7 to 14.2) (p < 0.001). This constitutes a change from severe/moderate to mild symptoms for the participants taking the prebiotic powder.

Abdominal symptoms were commonly reported at baseline in both groups. The prevalence of abdominal symptoms in the prebiotic powder and capsule groups were as follows: bloating (96 %; 97 % respectively) and discomfort (96 %, 90 % respectively), pain in the abdomen (75 %, 74 % respectively) and stomach cramps (79 %, 67 % respectively). All four abdominal symptoms and the overall abdominal symptom sub-score were significantly lower for the participants who took the prebiotic powder than those who took the capsule for 21 days (Table 2).

Rectal symptoms were less frequently reported than abdominal symptoms and mean scores were low (Table 2), but even so there was a significantly lower value observed in this sub-score after 3 weeks taking the prebiotic powder than the capsule (p = 0.004). This was primarily associated with the lower score given by those taking the prebiotic powder regarding painful bowel movements (p = 0.004). Other individual rectal symptoms did not show a statistically significant difference between groups, however there was a 14 % reduction in the number of participants who took the prebiotic powder reporting rectal burning during or after a bowel movement and rectal bleeding or tearing during or after a bowel movement.

Over 75 % of the cohort reported experiencing the symptoms in the stool sub-score at baseline. There was a significantly lower mean score given by those who took the prebiotic powder for 21 days than those who took the capsule in terms of bowel movements that were too hard (p = 0.004) or too small (p < 0.001), straining or squeezing (p < 0.001), and feeling like you had to pass a bowel movement, but couldn't (p < 0.001). This led to a significant difference in overall stool symptom sub-score between groups at 21 days (p = 0.022).

It is noteworthy that the threshold for reduction in total PAC-SYM score to define a clinical response on this 0–4-point scale has been determined [38], with the minimal important difference in clinical practice determined to be −0.6, and for clinical trials (to reduce the placebo response rate) it is deemed to be −0.75. Applied to this study, the results indicate that for the group taking the prebiotic powder, the reduction of the mean question score from 1.39 to 0.47 (−0.92) was associated with substantial clinical improvement.

The groups had a similar average total quality of life score (PAC-QoL) at baseline (p = 0.873). After 21 days of treatment there was a

Table 2
Patient Assessment of Constipation – Symptoms (PAC-SYM) total score and sub-scores for participants randomized to the prebiotic powder formulation and capsule groups. Questionnaires were completed at the beginning and the end of the 21-day treatment period, and the mean and standard deviation are shown, with the probability (p) of the means being different according to paired t-tests.

	Baseline					Day 21				
	Powder		Capsule		p	Powder		Capsule		p
	mean	SD	mean	SD		mean	SD	mean	SD	
Abdominal symptoms – sub-score	6.8	3.3	6.6	3.5	0.784	2.3	2.2	5.7	2.5	<0.001
Discomfort in abdomen	1.8	0.8	1.8	1.1	0.979	0.7	0.7	1.6	0.7	<0.001
Pain in abdomen	1.4	1.0	1.3	1.1	0.744	0.6	0.8	1.0	0.8	0.023
Bloating in abdomen	2.2	0.9	2.3	1.0	0.663	0.9	0.8	1.9	0.9	<0.001
Stomach cramps	1.5	1.2	1.3	1.1	0.411	0.4	0.6	1.2	0.6	<0.001
Rectal symptoms – sub-score	2.2	2.3	2.0	2.0	0.815	0.6	1.0	1.4	1.2	0.004
Painful bowel movements	0.9	1.1	0.7	0.9	0.459	0.3	0.6	0.9	0.8	0.004
Rectal burning before or after bowel movement	0.7	0.9	0.5	0.8	0.335	0.1	0.4	0.3	0.5	0.157
Rectal bleeding or tearing before or after bowel movement	0.5	0.9	0.4	0.7	0.564	0.1	0.4	0.2	0.4	0.389
Stool symptoms – sub-score	7.6	3.5	8.0	4.2	0.669	0.5	0.5	0.2	0.4	0.022
Incomplete bowel movement, like you didn't "finish"	1.9	1.0	1.6	0.9	0.267	1.0	2.1	1.6	0.8	0.150
Bowel movements that were too hard	1.6	1.1	1.4	1.1	0.679	0.6	0.6	1.2	0.9	0.004
Bowel movements that were too small	1.4	0.9	1.5	1.1	0.494	0.3	0.6	1.2	0.8	<0.001
Straining or squeezing to try to pass bowel movements	1.6	1.1	1.8	0.9	0.327	0.7	0.7	1.7	0.9	<0.001
Feeling like you had to pass a bowel movement but couldn't (false alarm)	1.3	1.0	1.6	1.2	0.185	0.5	0.6	1.4	0.9	<0.001
Total score	16.6	6.8	16.7	7.7	0.077	5.7	4.7	14.2	5.5	<0.001

