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Efficacy of a Kiwifruit Extract (PhenActiv™) on Gastrointestinal Tract Function: A Randomised Double-Blind Placebo-Controlled Study

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Abstract

Objective: Gastrointestinal (GI) discomfort is experienced by millions of people every day. This study aimed to evaluate the effect of PhenActiv™, a novel green kiwifruit extract, on gastrointestinal tract (GIT) function in otherwise healthy adults. **Methods:** 41 healthy adults with mild GI discomfort were enrolled in this double-blind, randomized, placebo-controlled study. Participants were randomized to either take 3.0 g/day of PhenActiv™ or a placebo for 6 weeks. Interviews were conducted at baseline, week 3 and week 6, with participants completing questionnaires regarding GI symptoms. Frequency of bowel movements was self-recorded daily. **Results:** There were no differences in daily and weekly defecation frequency and stool characteristics in either group. The active and placebo groups significantly improve GSRS scores ($p < 0.05$), however, only the active group had a significant improvement in the IBSSS and PAC-QOL scores ($p < 0.05$) from baseline. Neither group had changes in sleep quality, quality of life and fatigue, plasma zonulin concentrations or macular pigment optical density scores. The product was well tolerated with no GI disturbances or adverse events being reported. **Conclusion:** Supplementation of 3.0 g/day of PhenActiv™ for 6 weeks did not improve defecation frequency or stool composition in healthy adults, but did improve perceived symptoms of GIT function, including symptoms of functional GIT disorders, IBS and constipation. The product was well tolerated and future trials investigating higher doses with more participants and/or a different population would be beneficial.

Keywords

Kiwifruit Extract, Gastrointestinal Tract Function, Stool, Gastrointestinal

Health, Bowel Function, Defecation Frequency

1. Introduction

Gastrointestinal (GI) discomfort, including symptoms of bloating, abdominal pain, constipation, and diarrhoea, is estimated to affect one in five Australians [1]. While the exact etiology of functional GI disorders is currently unknown, it is thought to be caused by a variety of factors including diet, food allergies/intolerances, infection, inflammation, dysbiosis, visceral hypersensitivity, genetics, neurological disturbances, mood disorders, epithelial hyperpermeability and certain medications [2]. Dietary factors, including food allergies and intolerances, can lead to gastrointestinal (GI) symptoms due to the body's response to specific substances in the food. The immune system may mistakenly identify specific substances in the food as harmful invaders, leading to an allergic response or the digestive system has difficulty processing certain substances found in food. Infection and inflammation can occur independently or in conjunction with each other. Common causes of infection and inflammation include bacteria, viruses, parasites, or other pathogens, and can lead to GI disorders due to the body's natural defense mechanisms and the impact of pathogens on the digestive system. Dysbiosis and visceral hypersensitivity are two interconnected factors that can contribute to GI disorders. Dysbiosis may lead to inflammation and gut barrier disruption, leading to increased visceral hypersensitivity. Conversely, visceral hypersensitivity can lead to stress, which can disrupt the gut microbiota.

Genetic factors can influence the structure and function of the digestive system, making individuals more susceptible to specific GI disorders (e.g., Celiac disease, hereditary hemochromatosis). Genetic mutations may also lead to deficiencies in specific enzymes responsible for digesting substances (e.g., lactase deficiency, sucrase-isomaltase deficiency). Neurological and mood disturbances can lead to GI disorders because the nervous system and the GI tract are intricately connected. The enteric nervous system, often referred to as the "second brain," is a complex network of neurons that controls various GI functions (referred to as the brain-gut axis), including digestion, motility, and the secretion of digestive enzymes and hormones. Neurological disturbances can disrupt these processes, leading to a range of GI symptoms. Normally, the epithelial cells lining the GI tract act as a selective barrier, allowing nutrients to be absorbed while preventing harmful substances from entering the bloodstream Epithelial hyperpermeability can lead to GI disorders through leakage of toxins and undigested particles into the bloodstream, increasing inflammation, food sensitivities and allergies and altering the gut microbiota. Medications can lead to GI disorders as side effects for several reasons. The most common reasons being irritation of the epithelial lining, altering the gut microbiota (e.g., antibiotics), changes to motili-

ty, altering the acidity/pH and nutrient absorption and having a laxative effect.

