Encapsulated green kiwifruit extract: a randomised controlled trial investigating alleviation of constipation in otherwise healthy adults

Asia Pac J Clin Nutr 2015;24(3):xxx-xxx
doi:10.6133/apjcn.2015.24.3.15

Running title: Investigating kiwifruit extract for bowel function

Sophie Kindleysides MSc[1], Barbara Kuhn-Sherlock PhD[4],WilsonYip MSc[1],Sally D. Poppitt PhD[1,2,3,]

Affiliations:[1]Human Nutrition Unit, [2]School of Biological Sciences, [3]Department of Medicine, University of Auckland, Auckland, New Zealand, [4]Consultant Statistician, Hamilton, New Zealand.

Email address of authors: Sally D. Poppitt [s.poppitt@auckland.ac.nz]

Corresponding author: Prof SD Poppitt
Human Nutrition Unit, University of Auckland, 18 Carrick Place, Mount Eden, Auckland, New Zealand.
Email:s.poppitt@auckland.ac.nz
Tel +64 9 6305160
Fax +64 9 6305764

ABSTRACT

Objective: Previous clinical trials have shown bowel function is improved through consumption of whole kiwifruit (Actinidia deliciosa). This study investigated whether encapsulated kiwifruit extract (1 g/day) could alleviate constipation in otherwise healthy adults. **Methods:** Forty adults with confirmed constipation entered this trial, of which 32 completed with >80% compliance. Two capsules were self-administered morning and evening for 2 periods, each of 3 weeks duration, separated by a 3+ week washout in a double blind, randomised, placebo controlled crossover. Inclusion criteria included constipation with ≤3 bowel movements (BM) per week. Daily records of defecation frequency and stool characteristics were obtained throughout treatment, as well as a measurement of gastrointestinal symptoms rating scale (GSRS) and quality of life (QoL) before and after each intervention arm. **Results**: There was no difference in total BM over 3 weeks (p>0.05) or mean BM during each of weeks 1, 2 and 3 (p>0.05) between the kiwifruit extract and placebo when assessed from a faecal diary. There was also no detectable difference in defecation related scores of BM ease of defecation, volume, consistency or BM type assessed using Bristol stool chart scores. Nor was there a significant change in GSRS or QoL between pre and post treatment measures, when compared to placebo (p>0.05). **Conclusions:** This trial showed that improvement in bowel function or comfort was not achieved through supplementation with 1 g/day freeze dried kiwifruit extract. Efficacy from prior kiwifruit powder and whole fruit trials indicate that investigating higher doses of encapsulated kiwifruit extract may be worthwhile.

Key Words: Actinidin, bowel function, constipation, defecation frequency, kiwifruit extract

INTRODUCTION

Constipation is a common condition estimated to effect up to ~25% of the population at any given time, and is characterised by bowel movements (BM) that are infrequent or hard to pass.[1] Constipation is reported more commonly by women than men, with other contributing factors including older age, diet, lifestyle, bowel habits and the use of some medications.[2] The cause in some individuals may also be attributed to neurological or psychological conditions which have been correlated with gut-related inflammation.[3,4] Self reported constipation as defined by the Rome III Criteria can lead to impairment of quality of life (QoL) as well as other significant consequences, such as an increased risk of colon cancer.[5]

Use of laxatives and treatments for functional bowel disorders, constipation and irritable bowel syndrome (IBS) can lead to unwanted side-effects and there is increasing demand for natural remedies to alleviate such conditions.

Kiwifruit (*Actinidia deliciosa*) are a common berry fruit, endemic to Asia but which have been grown within New Zealand since the early 1900s. They are a commonly consumed fruit in many countries and across many population groups. It has been postulated that both the entire fruit and specific extracts of the fruit may help to maintain healthy gut function if regularly consumed as part of the habitual diet. Clinical trials have shown that green kiwifruit, when given as whole fruit, can enhance several parameters of laxation in adults reporting a history of constipation, or constipation associated IBS.[6-8] Positive effects of supplementation include increased frequency and ease of BM, and increased stool bulk and softness. In addition, in a recent study conducted by Udani and Bloom, a kiwifruit extract was also found to have a positive effect on BM[9] when constipated but otherwise healthy adults were given high dose 5.5 g/day of a commercial green kiwifruit dry powder (Kivia powder), diluted with water into a fruit beverage. In addition, a poorly designed non-randomised, uncontrolled and unblinded encapsulated kiwifruit extract trial conducted in Japan has also indicated improved bowel function in elderly participants,[10] although these data are likely unreliable.

There are a number of proposed mechanisms for these enhanced gastrointestinal (GI) effects including the action of actinidin, a proteolytic enzyme within the class of thiol-proteases present only in green kiwifruit; presence of soluble fibre with high cell wall water-holding capacity[11] and high viscosity; and high levels of prebiotic carbohydrates (CHO) such as the oligosaccharide inulin in addition to prebiotic phenolics. *In vitro* studies on kiwifruit-derived actinidin have confirmed that enzyme activity is maintained following extraction of isolates of the whole kiwifruit[12], and rodent studies have also demonstrated enhanced gastric hydrolysis of food proteins in the presence of this enzyme.[13]

Several commercial companies use kiwifruit extract in their branded products, sold in health food stores and other commercial outlets. Kiwifruit-derived soluble fibre supplements and encapsulated kiwifruit extract are commonly proposed to '*regulate gut function'*. An example of a recommended dose of these extracts is 500 mg/day, taken as divided 250 mg doses each morning and evening. Our objective was to test whether the positive effects on GI function and comfort observed in clinical studies of whole green kiwifruit were maintained when an encapsulated dry extract of the fruit was administered over a period of 3 weeks to constipated but otherwise healthy adults.