significantly lower total score for the prebiotic powder group compared to the capsule group ($p < 0.001$), indicating that the impact of constipation-related symptoms on quality of life had reduced (Table 3). This was associated with improvement in all four sections of the PAC-QoL questionnaire for those who took the prebiotic powder than the capsule. The physical discomfort sub-score was significantly lower at 21 days across all four of the component questions ($p < 0.001$). The psychosocial sub-score was also significantly lower ($p = 0.006$), although only questions 6, 8 and 11 were found to be significant. In the worries and concerns sub-score, all 11 questions except for question 18 were statistically different. In the treatment satisfaction sub-score, one of the five questions was significantly different at baseline, with the prebiotic powder group having a significantly higher (worse) average score for the question (3.14) than the group taking the capsule (2.77). After 21 days of treatment, scores for all five treatment satisfaction questions were significantly lower for those who took the prebiotic powder than the capsule, leading to the overall significant difference in this subscale ($p < 0.001$).

Previous studies on clinical validity of the PAC-QoL have shown the minimum important difference using distribution- and anchor-based methods to be < 0.5 and < 0.9, respectively, indicating a 1-point difference in the score to be clinically relevant, with an improvement (reduction) of ≥ 1 point considered clinically significant [39]. In this study, the change score for the group taking prebiotic powder was just below this threshold (0.74). However, taken together, the positive significant changes reported for both the PAC-QoL and PAC-SYM support an earlier study showing that there is a significant correlation between the PAC-QoL and the PAC-SYM (of 0.577; $p < 0.001$) [40].

3.5. Effect of treatment on mood (DASS-21)

At the baseline assessment, only 18 of the individuals (31 %) in the study scored in the normal range for the depression, anxiety and stress sections. In fact, 20 individuals (34 %) scored within the severe or extremely severe range, with the remaining 20 (34 %) being mild or moderate for one or more of the DASS sections.

After 21 days in the trial, there was a significant reduction in mean score for depression, anxiety and stress for participants in both groups (Table 4). Indeed, the number of individuals scoring in the normal range for all three components of the DASS had increased to 30 (52 %) and the number of individuals expressing severe or extremely severe symptoms in any section had halved to 10 (17 %). Only six individuals – two taking the prebiotic powder and four taking the capsule – exhibited an increase in score over the 21 days such that they moved to a higher category in the depression, anxiety or stress section.

3.6. Effect of treatment on laboratory pathology markers – safety assessment

There was no difference in the safety measurements for full blood count, lipids, blood glucose, liver or kidney function at baseline or at day 21 in either group. The inflammatory marker, C-reactive protein was, on average, in the normal range (< 5 mmol/L) at both timepoints in both groups.

3.7. Dietary analysis

The amount dietary fibre that participants reported they were

Table 3
Patient Assessment of Constipation – Quality of Life (PAC-QoL) scores for participants randomized to the prebiotic powder formulation and capsule groups. Questionnaires were completed at the beginning and the end of the 21-day treatment period, and the mean and standard deviation are shown, with the probability (p) of the means being different according to paired t-tests.