GI disorders and their associated effects can severely impact an individual's quality of life, especially those of low socioeconomic status [2] [3]. The severity and duration of GI disorders and their effects can vary from person to person and affect daily life and well-being in various ways. Common daily effects of GI disorders include physical discomfort, dietary restrictions, nutrient deficiencies, emotional impact, productivity (work and in at home), social restrictions and sleep disorders. The effects of GI disorders may be more pronounced in the lower socioeconomic status population due to typically limited or delayed health care access, poor diet and increased stress and anxiety. Therefore, effective therapeutic interventions targeting symptoms to improve the symptoms experienced by these individuals are required.

Current interventions for GI-related disturbances and disorders encompass a combination of pharmacological therapy, lifestyle, and dietary modifications [3] [4]. Common pharmacological agents administered to patients include stool softeners, laxatives, 5HT4 receptor antagonists and antidepressants along with recommendations for intake of fiber-rich food, adequate hydration, and exercise [3] [4] [5] [6]. However, pharmacological therapies are not cost effective, and they typically have negative effects leading to dissatisfaction with consumers [3] [4] [5] [6]. This highlights the need for remedies that are both efficacious in treating symptoms while not causing secondary discomforts to users.

A functional food touted for health benefits towards improving gut health and immune functioning due to its high levels of dietary fiber, protease activity, antioxidants, vitamins, minerals, and polyphenols is kiwifruit (*Actinidia deliciosa*) [4] [5] [6] [7]. Green kiwifruit is also known to possess laxative properties, with dietary supplementation being shown to enhance bowel movements and improve stool composition in both healthy individuals and those with irritable bowel syndrome (IBS) [4] [6] [8]. The purported laxative effects of kiwifruit, in which it supposedly enhances fecal bulking and softening are thought to be due to several components, including prebiotic oligosaccharides and phenolics which are known to improve microbial composition, insoluble and soluble fiber with high cell water-holding capacity and the thiol protease, actinidin [3] [4] [5] [6] [9]. The high levels of actinidin present in kiwifruit have demonstrated proteolytic activity that significantly improved the gastric and intestinal digestion of dietary proteins, thus enhancing absorption of nutrients [5] [7] [9] [10]. Actinidin has also been shown to stimulate colon receptors, increase GI motility and speed up colon-transit time [4] [5] [7] [9]. Kiwifruits' dietary insoluble and soluble fiber content has been shown to promote microbial health and laxation, due to its high water-holding capacity and viscosity increasing fecal bulking [5] [6] [9].

Daily consumption of kiwifruit has been shown to improve functional gastrointestinal disorders, colon transit time, defecation frequency and bowel function in constipated, elderly, and IBS patients [4] [6] [8]. Rush and colleagues found regular consumption of kiwifruit by elderly adults for three weeks led to

bulkier and softer stools, in-line with kiwifruit's purported method of improving stool composition [6]. Udani and Bloom administering 5.5 g of kiwifruit extract (Kivia powder containing Zyactinase™) daily for 4 weeks to 87 healthy adults with occasional constipation [9]. Kivia supplementation significantly improved spontaneous and complete bowel movements while reducing abdominal pain and flatulence compared to placebo [9]. In contrast, Kindleysides and colleagues failed to find any significant improvement in bowel function and comfort following supplementation with 1 g/day freeze-dried kiwifruit extract compared to placebo for 3 weeks to 40 adults with confirmed constipation [5]. Similarly, Ansell and colleagues assessed stool function by administering 2.4 g of two different kiwifruit-derived nutritional supplements (Actazin and Gold) daily for 4 weeks to both healthy (n = 19) and functionally constipated (n = 9) cohorts in a cross-over design. Ansell and colleagues found supplementation increased bowel movements compared to a control period in the healthy group, but no significant effect was found in functionally constipated individuals [3].

A second benefit of kiwifruit is proposed due to it being a source of carotenoids. Lutein and zeaxanthin are two carotenoids found in high concentrations in the retina and play an important function in maintaining the health of the eyes [11]. Specifically, lutein and zeaxanthin's proposed antioxidant activity may protect the retina from oxidative damage by scavenging reactive oxygen species and filtering blue light [12]. The effect kiwifruit extract supplementation may have on MPOD is yet to be established.

