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Original Research

Kiwifruit-derived supplements increase stool frequency in healthy adults: a randomized, double-blind, placebo-controlled study

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ABSTRACT

The worldwide growth in the incidence of gastrointestinal disorders has created an immediate need to identify safe and effective interventions. In this randomized, double-blind, placebo-controlled study, we examined the effects of Actazin and Gold, kiwifruit-derived nutritional ingredients, on stool frequency, stool form, and gastrointestinal comfort in healthy and functionally constipated (Rome III criteria for C3 functional constipation) individuals. Using a crossover design, all participants consumed all 4 dietary interventions (Placebo, Actazin low dose [Actazin-L] [600 mg/day], Actazin high dose [Actazin-H] [2400 mg/day], and Gold [2400 mg/day]). Each intervention was taken for 28 days followed by a 14-day washout period between interventions. Participants recorded their daily bowel movements and well-being parameters in daily questionnaires. In the healthy cohort (n = 19), the Actazin-H ($P = .014$) and Gold ($P = .009$) interventions significantly increased the mean daily bowel movements compared with the washout. No significant differences were observed in stool form as determined by use of the Bristol stool scale. In a subgroup analysis of responders in the healthy cohort, Actazin-L ($P = .005$), Actazin-H ($P < .001$), and Gold ($P = .001$) consumption significantly increased the number of daily bowel movements by greater than 1 bowel movement per week. In the functionally constipated cohort (n = 9), there were no significant differences between interventions for bowel movements and the Bristol stool scale values or in the subsequent subgroup analysis of responders. This study demonstrated that Actazin and Gold produced clinically meaningful increases in bowel movements in healthy individuals.

Abbreviations: Actazin-H, Actazin high dose; Actazin-L, Actazin low dose; BMI, body mass index.

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1. Introduction

Gastrointestinal issues, including constipation, are common conditions worldwide in adults and children [1,2], which can severely affect the individual's quality of life and feeling of general well-being. Factors such as sex, aging, socioeconomic status, and educational level can affect the prevalence of constipation worldwide [2]. The intervention options for constipation remain difficult and challenging, and many individuals are dissatisfied with current therapies and medication. The current interventions for constipation include lifestyle and dietary modifications as well as pharmacologic interventions with stool softeners, osmotic laxatives, and stimulant laxatives. The worldwide growth in the incidence of gastrointestinal disorders has created an immediate need to identify safe and effective interventions.

A food-based approach to prevent constipation can be considered as an effective long-term solution [3]. Food ingredients such as psyllium and wheat bran are the most studied for preventing constipation. It is generally regarded that adequate intakes of fiber-rich fruits and vegetables daily with sufficient water prevent the incidences of constipation. Green kiwifruit are excellent sources of vitamins (A, C, and E), minerals (potassium), dietary fiber, and polyphenols [4]. Whole kiwifruit consumption has been shown to have beneficial effects on constipation, with several clinical studies demonstrating its efficacy [5] by improving laxation in healthy individuals [6,7] and in patients with irritable bowel syndrome with constipation [8]. It is thought that the unique combination of soluble and insoluble fibers; polyphenols; and the enzyme, actinidin, present in kiwifruit confers this and other health benefits.

Actazin and Gold are powdered ingredients derived from whole New Zealand green (*Actinidia deliciosa* "Hayward") and gold (*Actinidia chinensis* "Zesy002") kiwifruit from which the skin and seeds are removed and the remaining flesh cold processed for use in food and dietary supplements. We hypothesized that kiwifruit components present in Actazin and Gold improve stool frequency, stool form, and gastrointestinal comfort in healthy and constipated individuals (Rome III criteria for C3 functional constipation).