MATERIALS AND METHODS

Participants

Participants in this study were healthy adults, aged between 20 and 63 years, recruited from advertising in local newspapers, community notice boards and community/workplace email newsletters within Auckland, New Zealand. Participants were pre-screened over the telephone to assess inclusion and exclusion criteria, and each was required to have symptoms consistent with constipation. If eligible, participants then completed a pre-trial 1 week faecal diary in order to confirm three or less (≤3) BM per week, and requested to attend a clinic screening visit. Participants with any inflammatory or malabsorptive GI condition that would interfere with the evaluation of the extract, including confirmed diagnosis of inflammatory bowel disease (IBD), ulcerative colitis (UC), coeliac disease, Crohn's disease, or previous significant GI surgery including bariatric, were excluded. Current medication prescribed for constipation, and any known allergy or sensitivity to kiwifruit were further exclusion criteria. Participants were asked to maintain their normal lifestyle habits and food intake throughout the study period, although this was not independently assessed.

Design

This was a randomised, double-blind, placebo controlled, cross-over study with two 3 week intervention periods. Forty (40) men and women were randomised into the trial. Participants, principal investigator, clinical and data entry staff, and statistician were blinded throughout the trial. The study was conducted at the University of Auckland Human Nutrition Unit, located in Mt Eden, Auckland. Ethical approval was obtained from the Northern B Health and Disability Ethics Committee, Wellington, New Zealand (13/NTB/132). This trial was registered with the Australia New Zealand clinical trial registry (ANZCTR): ACTRN12613001163796.

Study visits

The trial protocol is shown in Figure 1. At the screen visit, participants completed the consent process, demographic data was obtained and the pre-trial BM record reviewed. Study participants meeting inclusion criteria including ≤3 BM/week were then randomised in the order recruited, and their 3 week treatment allocation confirmed. At this first visit (V1), participants were given a 4 week supply of encapsulated kiwifruit extract, instructed on the use of the product (2 x 500 mg capsules per day, morning and evening), the length of treatment, how to complete the trial faecal diary for daily assessment, and asked to return any

unused capsules at their next visit (V2). They also completed two pre-treatment questionnaires; GI symptoms rating scale (GSRS) and the QoL, short-form health questionnaire SF-12. At the end of week 1 and week 2 of both intervention arms, participants were given a follow-up phone call and reminded to continue to take 2 capsules per day and to fill in the faecal diary for all BM. At the end of week 3 participants returned to the clinic for V2, and again completed the GSRS and SF-12 questionnaires as post treatment measures, returned completed faecal diaries, and any unused capsules. Each subject then had a washout period of between 3-9 weeks. At the third study visit (V3) the second treatment was allocated and a further 4 week supply of capsules provided, and GSRS and SF-12 pre treatment questionnaires were administered. After 3 weeks participants then returned to the clinic for the fourth study visit (V4) with completed faecal diaries, leftover capsules, and to complete post treatment questionnaires.

Encapsulated green kiwifruit extract

The investigational product for this study was an encapsulated extract of whole green kiwifruit (*Actinidia deliciosa*), comprising both flesh, skin and seeds of the whole fruit. The product was provided by NZ Extracts Ltd, Marlborough, New Zealand. The extract was prepared by a water extraction process and then freeze dried. It appeared as a dry brown powder. The encapsulated extract contained the proteolytic enzyme actinidin (EC 3.4.22.14) obtained from kiwifruit flesh, and prebiotic polyphenols (>30 mg/g) and soluble fibre (320 mg/g) obtained from kiwifruit skin(Table 2).[14] Measurements of *in vitro* protein digestion of beef, tofu and cow's milk, using the methods of Kaur *et al*,[12] showed an increase in digestion rates of 2-3 fold after 30 minutes in the presence of the extract incubated with pepsin at pH2 and 37^{o}C, versus pepsin control[14] (Trinity Bioactives Ltd, Wellington, New Zealand). The extract was also shown to increase levels of probiotic bacteria *Lactobacillus acidophilus* (ATCC 4356) by 21 fold and *Bifidobacterium bifidum* (DSM 20082) by 6 fold over 48 hours within an artificially innoculated *in vitro* culture system, versus a sterile water control[14] (Trinity Bioactives Ltd, Wellington, New Zealand). The daily dose administered was 2 capsules per day, where each capsule contained 500mg of kiwifruit extract (total intake of 1,000 mg/day), with one capsule taken morning and one capsule in the evening, administered with food. The placebo was encapsulated magnesium stearate Mg $(C_{18}H_{35}O_2)_2$, with product and placebo capsules matched for size, weight and colour. Both sets of capsules were GMP certified.