With methodologies of studies supplementing with kiwifruit extracts being variable, comparing results for a conclusion is difficult. Therefore, there is still a need for studies investigating the efficacy of different kiwifruit extracts on different GIT functions. The aim of this study was to compare the efficacy of 6-weeks of supplementation of the novel kiwifruit extract, PhenActiv™, to a placebo on GIT function in healthy adults reporting mild GI discomfort. A secondary aim was to assess the efficacy of kiwifruit supplementation on intestinal permeability, sleep, quality of life and macular pigment optical density (MPOD). We hypothesised supplementation for 6-weeks with PhenActiv™ would help alleviate GI discomfort, improve quality of life, and improve MPOD in those with poor MPOD values to start with.

2. Materials and Methods

This study was conducted as a randomised, double-blind, placebo-controlled study. Inclusion and exclusion criteria are detailed in **Table 1** below.

Potential participants were recruited from databases and public media outlets. Following preliminary screening via telehealth consult, 64 eligible participants attended the clinic and provided consent for inclusion into the trial. Once informed written consent was provided, participants were randomly allocated to one of the two treatment groups [active (n = 32) or placebo (n = 32)] using random allocation software (Sealedenvelop.com). All participants and investigators were blinded to the allocations until all statistical analysis had been completed.

Table 1. Inclusion and exclusion used for participant enrollment.

Inclusion	Exclusion
• Males and females aged over 18 years • Females using a prescribed form of birth control (e.g., oral contraceptive) • Experiencing three or more of the following symptoms of gastrointestinal discomfort including bloating, flatulence, diarrhoea, constipation, reflux, heart burn, abdominal pain/discomfort experienced at least 3 days in the last month • Normal dietary habits (no FODMAP diet, elimination diet, vegan diet, etc) with a minimum 2-month period of self-reported dietary stability. • Agree to not change current diet or exercise regime during entire study period • Agree to not use any other dietary supplements or digestive enzymes during the study period • Able to provide informed consent	• Unstable or serious illness (e.g., kidney, liver, GIT, heart conditions, diabetes, thyroid gland function Malignancy) • People with a past or current history of inflammatory bowel disease or gastrointestinal tract surgery • Pregnant or breastfeeding mothers • Malignancy or treatment for malignancy within the previous 2 years • Receiving/ prescribed coumadin (Warfarin), heparin, dalteparin, enoxaparin or other anticoagulation therapy including low dose aspirin • Active smokers, nicotine, alcohol, drug abuse • Chronic past and/or current alcohol use (>14 alcoholic drinks week) • Allergic to any of the ingredients in active or placebo formula • Any history of kiwi fruit allergy • Those suffering from insomnia or have night-shift employment and unable to have a normal night's sleep • People suffering any neurological disorders such as MS • Any condition which in the opinion of the investigator makes the participant unsuitable for inclusion (including hypercholesterolemia) • Participants who have participated in any other clinical trial during the past 3 months • Clinically significant acute or chronic inflammation, or connective tissue disease or arthritis • History of infection in the month prior to the study or taking antibiotic therapy • Hydration therapy during study period

Following consent and group allocation, participants completed baseline measures included lifestyle questionnaires, blood pressure, heart rate, current medications, medical history, body composition, dietary intake, GIT function (questionnaire), and quality of life (fatigue). All participants also undertook an MPOD test and had venous blood collected. After baseline assessments, participants were asked to take the allocated product according to the prescribed dose daily for 6 weeks. Participants attended the study clinic at weeks 3 and 6 for assessments identical to baseline. Between clinic visits, participants recorded the number of daily bowel movements in a stool frequency diary.

The active product arm (active group) was supplemented with a kiwifruit extract, PhenActiv™, at a total daily dose of 3.0 g (6 capsules). A matched placebo arm (placebo group) was supplemented with maltodextrin at a total daily dose of 3.0 g (6 capsules). Both trial arm products appeared identical, with the trial product being housed in opaque vegetarian microcrystalline hard shell, 2-piece capsules, filled in a GMP compliant facility. Participants were instructed to take 6 capsules daily, at breakfast time, with food and at least 250 mL of water for 6 weeks.