2. Methods and materials

2.1. Participants

The participants were recruited through newspaper and radio advertisements; community, local district health board, and tertiary institution newsletters; posters in doctors' general practice surgeries; and through our existing database of past participants. Participants were selected if they were aged 18 to 60 years, had a body mass index (BMI) between 19 and 30 kg/m^2, and fasting blood glucose less than 5.6 mmol/L. Participants were excluded if there were gastrointestinal alarm symptoms present (including blood in stools, frequent diarrhea, and unremitting abdominal pain); they were following a vegan, raw food, or very high-fiber diet (recommended fiber intake of 25-28 g/day for women and 30-38 g/day for men); had gastroparesis or lactose intolerance; surgery for weight loss (lap band or gastric bypass); clinically significant renal, hepatic, endocrine, cardiac, pulmonary, pancreatic, neurologic, hematologic, or biliary disorders as disclosed or detected through the comprehensive metabolic panel (Chem-20) taken at the initial screening visit; were pregnant; or had a known allergy or sensitivity to kiwifruit.

The subjects were asked to exclude high-fiber dietary supplements such as Metamucil, Benefibre, and Phloe to maintain their habitual food and beverage intakes and physical activity patterns as well as to refrain from eating fresh kiwifruit for the study period. They were also asked to avoid overseas travel for the period of the study because of the impact this may have on diet. Venous blood samples (~10 mL) were collected at the beginning and end of the study for biochemical analysis (Chem-20).

2.2. Study design

The study was a randomized, double-blind, placebo-controlled, crossover trial. Participants were recruited from Christchurch, New Zealand, into 2 cohorts (Figure): healthy participants who had no clinical symptoms of constipation and functionally constipated participants who met the Rome III criteria for C3 functional constipation [9] at recruitment. The Rome III criteria for C3 functional constipation includes 2 or more of the following: straining during at least 25% of defecations, lumpy or hard stools in at least 25% defecations, a sensation of anorectal obstruction or blockage for at least 25% defecations, sensation of incomplete evacuation for at least 25% defecations, manual maneuvers to facilitate at least 25% defecations, 3 or fewer defecations per week, loose stools rarely present without the use of laxatives, and insufficient criteria for irritable bowel syndrome.

Before the start of the study, there was a 14-day washout period to establish baseline measurements. All participants then consumed 4 dietary interventions each for 28 days, with a 14-day washout period between interventions. The washout period of 2 weeks was chosen to allow sufficient time to return bowel habits to baseline for the parameters measured. The dietary interventions were placebo (isomalt), Actazin low dose (Actazin-L) (600 mg/day), Actazin high dose (Actazin-H) (2400 mg/day), and Gold (2400 mg/day). The interventions were delivered in 4 × 600 mg capsules (Table 1) manufactured to appear the same to maintain intervention blinding and were supplied by Anagenix Ltd (Wellington, New Zealand). The intervention was taken in the morning with a glass of water. Nutritional information for the Actazin and Gold powders is presented in Table 2. The Gold powder contained no additional ingredients, whereas the Actazin powder contained silica and microcrystalline cellulose (<7.5%). The personnel recruiting participants were blinded to the order of interventions and the intervention identifications. The order in which participants were allocated their intervention was randomized by a biostatistician using a Williams Latin square design and computer-generated random numbers. Upon completion of the analyses, the study was unblinded to reveal the intervention order.

Participants completed a 3-day food diary at the beginning and end of the trial to assess their normal dietary intake. Participants recorded their daily bowel movements and well-