Assessment of bowel habits and general health

Prior to randomisation into the trial, a one week pre-trial faecal diary was completed to confirm the inclusion criteria of ≤3 BM per week. This was assessed on 1 occasion only prior to randomisation into the intervention at Visit 1. During both subsequent intervention periods, the faecal diary was also used to record both number of BM and faecal characteristics. The Bristol stool scale for type was used to classify BM into categories where seven forms are designated. The first form describes a stool as 'type 1= separate hard lumps, like nuts (hard to pass)', and continues on to form seven, described as 'type 7=watery, no solid pieces, entirely liquid'.[15] Further assessment included: stool consistency (1='runny', 2='soft', 3='medium', and 4='hard'), stool volume (1='very small', 2='small', 3='medium', 4='greater' and 5='lots'), and stool ease (1='very easy', 2='easy', 3='OK', 4='hard' and 5='difficult') evaluated for every BM recorded during intervention. Before and after each treatment arm, GSRS and QoL were assessed. The GSRS questionnaire assessed GI related symptoms ranging from evaluation of 'abdominal pains' to 'feeling of incomplete evacuation'.[16] The GSRS has a seven point graded Likert-type scale where 1 represents absence of troublesome symptoms and 7 represents very troublesome symptoms. QoL was assessed using the SF-12 where questions on general, physical and mental health were assessed.[17]

Adverse events

Adverse events (AEs) and serious adverse events (SAEs) were recorded throughout the study. Only one participant experienced an AE during the study (mild bloating, nausea, vomiting), symptoms were mild, no medical treatment was required, and the AE resolved within two days of stopping treatment. This event did not require unblinding of the randomisation, but the participant chose to withdraw from the study. No other AEs occurred during the study.

Data analysis

Primary and secondary outcomes were analysed using mixed models approach to repeated measures analysis of variance (Proc Mixed, SAS version 9.3, SAS Institute Inc., Cary, NC, USA). The structure of repeated measurements within each treatment period was modeled using an unstructured covariance pattern across treatment periods and compound symmetry across repeats. Analysis of variance (ANOVA) was followed by Tukey's post-hoc test for pair-wise comparisons. The models for analysis included baseline results, compliance, duration of washout period, as well as age and BMI of the subject as covariates. Mean results

are plotted as least square means ± standard error (SE). Significance was declared if $p<0.05$. Data was analysed as both intention to treat (ITT, n=40) and per protocol (PP, n=32, >80% compliance).

RESULTS

Of the 40 participants who were randomised into the study (ITT population), a total of 32 (29 female, 3 male) completed both intervention arms with >80% compliance to treatment (PP population). The study flow chart is provided in Figure 2. The 8 participants who did not complete the study, were excluded or were not compliant to treatment, as follows: 1 withdrew/lost to contact, 1 withdrew due to family crisis, 1 withdrew due to adverse reaction, 3 were excluded following prescription of GI altering medications and 2 were excluded with <80% compliance to capsules. In the 32 completing participants compliance was good with>95% of capsules consumed during both treatment periods, with no significant difference between kiwifruit extract and placebo ($p>0.05$). The baseline characteristics of all participants randomised into the trial are detailed in Table 1.

Primary endpoint – BM frequency

The primary endpoint of this study was BM or defecation frequency. When data from the PP population (Figure 3a) was analysed as total BM during both 3 week intervention periods there was no significant difference in frequency between the encapsulated kiwifruit extract (mean, SE: 4.5, 0.3 BM/wk) and placebo (mean, SE: 4.1, 0.3 BM/wk; $p=0.218$), despite excellent compliance to treatment on both arms. BM frequency changed little between weeks 1, 2 and 3 for both kiwifruit extract (4.46, 4.64 and 4.42 BM/wk) and placebo (4.48, 4.24, and 3.70 BM/wk; ANOVA, treatment*week interaction, $p=0.110$), although both were significantly greater than the pre-trial frequency of 2.3, 0.1 BM/wk. All participants randomised into this intervention recorded ≤3 BM/wk prior to the trial. These outcomes were unchanged when all randomised participants were included in an analysis of the ITT population (treatment* week interaction, $p>0.05$).

Secondary endpoints – Bristol stool chart characteritics, GSRS, QoL (SF-12)

The secondary endpoints were self reported Bristol stool characteristics obtained from the faecal diary throughout the 3 week intervention periods (Figure 3b-e), and GSRS and QoL questionnaires pre and post treatment (Figure 4). When data from the PP population was analysed over both 3 week intervention periods there was no significant difference between

encapsulated extract and placebo for stool ease (3.10 vs 3.10 units, p=0.868), stool volume (2.72 vs 2.66 units, p=0.602), stool consistency (3.00 vs. 2.95 units, p=0.687), or stool type (2.93 vs 2.97 units, p=0.873). Nor was there a significant effect of kiwifruit extract compared with placebo on any Bristol stool chart parameter between weeks 1, 2 or 3 (interaction, treatment*week, all, p>0.05). Figure 4 shows the pre and post treatment GSRS questionnaire and QoL data for the PP population. Whilst there was a significant decrease in GSRS symptoms (top panel) on kiwifruit treatment from (2.26 to 1.96 units, p=0.0204), there was no signficant difference when compared with placebo (interaction, treatment*week, p=0.124). QoL physical component score (PCS, Figure 4b) and mental component score (MCS, Figure 4c) both improved between pre and post treatment on the kiwifruit arm (PCS, 50.7 vs 53.5, p=0.0246; MCS 50.3 vs 52.7, p=0.0413), but again there was no significant difference when compared with placebo which also tended to improve (interaction, treatment*week, p=0.781 and p=0.557, respectively). Outcome remained unchanged when all randomised participants were included in an ITT population analysis (treatment*week interaction, p>0.05).