The aim of this study was to evaluate the efficacy of PhenActiv™ a novel green kiwifruit extract, on GIT function in healthy adults over 6-weeks. The primary outcome measure of this study was change in GIT function with stool frequency as the primary focus. Secondary outcome measures included change in perceived GIT function (The Patient Assessment of Constipation Quality of Life Questionnaire, Gastrointestinal Symptom Rating Scale, IBSS Symptom

Scoring System, Bristol Stool Chart, Gastrointestinal Tolerance Questionnaire), change in GIT permeability (plasma zonulin concentration), change in MPOD score (MPS II Macular Pigment Screener, Elektron Technology, Cambridgeshire, England), change in sleep quality (Pittsburgh Sleep Quality Index), change in quality of life and fatigue (36-Item Short Form Survey) and adverse reactions.

Funding and product for the trial was provided by Waitaki Biosciences (Christchurch, New Zealand) and conducted in Brisbane, Australia between November 2018, and December 2019. This study was conducted in compliance with the current International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), the Therapeutic Goods Administration (TGA), Notice for Guidance on Good Clinical Practice and ethical guidelines are outlined in Additional Ethical Considerations. The study was approved by Bellberry Limited Human Research and Ethics committee (approval number 201712968) and registered on the Australia New Zealand Clinical Trials Registry ACTRN12618000875202. The study procedure flowchart is provided in Figure 1.

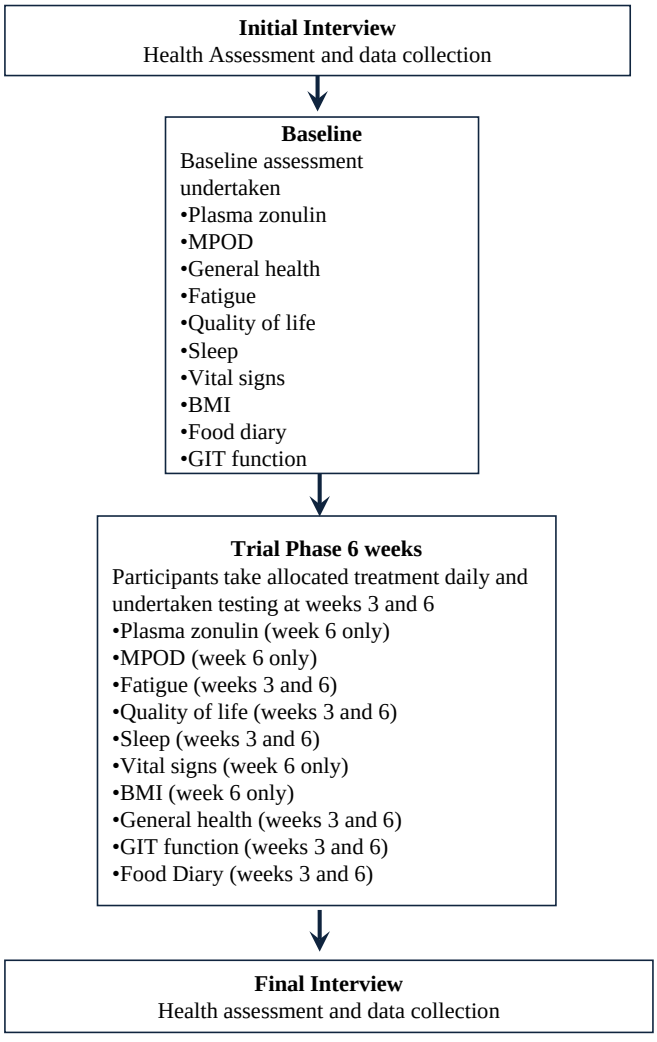

Figure 1. Study Procedure Flowchart for the 6-week study period indicating the timing of each outcome measure.

Macular Pigment Optical Density (MPOD) was measured in duplicate by the MPS II Macular Pigment Screener (Elecktron Technology). If duplicate values differed by greater than 10% a third value was recorded, and values were averaged.

Plasma zonulin was measured using enzyme linked immunosorbent assay as per instructions by the manufacturer (Jomar Life Research, Victoria, Australia).

The study was powered for the number of daily bowel movements as the primary outcome measure. The study was powered to detect a minimum change of 15% (1 movement per week) in bowel movement frequency in the supplemented group compared with the placebo group at the completion of supplementation.