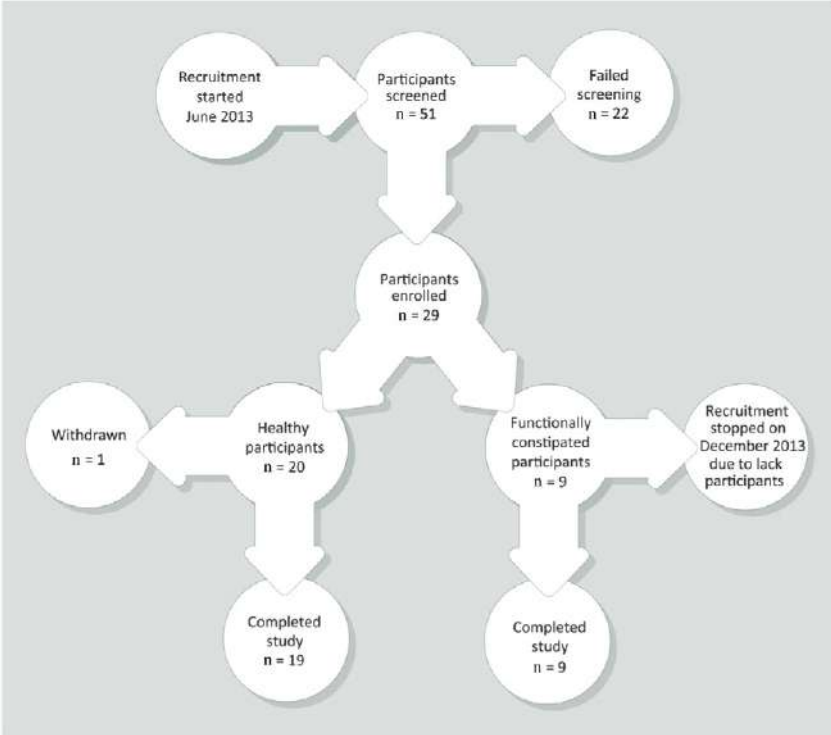

Figure – Recruitment flow chart of participants in the healthy and functionally constipated cohorts. Recruitment into the functionally constipated cohort proved challenging, with the primary reasons for not participating being preexisting medical conditions, the length of the study, and the requirement to refrain from eating fresh kiwifruit for the study duration.

being parameters in daily questionnaires. These included questions about numbers of bowel movements; incomplete and assisted bowel movements; assessment of stools on the Bristol stool scale [11]; and about bloating, flatulence, laxatives, and abdominal pain. For the Bristol stool score, where several stools may be evaluated per day, a mean score per day was calculated and then a mean of the daily means. The Bristol stool score was evaluated visually, scoring was from 1 (hard to pass) to 7 (entirely liquid).

This study was conducted according to guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the New Zealand Human Disability and Ethics Committee (12/STH/72/AM01). Written informed consent was obtained from all participants. The trial was registered with the Australia New Zealand Clinical Trials Registry (ACTRN: 12612001270808).

2.3. *Statistical analyses*

Data were analyzed using analysis of variance (ANOVA) in GenStat (version 16; VSN International Ltd, Hemel Hempstead, UK). Data from the healthy and functionally constipated cohorts were analyzed separately. Results from each observation (end of each washout or intervention) were analyzed as a complete block design, with participant and participant × phase as blocks and phase (1, 2, 3, or 4) and intervention (washout, placebo, Actazin-L, Actazin-H, or Gold) as factors. Washout results were included because of concerns that the placebo treatment may have had prebiotic effects. Residuals were inspected to ensure that the assumptions of ANOVA were met; where necessary, data were log transformed to stabilize variance. The means presented for the log-transformed variables have been transformed back to the original scale. Standard errors of the differences (SEDs) and *t* tests were used to calculate *P* values for the difference between the washout mean and the means for each intervention. Cochran Q test [12] was used to compare the proportion of participants responding to each intervention (ie, with a rise of at least 1 bowel movement per week over the preceding washout period). Participants were classified as either responders (showed a response to at least 1 of the nonplacebo interventions) or nonresponders.