DISCUSSION

In this study, we examined the effects of encapsulated freeze dried kiwifruit extract on alleviation of the symptoms of constipation in otherwise healthy adults, and found that 500mg administered twice daily (1g/day of encapsulated extract) over a 3 week period did not significantly increase BM frequency when compared to a matched placebo. No significant changes in stool type or associated Bristol stool measures were also observed over 3 weeks, nor was any significant difference found in GI symptoms or QoL immediately pre- and post-treatment. Compliance to treatment was excellent in this trial, and analysis of PP and ITT populations had no effect on these findings. The lack of effect may be unexpected in light of prior evidence demonstrating clear laxation benefits of freeze dried green kiwfruit powder in a similar group of healthy individuals with constipation,[9] which supported earlier reports for fresh whole green kiwifruit.[7] Laxation effects of fresh kiwifruit have also been reported in patients with IBS and constipation,[8] and older or elderly adults.[6] Whilst laxation is not improved in all participants, literature to date shows that most of those who maintain supplementation with fresh fruit over 3-4 weeks report enhanced faecal regularity.[6] There are a number of hypothesised mechanisms for enhanced laxation effects. These include the action of actinidin, a proteolytic enzyme within the class of thiol-proteases which may act both on the fore and hind gut,[13,18] whereby peptide products of protein hydrolysis stimulate large bowel receptors, increasing GI motility and speed of transit through the colon; shown to

remain active in freeze dried kiwifruit extracts[14] assessed using an *in vitro* gastric digestion model;[12] the presence of both insoluble and soluble fibre with properties of the latter being high cell wall water-holding capacity and high viscosity when suspended in aqueous solution; and prebiotic compounds such as the oligosaccharide inulin and kiwifruit polyphenols. However, why this whole berryfruit may be effective for some participants and not others is not understood.

In our current trial we propose that the absence of a laxation effect in the test extract, as previously reported following supplementation with fresh whole kiwifruit, is likely the result of compositional differences between fresh whole fruit and a freeze dried extract.[6-8] It is notable however that a similar freeze dried kiwifruit powder (Kivia) was previously reported to enhance laxation in a similar healthy but constipated population.[9] In the study Udani and Bloom reported significant effects of high dose (5.5 g/day) supplementation with this commercial freeze-dried kiwifruit powder also obtained from green *Actinidia deliciosa,* on gut comfort and function. This was a placebo controlled study which supplemented constipated adults with a powder premixed with water into a beverage format, at a 5-fold higher dose by weight than in our current encapsulation trial (1 g/day). Little information on composition or activity of freeze dried Kivia powder is provided in the publication,[9] however review of the Kivia website[19] shows the composition as 'active ingredients': *Actinidia deliciosa* (kiwifruit) fruit powder (Zyactinase™) 1375mg, *Phaseolus vulgaris* (white bean) seed concentrated dry extract 45mg, equiv dry seed 540mg; plus additional fructose, *Malus x. domestica* (apple) fruit powder, anhydrous citric acid, *Citrus limon* (lemon) fruit powder, sucralose, chlorophyllin-copper complex, and nature-identical (NI) tropical powder flavour. We are unable to determine whether lower dose or simply compositional differences between our encapsulated freeze dried extract and this freeze dried powder explain the differential effects on laxation. Formulation of the encapsulated test extract in our current trial to include kiwifruit flesh, seeds and skin[14] resulted in high actinidin enzyme activity (~2-3 fold increase in *in vitro* protein digestion of beef, tofu and cow's milk), soluble fibre (320 mg/g) and prebiotic polyphenols (>30 mg/g) leading to a many-fold increase in growth of probiotics *Lactobacillus acidophilus* and *Bifidobacterium bifidum* when assessed by *in vitro* test systems, compared to an extract of flesh alone. Absence of published information for Kivia powder prevents direct comparison of these characteristics with our test extract. Whether premixing of Kivia powder in water prior to consumption, which may also have a differential effect on viscosity or other potentially important GI parameters,[20] rather than consuming as a dry ingredient, enhances its laxation effects is not known.

A second inadequately designed kiwifruit extract trial has also previously been conducted in Japan.[10] This was a non-randomised, unblinded, uncontrolled 4 week study where laxation effects were assessed in a group of elderly patients given encapsulated extracts comprising fresh kiwifruit freeze dried juice. Two capsules were self-administered 3 times daily up to a total of 6 capsules per day. Information on encapsulated dose (g/day) was not provided within the English abstract but the large number of daily capsules indicates a higher dose than our current study, although the composition of the extract clearly differed from our current trial since this was freezed dried juice rather than flesh and skin. The findings from this Japanese trial, which are unreliable due to the absence of blinding, placebo treatment, or control group, described a positive improvement in bowel habits compared to a 1 week pretreatment period.[10] It is important to note that in the absence of a placebo control our current study would also have wrongly concluded that freeze dried, encapsulated green kiwifruit extract improved laxation, with an increase in BM from ≤3/wk during screening to >4/wk at the end of the 3 week study. It was entry into a nutrition related clinical trial, with improvements in laxation on both active treatment and placebo arms, that was the cause of the improvement. An increase in BM frequency above pre-screen levels following enrolment into a nutrition intervention study was not entirely unexpected. Similar results were seen in the Udani and Bloom kiwifruit powder trial, with BM frequency increasing from 3/wk at pre-screen to >5/wk at the end of the 4 week intervention.[9] Psychological, dietary and lifestyle factors may all affect constipation and its associated symptoms. Administration of placebo treatments has long been known to alter subjective GI scores, with a recent open label trial even showing that prescription of an inert placebo without deception may significantly improved symptoms of IBS and constipation.[21] Similar effects have been seen with supportive patient-practioner aid in the absence of dietary or pharmaceutical treatment in IBS patients.[22] It is clear that rigorous controlled trials are necessary in order to interpret data from GI dietary interventions.