Statistical analysis was undertaken using SPSS (V 27. Armonk, NY: IBM Corp) or GraphPad Prism (V 9. San Diego, CA) software. Samples were analysed per protocol, with only those completing the study including in the analysis. Descriptive statistics included but were not limited to mean, range, SD, SE. Data was assessed for normality and appropriate tests were used based on the distribution. Based on the normality of the data, ANOVA (or non-parametric equivalent) was used to determine statistical difference between groups as well as relevant post-hoc testing where needed.

3. Results

There was no statistical difference between group demographics at any study time point (Table 2). Of the 64 participants that enrolled, 41 participants completed the study and were included in the analysis. Of the 23 participants that withdrew, seven were lost to follow-up (n = 4 in placebo and n = 3 in active), ten withdrew for non-study related reasons (n = 3 in placebo and n = 7 in active) and six withdrew due to adverse events. In total, eight adverse events were recorded, of which two remained in the study and six withdrew. The two adverse events that remained in the study (n = 1 in placebo and n = 1 in active) both included mild headache and nausea (resolved by taking the trial supplements with food). The six adverse events that resulting in withdrawal (n = 4 in placebo and n = 1 in active) included three experiencing gastrointestinal symptoms (n = 2 in placebo and n = 1 in active; cramps, diarrhea, nausea), one developed a urinary tract infection (unrelated to trial product), one reported reduced stamina and one reported itchy eyes, ears, mouth, and sneezing.

There were no statistical differences in stool frequency, number, or consistency between groups (Table 3).

Both the placebo and active group had a significant change from baseline in the total GSRS score at week 3 ($p < 0.05$) and week 6 ($p < 0.05$). The active group had a statistically significant reduction in total Irritable Bowel Symptom Severity Score (IBSSS) score at week 3 ($p < 0.05$) and week 6 ($p < 0.05$) and PAC-QOL score at week 6 ($p < 0.05$) compared to baseline (Table 4). However, only 11 participants in the active and 8 in the placebo group completed the PAC-QOL at both baseline and week 6 due to not having constipation or having relief of constipation.

Both the placebo and active group reported a reduction in participants who no longer reported constipation from baseline to week 6 (n = 6 per group). However, more people reported having constipation at the start of the trial in the active group [85% (18 of 21)] than the placebo group [70% (14 of 20)]. One person in the placebo group reported developing constipation over the trial period.

There were no significant changes either between or within groups for plasma zonulin concentrations or MPOD scores (Table 5).

Table 2. Participant characteristics for participants that completed the study and were included in the analysis.

	Baseline		Week 3		Week 6	
	Active	Placebo	Active	Placebo	Active	Placebo
N (F)	21 (19)	20 (16)	21 (19)	20 (16)	21 (19)	20 (16)
Age	50.0 ± 12.8	46.4 ± 14.8	N/A	N/A	N/A	N/A
WC (cm)	92.6 ± 15.4	89.1 ± 11.3	92.7 ± 15.5	88.6 ± 12.2	92.3 ± 16.5	87.8 ± 12.0
HC (cm)	107.2 ± 12.1	104.6 ± 9.9	107.6 ± 12.3	105.0 ± 10.4	107.2 ± 12.4	104.5 ± 11.2
Waist to hip ratio	0.86 ± 0.07	0.85 ± 0.07	0.86 ± 0.07	0.84 ± 0.06	0.86 ± 0.08	0.84 ± 0.06
Systolic BP (mmHg)	121.1 ± 13.0	125.3 ± 17.1	N/A	N/A	123.1 ± 15.6	124.1 ± 20.0
Diastolic BP (mmHg)	81.0 ± 11.0	80.6 ± 14.5	N/A	N/A	81.8 ± 10.5	79.4 ± 12.8
Heart rate (BPM)	70.4 ± 7.31	65.1 ± 10.2	N/A	N/A	69.8 ± 6.0	67.3 ± 10.0
Height (cm)	167.9 ± 6.7	167.3 ± 11.5	N/A	N/A	168.0 ± 6.7	167.2 ± 11.2
Weight (kg)	77.8 ± 16.5	74.7 ± 18.5	78.4 ± 16.7	75.2 ± 19.0	78.2 ± 16.8	75.0 ± 19.2
BMI (m/kg^2)	27.7 ± 6.5	26.4 ± 4.7	N/A	N/A	27.8 ± 6.6	26.6 ± 5.1

N = number of participants; F = number of females; N/A = not applicable as measure not recorded; WC = waist circumference; HC = hip circumference; BP = blood pressure; BPM = beats per minute.