	Baseline					Day 21				
	Powder		Capsule		p	Powder		Capsule		p
	mean	SD	mean	SD		mean	SD	mean	SD	
Physical discomfort sub-score	6.3	2.9	6.6	3.8	0.750	2.4	2.9	6.4	3.5	<0.001
Psychosocial discomfort sub-score	9.2	6.9	8.9	6.3	0.848	3.7	4.2	7.5	5.7	0.006
Worries and concerns sub-score	18.9	7.4	17.4	9.4	0.470	7.4	5.9	16.9	8.5	<0.001
Treatment satisfaction sub-score	13.9	4.9	13.7	4.0	0.204	8.1	5.4	14.1	3.2	<0.001
Total score (max. 112)	39.0	17.0	40.0	20.2	0.873	21.0	15.3	37.0	17.9	<0.001

Table 4
Mean and range for depression, anxiety and stress scores on the DASS-21 questionnaire before (baseline) and after 21 days of treatment for participants randomized to take the prebiotic powder formulation (n = 28) and the capsule (n = 30).

	Prebiotic powder (n = 28)					Capsule (n = 30)				
	Baseline		Day 21		p	Baseline		Day 21		p
	mean	range	mean	range		mean	range	mean	range	
Depression	10.6	0–32	5.6	0–22	<0.001	6.8	0–30	5.1	0–22	0.091
Anxiety	10.1	0–34	6.2	0–24	<0.001	9.0	0–34	7.7	0–28	0.081
Stress	18.4	2–36	11.8	0–28	<0.001	16.3	2–40	12.7	0–34	0.004

consuming in their 3-day diary was less than the recommended daily intake for the majority of participants across both groups (n = 55; 95 %). Average daily fibre intake was 16 g for both groups at baseline (p = 0.592), ranging from 7 to 28 g for those randomised to the prebiotic powder group and 7–42 g for the capsule group. At day 21 average daily fibre intake reported by those taking the prebiotic powder was 18 g (4–29 g), and 14 g (5–36 g) for those taking the capsule, which were not significantly different (p = 0.084).

4. Discussion

Daily consumption for 21 days of this prebiotic formulation consisting of partially hydrolysed guar gum (PHGG), acacia gum, modified citrus pectin, *Ulmus rubra*, *Hylocereus polyrhizus*, and *Theobroma cacao* extract increased the frequency of bowel motions, along with improvements in stool consistency, a reduction in associated gastrointestinal symptoms and an improvement in quality of life in a group of people with functional constipation. Improvements in DASS scores for depression, anxiety, and stress in both arms of the study is commensurate with often observed improvements in placebo groups where just taking part in a study affords participants with a sensation of care that translates into a reduction in negative feelings [41]. However, even though psychological measures improved irrespective of treatment group, changes in constipation-related measures were specific to those taking the prebiotic powder.

The main ingredient of the study product, PHGG, is produced by the controlled partial enzymatic hydrolysis of guar gum, obtained from the seeds of the guar bean, *Cyamopsis tetragonoloba*. PHGG is associated with a significant reduction in laxative use [42], acceleration of colon transit time and increase in stool frequency [13,43,44] in previous studies involving participants with constipation. In fact, a recent meta-analysis of 15 clinical studies involving 325 healthy participants taking dosages between 5 g/d and 32 g/d of PHGG found that as little as 5 g/day improved bowel function [45], so 3 g PHGG taken twice per day in the present study is at the lower end of the effective range. The proposed mechanism of action of PHGG is via increasing water absorption and thereby faecal bulk, softening stools and reducing luminal pH [43]. PHGG has also been reported to modulate the composition of the gut microbiome [46,47], possibly through water retention causing a reduction in pH of the gut lumen creating a more favourable growing condition for some species such as *Lactobacillus spp*. and *Bifidobacterium spp*. that are generally considered to be beneficial to gut health [48].