An alternate plant-derived treatment for constipation may be of considerable value, since laxatives and constipation medications may be high cost, and longterm have been reported to exhibit a variety of side-effects including ischemic colitis or even cardiovascular disease[23]. Whole fresh kiwifruit has been reported to have a gentle laxation effect[6-8] with possible other health benefits from its various nutrient components,[24] and an effective dried and encapsulated form is more convenient, less time consuming and a highly marketable alternative. Few individuals do report mild allergic response to kiwifruit, however through the selection and breeding of low allergenic cultivars, a novel product suitable for a wider

range of individuals may also be possible.[25] There is certainly an opportunity to obtain an optimised, encapsulated and natural product that suits a wider range of individuals suffering from functional bowel disorders, should efficacy be established.

Conclusions

In our current study, there was no improvement in BM frequency, defecation related scores, GI symptoms or QoL following 3 week administration of 1 g/day, freeze dried, encapsulated, whole kiwifruit (flesh, seeds, skin) extract, despite excellent compliance to treatment. Positive effects on laxation have been previously shown through supplementation with fresh green kiwifruit,[6-8] as well as freeze dried kiwifruit powder when given at higher dose of 5.5 g/day.[9] Efficacy data from an inadequately designed Japanese extract trial[10] should be disregarded. Absence of laxation effects in our current study are likely due to differences in composition from both fresh fruit[6-8] and Kivia powder,[9] whilst questions concerning efficacious dose of encapsulated extract also cannot be ruled out. These results may warrant further well designed studies to investigate the effect of higher dose encapsulated green kiwifruit extract for laxation and associated GI effects.

ACKNOWLEDGEMENTS

NZ Extracts Ltd, New Zealand provided the funding and the extracts for this trial. We would like to thank the participants in this trial. We also thank Dr Robin McGregor for his assistance during the study.

DISCLOSURES AND CONFLICT OF INTEREST

SDP holds the Fonterra Chair in Human Nutrition at the University of Auckland. SK and BKS were funded by NZ Extracts Ltd, Marlborough, New Zealand. WP has no conflict to declare.

REFERENCES

1. Schmidt FMQ, De Gouveia Santos VLC. Prevalence of constipation in the general adult population: An integrative review. J Wound Ostomy Continence Nurs. 2014;41:70-6.
2. Shaheen NJ, Hansen RA, Morgan DR, Gangarosa LM, Ringel Y, Thiny MT, Russo MW, Sandler RS. The burden of gastrointestinal and liver diseases, 2006. Am J Gastroenterol. 2006;101:2128-38.
3. Winge K, Rasmussen D, Werdelin LM. Constipation in neurological diseases. J Neurol Neurosurg Psychiatry. 2003;74:13-9.

4. Daulatzai MA. Chronic functional bowel syndrome enhances gut-brain axis dysfunction, neuroinflammation, cognitive impairment, and vulnerability to dementia. Neurochem Res. 2014:1-21.
5. Talley NJ. Definitions, epidemiology, and impact of chronic constipation. Rev gastroenterol di. 2004;4 Suppl 2:S3-10.
6. Rush EC, Patel M, Plank LD, Ferguson LR. Kiwifruit promotes laxation in the elderly. Asia Pac J Clin Nutr. 2002;11:164-8.
7. Chan AOO, Leung G, Tong T, Wong NYH. Increasing dietary fiber intake in terms of kiwifruit improves constipation in Chinese patients. World J Gastroenterol. 2007;13:4771-5.
8. Chang CC, Lin YT, Lu YT, Liu YS, Liu JF. Kiwifruit improves bowel function in patients with irritable bowel syndrome with constipation. Asia Pac J Clin Nutr. 2010;19:451-7.
9. Udani JK, Bloom DW. Effects of kivia powder on gut health in patients with occasional constipation: A randomized, double-blind, placebo-controlled study. Nutr J. 2013;12:78
10. Uebaba K, Urata T, Suzuki N, Arai T, Strong J, Oono S, Hayashi H. Mild laxative and QOL-improving effects of kiwi fruit extract in the elderly. Jpn J Complement Altern Med. 2009;6:97-103.
11. Harris PJ, Ferguson LR. Dietary fibre: its composition and role in protection against colorectal cancer. Mutat Res-Fund Mol M. 1993;290:97-110.
12. Kaur L, Rutherfurd SM, Moughan PJ, Drummond L, Boland MJ. Actinidin enhances gastric protein digestion as assessed using an in vitro gastric digestion model. J Agric Food Chem 2010;28:5068-73.
13. Rutherfurd SM, Montoya CA, Zou ML, Moughan PJ, Drummond LN, Boland MJ. Effect of actinidin from kiwifruit (*Actinidia deliciosa* cv. Hayward) on the digestion of food proteins determined in the growing rat. Food Chem. 2011;129:1681-9.
14. www.nzextracts.com. Digesten: Digestive health. accessed 23 September 2014.
15. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroentero. 1997;32:920-4.
16. Svedlund J, Sjodin I, Dotevall G. GSRS - A clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Digest Dis Sci. 1988;33:129-34.
17. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE *et al*. Cross-validation of item selection and scoring for the SF-12 health survey in nine countries: results from the IQOLA project. J Clin Epidemiol. 1998;51:1171-8.
18. Jahan-Mihan A, Luhovyy BL, El Khoury D, Anderson GH. Dietary proteins as determinants of metabolic and physiologic functions of the gastrointestinal tract. Nutrients 2011;3:574-603.
19. www.kivia.com.au/Our-Products/Kivia-Powder. accessed 23 September 2014.
20. Marlett JA, Kajs TM, Fischer MH. An unfermented gel component of psyllium seed husk promotes laxation as a lubricant in humans. Am J Clin Nutr 2000;72:784-9.
21. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, Kowalczykowski M, Miller FG, Kirsch I, Lembo AI. Placebos without deception: A randomized controlled trial in irritable bowel syndrome. PLoS ONE 2010;5:e15591

22. Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE *et al*. Components of placebo effect: Randomised controlled trial in patients with irritable bowel syndrome. BMJ. 2008;336:999-1003.
23. Hammerle CW, Surawicz CM. Updates on treatment of irritable bowel syndrome. World J Gastroenterol. 2008;14:2639-49.
24. Singletary K. Kiwifruit: Overview of potential health benefits. Nutr Today. 2012;47:133-147.
25. Bublin M. Kiwifruit allergies. Adv Food Nutr Res. 2013;68:321-40.