Table 3. Stool consistency and frequency.

	Baseline		Week 3		Week 6	
	Active	Placebo	Active	Placebo	Active	Placebo
Number per week (n)	12.0 ± 7.3	10.6 ± 4.6	11.1 ± 5.6	11.2 ± 4.2	11.7 ± 6.4	11.2 ± 4.9
Average number per day (n)	1.7 ± 1.0	1.5 ± 0.7	1.6 ± 0.8	1.6 ± 0.6	1.6 ± 0.9	1.6 ± 0.7
Consistency (Bristol stool chart)	3.9 ± 1.9	3.3 ± 1.4	4.0 ± 1.2	3.7 ± 1.0	3.9 ± 1.4	3.5 ± 1.2

Table 4. GSRS, IBSSS and PAC-QOL Scores over the 6 Week study period.

	Baseline		Week 3		Week 6	
	Active	Placebo	Active	Placebo	Active	Placebo
GSRS total	7.7 ± 2.5	7.5 ± 2.0	4.6 ± 2.8*	5.8 ± 2.8*	4.9 ± 2.9*	6.2 ± 3.2*
IBSSS total	12.5 ± 5.1	11.8 ± 4.1	7.0 ± 4.2*	9.4 ± 5.5	7.9 ± 5.1*	10.7 ± 5.7
PAC-QOL total	32.8 ± 15.7	42.1 ± 7.8	25.5 ± 15.9	40.1 ± 19.7	29.2 ± 10.7[a]	44.8 ± 17.2

* Denotes a significant difference from baseline ($p < 0.05$); [a]Denotes a significant difference to placebo ($p < 0.05$).

Table 5. Zonulin and MPOD Score.

	Baseline		Week 6		change	
	Active	Placebo	Active	Placebo	Active	Placebo
Zonulin (ng/mL)	8.61 ± 3.45	7.81 ± 3.77	8.75 ± 3.04	7.95 ± 3.34	0.14 ± 1.97	0.14 ± 1.95
MPOD left eye	0.44 ± 0.21	0.40 ± 0.17	0.40 ± 0.15	0.42 ± 0.15	−0.04 ± 0.12	0.02 ± 0.15
MPOD right eye	0.41 ± 0.20	0.42 ± 0.20	0.43 ± 0.19	0.43 ± 0.15	0.02 ± 0.09	0.02 ± 0.15

Neither the active or placebo group reported any changes in sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI) or change in quality of life and fatigue as measured by the 36-Item Short Form Survey (SF-36) (data not shown). There were no serious adverse events reported in this study and GI disturbances did not differ in both groups from baseline to week 6.

4. Discussion

This study investigated the efficacy of PhenActiv™ to modulate GIT function in healthy adults reporting GI disturbances. Following 6-weeks of supplementation with PhenActiv™ at 3.0 g/day, stool frequency and consistency did not change in either group. The results of this study are similar to that of Kindleysides and colleagues who administered 1 g/day for 4-weeks of freeze-dried encapsulated green kiwifruit extract to otherwise healthy adults with confirmed constipation and did not significantly improve bowel movement frequency and composition compared to a placebo [5]. Kindleysides reported the bowel movement frequency of both groups significantly increasing from the reported pre-trial frequency, but there was no difference either between groups or weeks throughout the study. Whilst pooled group results showed no change, it was reported that individual results varied with some participants improving both consistency and frequency. The individual variation reported may indicate that kiwifruit has greater efficacy for certain etiologies. It may also be that a longer duration, or greater dose is required to achieve an effect in some people. Kindleysides study also indicates that either there can be a strong placebo effect, or there is a learning effect, with the self-reported frequency doubling from pre-trial values to week 1 values [13]. This could be due to participants becoming more aware of their actual frequency and having greater reporting accuracy once they started on the trial, or it could be participants being more conscious of their bowels and increasing their frequency.