Table 1 – Clinical trial interventions

Intervention	Composition	Dose	Capsules/day
Placebo	Isomalt	2400 mg	4 × Placebo
Actazin-L	Green kiwifruit powder	600 mg	1 × Actazin + 3 × placebo
Actazin-H	Green kiwifruit powder	2400 mg	4 × Actazin
Gold	Gold kiwifruit powder	2400 mg	4 × Gold

Table 2 – Nutritional information of Actazin and Gold dietary supplements

Nutrition information (per 100 g)	Actazin	Gold
Energy, kJ	1435	1420
Protein, g	3.4	3.9
Fat, total, g	3.0	1.8
Saturated, g	0.75	0.34
Unsaturated, g	2.4	1.4
Monounsaturated, g	0.53	<0.10
Polyunsaturated, g	1.8	1.4
Carbohydrate, g	67	71
Sugars, total, g	46	58
Sucrose, g	<0.05	<0.05
Glucose, g	21	27
Fructose, g	25	31
Lactose, g	<0.05	<0.05
Maltose, g	<0.05	<0.05
Dietary fiber, g	16	12
Sodium, mg	13	18
Total polyphenols, mg GAE	900	1100
Actinidin, AUs/g	40700	9100

Abbreviations: GAE, gallic acid equivalents; AUs, activity units.
The substrate used to monitor the activity levels of actinidin in Actazin and Gold is N_{α}-Z-L-lysine 4-nitrophenyl ester hydrochloride (Sigma-Aldrich, Auckland, New Zealand) [10].

3. Results

Twenty participants (2 male and 18 female) were recruited into the healthy cohort. The average age was 38 years (range, 23-56 years), and the average BMI was 23 kg/m^2 (range, 19-29 kg/m^2). Nine participants (1 male and 8 female) were recruited into the functionally constipated cohort. The average age was 44 years (range, 38-54 years), and the average BMI was 25 kg/m^2 (range, 21-29 kg/m^2). Table 3 shows the demographic and baseline characteristics of the study participants.

Of the 20 participants in the healthy cohort, 19 completed the study. One female participant withdrew for personal reasons, citing time limitations during the first intervention phase of the study. All 9 participants in the functionally constipated cohort completed the study. The reasons for the difficulty in recruitment into the functionally constipated cohort were hard to determine definitively but included preexisting medical conditions including Crohn disease and diverticulitis, BMI greater than 30 kg/m^2, and current medication regimes that did not fit the eligibility criteria. A number of participants who identified themselves as having constipation did not qualify under the Rome III diagnostic criteria applied in this study. Further screening ruled out several participants because of high fasting blood glucose concentrations (>5.7 mmol/L). The length of the trial, collection of fecal samples, and necessity to abstain from eating kiwifruit for the 26-week trial duration were also given as reasons not to participate.

The participant dietary nutrient intakes recorded at the beginning and end of the study showed no significant variations between individuals or during the course of the study. Compliance for this study was measured by asking participants to return their unused study product and counting the remaining supplement capsules. Compliance was calculated as the percentage of tablets taken from the original number dispensed. The healthy group of participants achieved a mean compliance level of 98% ± 9%, whereas the functionally constipated group reached a mean level of 99% ± 8% over the course of the study.

The blood samples were analyzed to assess the overall picture of the participant's metabolism by the Chem-20 panel for the healthy and functionally constipated cohorts; the results were within the reference ranges (data not shown). Consumption for 28 days of Actazin at the 2 rates of intake (Actazin-L and Actazin-H) and Gold was generally well tolerated, with no serious adverse events reported. There were no significant effects ($P > .05$) of consuming the interventions on the well-being parameters recorded in the daily questionnaires except for self-reported flatulence, which was higher with Actazin-H intervention ($P = .007$) in the healthy cohort (Table 4).

In the healthy cohort, Actazin-H ($P = .014$) and Gold ($P = .009$) consumption resulted in significant increases in the mean daily bowel movements, whereas Actazin-L consumption showed a nearly significant increase ($P = .060$) compared with the washout (Table 4). No significant differences were observed in stool form as determined by use of the Bristol stool scale [11]. In the responder subgroup (selected based on an increase of 1 bowel movement per week), consumption of Actazin-L ($P = .005$), Actazin-H ($P < .001$), and Gold ($P = .001$) resulted in significant increases in daily bowel movements compared with the washout (Table 4).

In the functionally constipated cohort, there were no significant differences between interventions for bowel movements, Bristol stool scale values, and other well-being parameters (Table 5).