Table 1. Characteristics of participants at baseline

	All, ITT				Completers, PP			
	N	Mean SD	Min	Max	N	Mean SD	Min	Max
Age (y)	40	40.8 13.2	23	63	32	41.0 12.5	23	59
Height (m)	40	1.7 0.1	1.5	1.9	32	1.7 0.1	1.5	1.9
Weight (kg)	40	68.3 14.7	48	112	32	67.4 15.7	48	112
BMI (kg/m^2)	40	24.6 4.6	18	37	32	24.3 4.6	18	37
Baseline BM (freq/week)	40	2.38 0.12	1	3	32	2.31 0.14	1	3
Group	N	%			N	%		
Gender								
Female	37	93			29	91		
Male	3	7			3	9		
Ethnicity								
Asian[$]	13	32			13	41		
European/other	26	65			19	59		
Māori	1	3			0	0		

ITT: intention to treat; PP, per protocol; N: number of participants; %: percentage of participants; BMI: body mass index; BM: bowel movement; [$]comprising Chinese, Filipino, Indian, Korean, South East Asian. 40 participants were randomised into the trial (ITT population) of which 32 completed the trial with >80% compliance to treatment (PP population).

Table 2. Composition of encapsulated green kiwifruit extract

Kiwifruit extract	Specification	Notes
Total encapsulated extract	1,000 mg	administered as 2 times 500mg doses
Phenolic compounds	>30 mg/g	from skin
Soluble fibre	320 mg/g	from skin
Actinidin, protease enzyme	+ve	EC 3.4.22.14; from flesh

Kiwifruit extract comprising freeze dried powder derived from flesh, skin and seeds of the green kiwifruit *Actinidia deliciosa* var. Hayward[14]; +ve, estimates of *in vitro* protein digestion of beef, tofu and cow's milk increased 2-3 fold after 30 minutes in the presence of extract plus pepsin at pH2 and at 37^{o}C, versus pepsin control; EC 3.4.22.14, enzyme nomenclature.

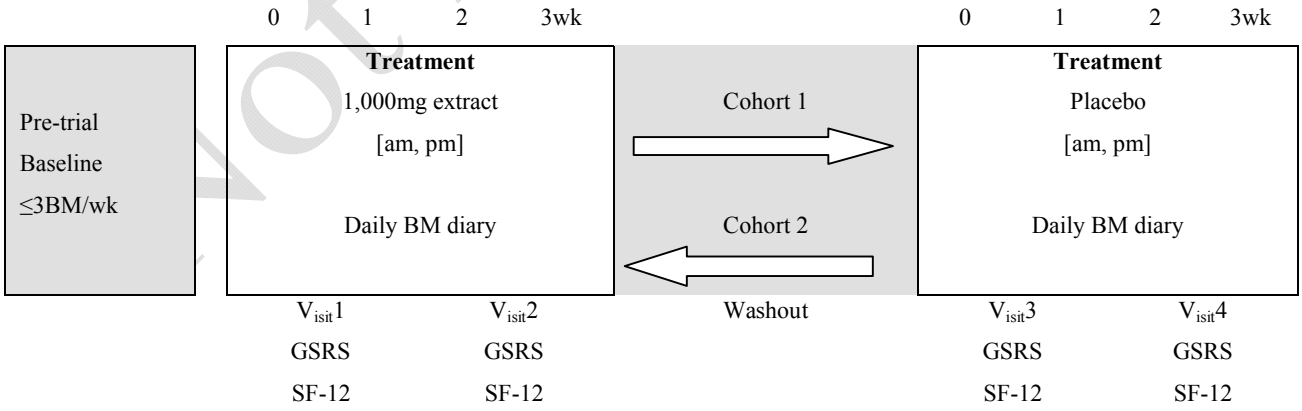

Figure 1. Study protocol, where 40 participants were randomised to 1,000mg/day encapsulated kiwifruit extract and placebo using a cross-over design. Recruitment criteria included constipation as defined by ≤3 bowel movements (BM) per week. wk, week; GSRS, gastrointestinal symptoms rating scale; SF-12, short-form health questionnaire