Udani and Bloom supplemented healthy individuals with occasional constipation with 5.5 g/day for 4-weeks with a freeze-dried green kiwifruit extract (Kivia powder). Supplementation with Kivia powder significantly increased spontaneous bowel movements after 3 weeks and complete spontaneous bowel movements after 2 weeks compared to a placebo [9]. However, like the study by Kindleysides, both the active and placebo groups reported a significant increase in bowel movement frequency at all four weeks compared to baseline values [9]. The increase in reported bowel movement frequency further supports a strong

placebo effect as previously reported (13), or variability in initial data collection. Ansell and colleagues supplemented healthy adults (n = 19) with 2.4 g/day for 4 weeks with kiwifruit extracts and significantly increased mean daily bowel movements compared to a washout period. The same effects were not seen in the functionally constipated cohort (n = 9) [3].

The variation in study findings could be due to several reasons. There may be a compositional difference between the various extracts used and the dose varied between studies ranging from 1 g/day to 5.5 g/day [3] [5] [9]. Participant numbers may also have had a significant effect on the studies outcomes. Udani and Bloom's [9] study recruited 87 participants compared to 40 by Kindleysides [5] and 19 by Ansell [3]. As suggested in the Kindleysides study, the efficacy of kiwifruit may be varied among individuals and a large sample size may be required to overcome the variability and see an effect. One similarity in the studies is the trend for increased bowel movement frequency [3] [5] [9]. Our study failed to see any change in stool frequency, with only the placebo group reporting a slight non-significant increase in frequency of stools post-baseline. However, the number of bowel movements per week reported in the present study is greater than those presented in other studies and may suggest either a difference in GI disturbance etiology or a difference in baseline reporting methodology. As the number of bowel movements reported in the present study population is normal, it is hard to expect any change in this measure.

While human clinical trials have found benefits in kiwifruit extract supplementation improving defecation frequency, significant benefits for its effect on altering stool composition are mixed. Our study reported no difference in stool consistency for both the active intervention and placebo group as measured by the Bristol stool chart. This is in line with Kindleysides [3] and Ansell [5] studies, who reported no difference in Bristol stool scale values between interventions. Udani and Bloom [9] reported improved stool features in both groups over the study period with significantly smoother and softer bowel movements in the active treatment group at weeks 2 and 3 compared to placebo [9]. A 2012 meta-analysis on the effect of dietary fiber on constipation found that while dietary fiber can increase stool frequency in patients with constipation, it did not significantly improve stool consistency, which is similar to the findings of most of the kiwifruit extract ?studies [14]. The lack of efficacy of kiwifruit supplementation affecting stool composition may be due to the number of studies investigating kiwifruit extracts and the lack of studies specifically recruiting participants with issues with stool composition. Future ?investigations may benefit from a greater number of subjects, more specific etiologies being recruited, and/or different types, doses, and administration methods of extracts for more favorable results.

Despite no difference in stool frequency and consistency, our study found the active treatment was beneficial for improving GI-related symptom severity and quality of life measures. Both the active treatment and placebo product were found to improve measures in the gastrointestinal symptom rating scale (GSRS)

at weeks 3 and 6 compared to baseline. However, there were no significant between-group differences in this parameter. Similarly, Kindleysides also reported a change from baseline, but no significant difference in GSRS or quality of life measures between the active and placebo groups [5]. Udani and Bloom reported improved abdominal discomfort and flatulence for the active treatment group compared to placebo at weeks 1 and 3 and weeks 2 and 3 respectively [9]. The findings of these studies again may indicate the need for a greater number of participants to see an effect.

The present study also found significance for the active treatment in improving IBSSS at weeks 3 and 6 compared to baseline levels. No significant change from baseline was seen in the placebo group and no significant difference seen between groups for each time point for IBSSS like other reported data. The active treatment significantly improved the PAC-QOL scores at week 6 compared to the placebo group, with no other significant changes seen. This suggests that over 6 weeks, kiwifruit extract may improve perceived GI-related symptoms, but evidence from more people is likely required. It is also important to note that while there was a reduction in PAC-QOL scores in the active treatment group compared to placebo at week 6, the placebo group reported a greater number of participants who had a complete reduction of constipation and may skew the data. The limited number of participants eligible to complete the PAC-QOL at both baseline and week 6 due to not having constipation could have affected result. Future studies focusing specifically on this population in sufficient numbers is therefore required to fully understand the effects seen.