Table 3 – Baseline demographics of the study participants

Baseline characteristics	Healthy	Functionally constipated
n	20	9
Male	2	1
Female	18	8
Age in y (mean ± SD)	38 ± 11	44 ± 6
Age (range)	23-56	38-54
Weight in kg (mean ± SD)	68 ± 13	67 ± 8
Weight (range)	47-101	53-79
BMI in kg/m^2 (mean ± SD)	23 ± 3	25 ± 2
BMI (range)	19-29	21-29

Abbreviation: SD, standard deviation.

Table 4 – Daily bowel movements and well-being parameters in the healthy cohort and responders' subgroup

	Mean (95% confidence intervals for difference from washout)					ANOVA *P values*		Post hoc *P* washout vs intervention			
	Placebo	Actazin-L	Actazin-H	Gold	Washout	Washout vs average of treatments (1 df)	Treatment differences (3 df)	Placebo	Actazin-L	Actazin-H	Gold
Healthy cohort (n = 19)											
No. of daily bowel movements [a]	1.12 (–0.05, 0.13)	1.16 (–0.00, 0.18)	1.19 (0.02, 0.21)	1.20 (0.03, 0.22)	1.08	.002	.918	.377	.060	.014	.009
Bristol stool scale	3.61 (–0.06, 0.44)	3.52 (–0.15, 0.35)	3.61 (–0.06, 0.44)	3.62 (–0.05, 0.45)	3.42	.036	.806	.134	.421	.138	.113
Strain	0.22 (–0.13, 0.02)	0.22 (–0.13, 0.02)	0.24 (–0.11, 0.04)	0.22 (–0.13, 0.02)	0.28	.044	.349	.157	.150	.363	.166
Incomplete evacuation	0.14 (–0.11, 0.04)	0.14 (–0.11, 0.04)	0.13 (–0.13, 0.02)	0.17 (–0.09, 0.06)	0.18	.137	.432	.310	.306	.174	.699
Bloating	0.17 (–0.02, 0.07)	0.15 (–0.04, 0.05)	0.13 (–0.06, 0.03)	0.16 (–0.03, 0.06)	0.14	.497	.490	.223	.757	.631	.503
Flatulence	0.60 (–0.04, 0.08)	0.64 (–0.01, 0.11)	0.67 (0.02, 0.14)	0.64 (–0.01, 0.11)	0.58	.007	.572	.511	.073	.007	.075
Manual maneuvers	0.00 (–0.03, 0.01)	0.02 (–0.01, 0.02)	0.01 (–0.02, 0.01)	0.02 (–0.01, 0.03)	0.01	.860	.339	.247	.637	.343	.234
Laxatives	0.01 (0.00, 0.01)	0.00 (–0.01, 0.00)	0.00 (–0.01, 0.00)	0.00 (–0.01, 0.00)	0.00	.786	.703	.156	.494	.475	.475
Abdominal pain	0.12 (0.01, 0.08)	0.11 (0.00, 0.07)	0.05 (–0.07, 0.01)	0.08 (–0.04, 0.04)	0.08	.339	.375	.021	.083	.103	.980
Responders (n = 14)											
No. of daily bowel movements [a]	1.27 (–0.02, 0.20)	1.35 (0.05, 0.29)	1.39 (0.09, 0.34)	1.38 (0.08, 0.33)	1.18	<.001	.999	.117	.005	<.001	.001

Abbreviation: df, degree of freedom.

The data were averaged for each 4-week dietary interventions (placebo, Actazin-L, Actazin-H, and Gold), and washout is an average of 4 preceding 2-week washouts. For the ANOVA, the intervention factor was split into a 1 degree of freedom contrast of washout against the average of the interventions and 3 degrees of freedom term testing the difference among the interventions. SEDs and *t* tests were used to calculate *P* values for difference between the washout mean and the means for each intervention.