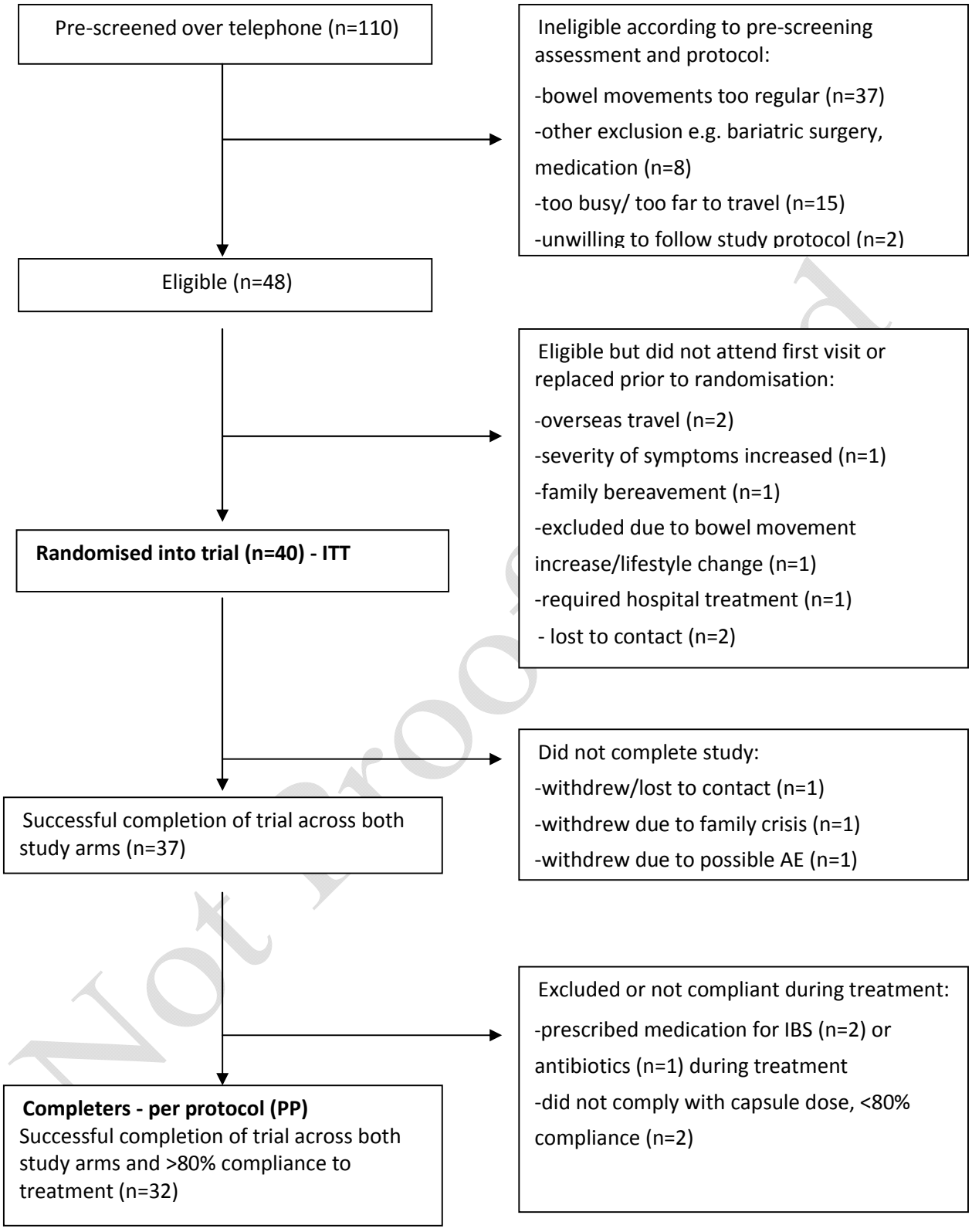

Figure 2. Participant flow chart.