Another purported mechanism through which active treatment could improve GIT symptoms is by improving gut microbial composition and intestinal health [7] [15]. Having a healthy gut microbial composition is crucial towards reducing gastrointestinal inflammation and discomfort, strengthening intestinal integrity and even improving psychological well-being [16]. Kiwifruit is thought to elicit some of its GI health benefits through improving gut microbial composition as a result of its prebiotic and dietary fiber content [7] [15]. Its high antioxidant content could further aid in alleviating damaging reactions to bodily tissues, including intestinal cells [7] [17] [18]. Hans and colleagues 2011 study found that inclusion of freeze-dried kiwifruit and kiwifruit fiber into the diet of pigs modulated their microbial composition by improving the abundance of beneficial species and reducing harmful pathogens [15]. Moreover, an open label trial including six healthy Chinese female adults found that administration of kiwifruit extract equivalent to two fresh kiwifruits daily for four days promoted fecal lactobacilli and bifidobacteria content compared to baseline for the duration of consumption [19] and is supported by in vitro studies [20] [21].

As intestinal barrier integrity is paramount to gut health, we analysed plasma zonulin concentration, a protein that reversibly regulates intestinal permeability and is often used as a key biomarker for impaired gut barrier function [22]. Gut microbial composition has been shown to play a key role in shaping intestinal

barrier function with shifts in composition either inducing or protecting from hyperpermeability [23]. Our study found that PhenActiv™ supplementation did not influence plasma zonulin concentration. Interestingly, actidin (enzyme in kiwifruit) has been reported to disrupt intestinal barrier function in *in vitro* and *in vivo* models, which may relate to it being reported as a possible allergen [24] [25]. However no serious adverse events were reported in previous human trials on kiwifruit extracts, suggesting that these products are well tolerated [3] [5] [9]. Our study also had no findings of GI-related disturbances suggesting that this product too, was well tolerated with no side effects. Future studies wanting to determine the efficacy of kiwifruit extracts on barrier function, would benefit by focusing on people with a barrier issue to begin with.

As kiwifruit is known to contain the carotenoids lutein and zeaxanthin, both of which are potent antioxidants that can protect the eyes and filter harmful blue light, we additionally tested the effect of PhenActiv™ supplementation for MPOD, which measures the ability of the macular pigment (MP) to filter blue light [11] [12] [26] [27]. The MP is composed of lutein and zeaxanthin, such that the MPOD can also be a measure of the content of these two carotenoids [27]. In our study there was no difference in MPOD score between groups or between baseline and week 6 measures. Future studies wanting to determine the efficacy of kiwifruit extracts on MPOD, would benefit by focusing on people with low MPOD values to begin with. The population in this study had normal MPOD values to start, therefore there was less room for improvement.

One limitation of our study was the sample size used. The study by Udani and Bloom has shown that a larger sample size was able to show greater differences between groups. The sample size used in this study was similar to prior human studies on kiwifruit extract [3] [5] and calculated to be sufficient to achieve statistical significance. Variation in gut etiology and health could impact the perceived and measurable GIT function improvements, and a lager sample size may help to account for these differences. Another limitation was the population recruited had normal bowel movement frequency at the start of the study. Therefore, it was not possible to alter the primary outcome. Future studies would benefit by more stringent selection criteria of participants based on certain levels of GI symptoms (e.g., related specifically to bloating, flatulence, diarrhoea, constipation, reflux, heartburn, and/or abdominal pain/discomfort) or being separated into different treatment groups based on the type and level of symptoms experienced may help improve trial outcomes. A large cohort would allow for subgroup analysis of responders vs. non-responders and may help establish the etiologies for kiwifruit extracts to have an effect on.

In conclusion, daily supplementation of 3.0 g/day PhenActiv™, a novel freeze-dried extract powder made from GMO-free green kiwifruit to healthy adults for 6 weeks was not found to significantly affect stool frequency and composition. While both the active and placebo treatments improved functional gastrointestinal symptoms, only the active treatment reduced IBS and constipation symp-

toms compared to baseline levels. The lack of GI disturbances reported during the study period suggests that the product was well tolerated by participants with no side effects.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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