The other fibres (acacia gum, slippery elm, and apple pectin) that were included in the formulation may have also contributed to the overall effect on bowel function. Acacia gum is a soluble fibre obtained from the *Acacia senegal* tree and contains predominantly arabinose and galactose polysaccharides, oligosaccharides and glycoproteins [49]. It has been associated with beneficial health effects such as satiety and lowering of plasma cholesterol and glucose levels, which may in part, be associated with fermentation in the large intestine to short chain fatty acids [50,51]. In a clinical trial, 5 g/d of acacia gum reduced symptoms of flatulence in a blend with another prebiotic fibre [52]. *Ulmus rubra* (slippery elm) has demulcent and bulking actions and was included in a formulation that was shown to reduce straining, bloating, abdominal pain in those with IBS-constipation [53]. More recently, a formulation that contained 500 mg slippery elm bark powder, 10 mg guar gum and 100 mg pectin, 30 mg curcumin, 2.5 g glutamine, 200 mg quercetin, 500 mg glucosamine, 2.5 g Aloe vera, and 3 mg peppermint oil was found to reduce frequency and severity of constipation, diarrhoea, abdominal pain and troublesome flatulence in those with GIT symptoms [54]. Preliminary data obtained using a mouse model showed pectin was associated with a reduction in constipation via bulking and prebiotic effects [55].

Cocoa and red dragon fruit are of interest because of their prebiotic properties. A clinical trial of red dragon fruit in 128 adults with regular bowel function showed a laxative effect at a dose of 225 g whole fruit [56]. In a clinical study involving 24 participants, 494 mg/d of cocoa was associated with increased counts of *Bifidobacteria* and *Lactobacilli* while reducing pathogenic *Clostridia* after a 4-week intervention period [57]. Collectively, these clinical studies were used to inform the formulation developed and evaluated for efficacy in this current study.

This study has some limitations. A placebo match for the treatment was not possible due to the volume of powder involved (6 g), so a control was designed that differed in form (capsule containing 0.5 g) and was not expected to have any gastrointestinal effect. As significant improvement in psychological measures was exhibited in both arms of the study, we conclude that concealment of the potential for minimal therapeutic benefit from the capsule was successful. While the sample size was powered to measure the primary outcome of CSBM, the small cohort may limit the generalisability of the findings to the broader functional constipation population. Lastly, although participant self-reporting of dietary intake, symptoms scores and other measures used in this study are widely used and validated instruments, the results should be interpreted within the natural limitations of using self-reported measures.

5. Conclusions

Consuming this prebiotic fibre blend at a dose of 6 g taken twice per day was effective in improving functional bowel health by increasing frequency of bowel movements, improving stool consistency, as well as reducing associated gastrointestinal symptoms and improving quality of life in a group of individuals with functional constipation.

Authorship contributions

Elizabeth Steels: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Visualization, Original Draft. Rene Erhardt: Data Curation, Review & Editing. Joanna Harnett: Methodology, Review & Editing, Supervision. Vanessa Vigar: Conceptualization, Methodology, Original Draft, Review & Editing. Kathryn Steadman: Methodology, Data Curation, Visualization, Review & Editing, Supervision.

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Ethical statement

Informed consent was obtained from each individual prior to enrolment in the trial. The trial design was approved by the Ethics Committees of the National Institute of Integrative Medicine, Melbourne Australia (0075E 2020) and ratified by the University of Queensland, Brisbane, Australia (2020/HE002481). The trial was registered with the Australia New Zealand Clinical Trials Registry (ACTRN12620001247965).

Declaration of Competing Interest

RE, JH and KS declare that they have no competing interests. RE is a postgraduate research student, ES is an Honorary Senior Research Fellow, and KS and JH are employees at their respective Universities. VV is an employee of the trial sponsor. The trial was conducted through a clinical trial research agreement between the CRO (Evidence Sciences, directed by ES) and the sponsor.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.aimed.2023.05.001.

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