[a] Data are log transformed for statistical analysis; means presented are back transformed. A subgroup analysis was conducted on the healthy cohort. Participants were classified as responders (showed an increase by at least 1 bowel movement per week over the preceding washout period on at least 1 of the nonplacebo interventions) or nonresponders. Data from the responders' subgroup in healthy (14/19 participants [74%]) cohort were analyzed using ANOVA.

Table 5 – Daily bowel movements and well-being parameters in the functionally constipated cohort and responders' subgroup

	Mean (95% confidence intervals for difference from washout)					ANOVA *P values*		Post hoc *P* washout vs intervention			
	Placebo	Actazin-L	Actazin-H	Gold	Washout	Washout vs average of treatments (1 df)	Treatment differences (3 df)	Placebo	Actazin-L	Actazin-H	Gold
Functionally constipated cohort (n = 9)											
No. of daily bowel movements [a]	0.96 (–0.14, 0.21)	0.92 (–0.17, 0.18)	0.88 (–0.21, 0.12)	0.99 (–0.11, 0.25)	0.93	.999	.840	.813	.894	.479	.546
Bristol stool scale	3.00 (–0.14, 0.58)	2.93 (–0.21, 0.51)	2.82 (–0.31, 0.40)	2.92 (–0.22, 0.50)	2.78	.210	.215	.223	.396	.799	.437
Strain	0.55 (–0.09, 0.21)	0.43 (–0.21, 0.10)	0.38 (–0.27, 0.04)	0.41 (–0.23, 0.08)	0.49	.321	.527	.433	.462	.147	.305
Incomplete evacuation	0.52 (–0.04, 0.24)	0.40 (–0.15, 0.13)	0.41 (–0.15, 0.14)	0.39 (–0.16, 0.12)	0.41	.720	.671	.155	.852	.957	.749
Bloating	0.09 (–0.12, 0.19)	0.14 (–0.27, 0.05)	0.12 (–0.10, 0.21)	0.14 (–0.36, –0.04)	0.12	.836	.533	.199	.313	.958	.461
Flatulence	0.46 (–0.02, 0.14)	0.32 (–0.01, 0.15)	0.49 (–0.14, 0.02)	0.23 (–0.10, 0.06)	0.43	.254	.228	.667	.158	.474	.015
Manual maneuvers	0.93 (–0.08, 0.02)	0.94 (–0.02, 0.07)	0.81 (–0.05, 0.05)	0.84 (–0.03, 0.07)	0.87	.609	.115	.132	.072	.140	.535
Laxatives	0.01 (–0.01, 0.01)	0.01 (–0.02, 0.01)	0.01 (–0.02, 0.01)	0.02 (–0.01, 0.02)	0.01	.615	.967	.795	.354	.673	.706
Abdominal pain	0.27 (0.02, 0.20)	0.12 (–0.14, 0.05)	0.15 (–0.10, 0.08)	0.12 (–0.14, 0.05)	0.17	.961	.639	.023	.316	.813	.323
Responders (n = 4)											
No. of daily bowel movements [a]	0.99 (–0.18, 0.41)	1.18 (–0.03, 0.66)	1.03 (–0.15, 0.46)	1.10 (–0.10, 0.56)	0.92	.086	.915	.584	.087	.399	.197

Abbreviation: df, degree of freedom.

The data were averaged for each 4-week dietary intervention (placebo, Actazin-L, Actazin-H, and Gold), and washout is an average of 4 preceding 2-week washouts. For the ANOVA, the intervention factor was split into a 1 degree of freedom contrast of washout against the average of the interventions and 3 degrees of freedom term testing the difference among the interventions. SEDs and *t* tests were used to calculate *P* values for difference between the washout mean and the means for each intervention.

[a] Data log transformed for statistical analysis; means presented are back transformed. A subgroup analysis was conducted on the functionally constipated cohort. Participants were classified as responders (showed an increase by at least 1 bowel movement per week over the preceding washout period on at least 1 of the nonplacebo interventions) or nonresponders. Data from the responders' subgroup in functionally constipated (4/9 participants [45%]) cohort were analyzed using ANOVA.