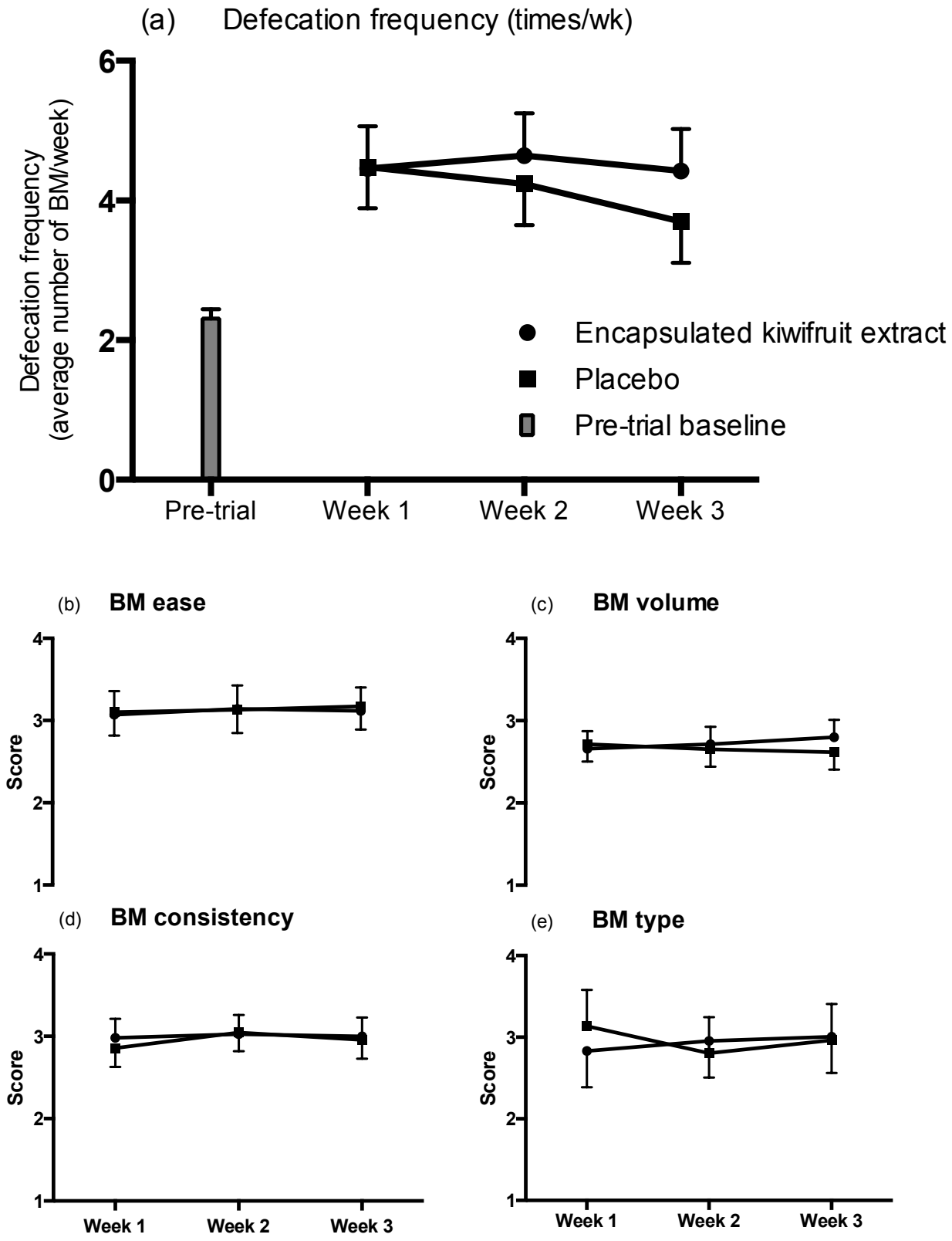

Figure 3. Change in bowel habits in participants with constipation assessed by faecal diary and Bristol stool scores: (a) BM or defecation frequency, with pre-trial baseline presented as a histogram (inclusion criteria ≤3 BM/wk); (b) BM ease; (c) BM volume; (d) BM consistency; (e) BM type. BM, bowel motion. Data presented from the per protocol (PP) population, as least-square means ± SE.

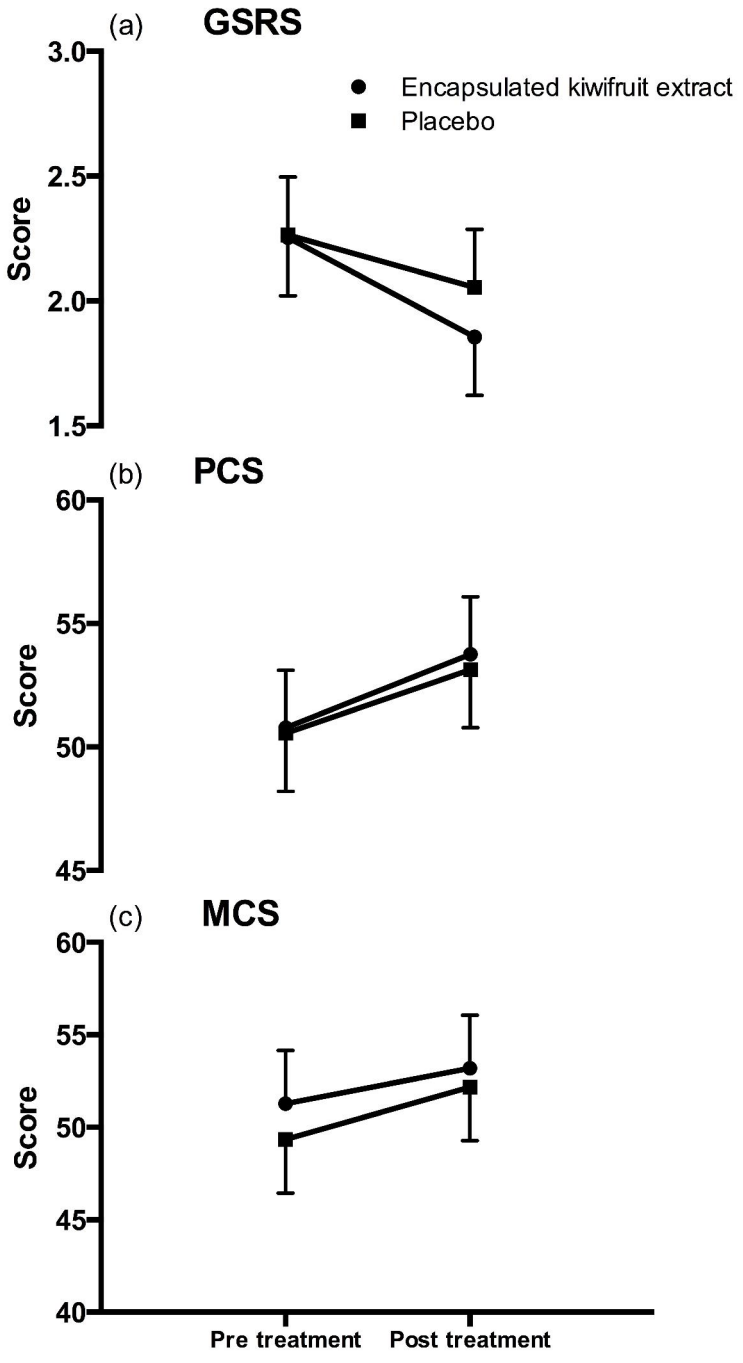

Figure 4. Gastrointestinal symptoms rating scale (GSRS) and quality of life (QoL, short-form health questionnaire, SF-12) measurement pre and post treatment: (a) GSRS total score; (b) SF-12 physical component score (PCS); (c) SF-12 mental component score (MCS). Data presented from the per protocol (PP) population, as least-square means ± SE.