The subgroup analysis of responders also showed no significant differences ($P = .086$) between interventions and washout for the numbers of bowel movements.

4. Discussion

This study demonstrated that the consumption of Actazin and Gold increased stool frequency but did not affect stool form as measured by the Bristol stool score or the other measures of gastrointestinal comfort. An increase of greater than 1 bowel movement per week in a symptomatic population is considered a clinically meaningful magnitude of effect [13]. The consumption of Actazin and Gold demonstrated this degree of efficacy in the healthy responders in the present study. This suggests that kiwifruit bioactive components present in these products (ie, fiber; polyphenols; and the enzyme, actinidin) [14] improved regularity and laxation without affecting the stool form. No prior studies have investigated the effect of fresh gold kiwifruit or its products on laxation in humans. Whereas, the beneficial effects of green kiwifruit have been investigated in several clinical studies demonstrating improved laxation in healthy individuals [6,7] and in patients with irritable bowel syndrome with constipation [8]. In a clinical study with freeze-dried green kiwifruit powder (5.5 g/day), the product was also well tolerated, and the numbers of bowel movements were significantly increased after 28 days [15]. It remains unclear which of the bioactive components or their combinations in kiwifruit are influencing laxation.

In the individuals with functional constipation (n = 9), the dietary interventions did not significantly increase the frequency of bowel movements compared with the washout. This is likely to be due to the small sample size resulting in inadequate statistical power to detect significant differences. It should be noted that, in the functionally constipated responders group, there was a numerical increase of bowel movements compared with the washout for the Actazin and Gold interventions. This is supported by a meta-analysis of randomized controlled trials showing that additional dietary fiber consumption increases stool frequency in patients with constipation; but stool consistency, laxative use, and painful defecation were not improved [16]; and an earlier study reported similar effects of prebiotic xylooligosaccharides in healthy adults [17].

In the present study, isomalt was the placebo intervention. Isomalt is an equimolar mixture of 2 disaccharides, each composed of 2 sugars: glucose and mannitol (α-D-glucopyranosido-1,6-mannitol) and glucose and sorbitol (α-D-glucopyranosido-1,6-sorbitol), respectively. In some studies, this product has been shown to have a prebiotic effect by increasing bifidobacteria population and the production of butyrate [18]; this prebiotic response was achieved after feeding 30 g of isomalt daily to participants. In the current study, the maximum amount of isomalt given at any one time was 2.4 g, which is 12 times lower than the amount used by Gostner et al [18] and is unlikely to have led to significant osmotic and fermentative effects.

Based on the power calculations [19], n = 25 individuals would be necessary to detect a difference of 1.6/week in stool frequency with 80% power with a $P = .05$ 1-tailed test. Therefore, the main limitation of this study was the low numbers of participants recruited into the functionally constipated cohort. In addition, the daily dietary intake was not monitored closely during this 26-week study, which means that changes in diet made by the participants could have been wide and varied, with the potential to affect bowel health. We also note most of the trial population were female and were not monitored for their menstrual cycle over the course of this study; this may also have had an impact on the measures of bowel health carried out in this study.

Further studies are required to confirm the results of this study in a larger group of participants to overcome some of the limitations, including the low recruitment into the functionally constipated group and the minimal monitoring of dietary intake during the interventions. The evaluation of other digestive health markers such as immune function and microbiota composition could provide further evidence for the roles of Actazin and Gold in enhancing gastrointestinal comfort and health beyond laxation.

Overall, the intake of Actazin (600 and 2400 mg/day) and Gold (2400 mg/day) was well tolerated, and Actazin-H and Gold significantly increased daily bowel movements by more than 1 bowel movement per week. The novel finding of this study was the influence of Gold in promoting laxation. These kiwifruit-derived supplements demonstrated a clinically meaningful increase in bowel movements in healthy individuals.

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