future pharmacology

MDPI

Systematic Review

Kiwifruit (*Actinidia* spp.) Dietary Consumption for Constipation: A Systematic Review and Meta-Analysis

Michele Antonelli [1,*] and Davide Donelli [2]

[1] Public Health Department, AUSL-IRCCS di Reggio Emilia, 42122 Reggio Emilia, Italy
[2] Department of Medicine and Surgery, University of Parma, 43121 Parma, Italy; donelli.davide@gmail.com
* Correspondence: michele.antonelli@ausl.re.it

Abstract: The aim of this systematic review is to understand if kiwifruit dietary consumption can effectively improve constipation and intestinal function. PubMed, EMBASE, and Cochrane Library were systematically searched for relevant studies from inception up to September 2021. After database search, nine clinical studies were considered eligible for inclusion. Most trials were characterised by a limited number of study participants (median: 20, min: 11, max: 79) and had a cross-over design. On average, study participants ate from two to four kiwifruits a day for a period varying from three days to four weeks. Included trials almost exclusively involved young or middle-aged adults with a high female-to-male ratio, whereas direct evidence for elderly people (>65 years old) is scant. Moderate quality evidence indicated that kiwifruit dietary consumption can improve complete bowel movements per week and decrease stool consistency in both healthy subjects and patients with constipation due to irritable bowel syndrome, probably owing to the fruit fibre and water content. Kiwifruit dietary consumption can also have beneficial effects beyond intestinal motility, such as a mild anti-inflammatory and antioxidant effect on the gut barrier, due to a combined activity of all its nutrients (enzymes, vitamins, minerals). When only patients affected by constipation were considered, kiwifruit consumption was likely associated with a short-term significant increase in defecation frequency but not always with significant changes in stool consistency. These results were also supported by studies characterised by the highest methodological quality and confirmed by the meta-analysis about the effects of kiwifruit-based interventions on defecation frequency (g = 0.576; 95% CI: (0.174; 0.978); p = 0.012). Further investigations on the topic are recommended to strengthen the consistency of current evidence with larger trials.

Keywords: kiwifruit; *Actinidia deliciosa*; constipation; nutrition; diet; review

Citation: Antonelli, M.; Donelli, D. Kiwifruit (*Actinidia* spp.) Dietary Consumption for Constipation: A Systematic Review and Meta-Analysis. *Future Pharmacol.* **2021**, *1*, 27–40. https://doi.org/10.3390/futurepharmacol1010003

Academic Editor: Fabrizio Schifano

Received: 29 September 2021
Accepted: 2 November 2021
Published: 4 November 2021

1. Introduction

1.1. Kiwifruit Species and Their Nutritional Characteristics

Actinidia is a genus of woody plants with a shrub- or vine-like appearance that originate from Asia and are well known for ornamental uses and food production [1]. The fruit has thin skin and is characterised by juicy flesh and edible seeds. Green (*Actinidia deliciosa*), yellow (*A. chinensis*), red and purple (*A. melanandra* and *A. arguta* var. *purpurea*) kiwifruits are the most common species available in the food market, and they partially differ in terms of both organoleptic properties and micronutrient content. For example, green kiwifruit has a higher phenolic content, while red kiwifruit is usually richer in anthocyanins, and yellow kiwifruit has more vitamin C than the other types [2,3]. According to data reported by the US Department of Agriculture, 100 g of raw green kiwifruit can provide almost 84 g of water, a little more than 1.0 g of proteins, less than 0.5 g of lipids, and around 13.0 g of carbohydrates [4]. Kiwifruits can also be a good source of fibre, minerals, and vitamins (Table 1).

Table 1. Average composition of yellow and green kiwifruit.

Components of Kiwifruit	Yellow Kiwifruit			Green Kiwifruit		
	Average Amount (Per 100 g of Product)	% DRI *-Males	% DRI *-Females	Average Amount (Per 100 g of Product)	% DRI *-Males	% DRI *-Females
Water	82.4 g	2%	3%	83.9 g	2%	3%
Proteins	1.02 g	2%	2%	1.06 g	2%	2%
Lipids	0.28 g	<1%	<1%	0.44 g	<1%	1%
Carbohydrates	15.8 g	12%	12%	12.0–14.0 g	10%	10%
Fiber	1.4 g	4%	6%	3.0 g	8%	12%
Calcium	17.0 mg	2%	2%	35.0 mg	4%	4%
Magnesium	12.0 mg	3%	4%	15.7 mg	4%	5%
Potassium	315.0 mg	10%	13%	198.0 mg	6%	8%
Beta-carotene	1.0 µg	<1%	<1%	52.0 µg	6%	7%
Vitamin C	161.3 mg	179%	216%	74.7 mg	83%	100%
Vitamin K	6.1 µg	5%	7%	40.3 µg	34%	45%

Source: 'FoodData Central' database issued by the US Department of Agriculture and available at: https://fdc.nal.usda.gov/fdc-app.html#/food-details/327046/nutrients (accessed on 26 October 2021). Nutritional characteristics of yellow kiwifruit were provided by a review authored by Xirui He et al. [5]. Values reported in Table 1 are expressed per 100 g of product and, on average, a green kiwifruit has an approximate weight of 72 g [6]. * DRI = dietary reference intakes: recommended dietary allowances and adequate daily intakes (percentage over the total for male and female healthy adults). Source: https://www.ncbi.nlm.nih.gov/books/NBK56068/ (accessed on 26 October 2021).

1.2. Constipation and Its Causes

Constipation is a health condition characterised by infrequent defecation (less than three times a week) and/or hard stools [7]. In high-income countries, it is estimated that the prevalence of constipation is quite high, probably affecting up to 27% of the entire population, with some gender- and age-related differences (constipation is more common in female subjects and elderly individuals) [8]. Common lifestyle causes of constipation are high-fat diets, poor intake of dietary fibre, insufficient hydration, and sedentarism [9]. When associated with irritable bowel syndrome (IBS), chronic constipation seems to have a multifactorial origin, probably arising from a combination of individual predisposition, altered intestinal microbiota, as well as impaired neuroimmune and enteric functions [10]. The most frequent pathological causes of constipation are intestinal disorders characterised by mechanical obstruction or reduced enteric functionality, neurologic problems, depression, hypothyroidism, diabetes mellitus, uraemia, and some electrolyte imbalances (hypercalcemia, hypokalaemia, hypomagnesemia) [11]. Although the specific aetiology of chronic constipation may be quite heterogeneous, the most frequent causes can be found in a combination of individual predispositions due to age and/or gender, functional digestive conditions sometimes associated with abnormal anatomic features such as dolichocolon, psychophysical stress, and unhealthy lifestyle habits [12].

1.3. A First-Line Clinical Approach to Constipation

Nutritional and lifestyle changes, along with probiotics and supplements, represent a first-line approach to improve chronic constipation, especially if characterised by mild severity and benign/functional aetiology [13]. Along with apples and prunes, kiwifruit (*Actinidia* spp.) consumption is often traditionally recommended to provide relief from intestinal constipation and to promote laxation [10,14]. Clinical studies with kiwifruit-derived dietary supplements have recently suggested their role as complementary remedies against occasional or moderate constipation in otherwise healthy adults [15–18]. Laboratory experiments with mice or pig models and literature reviews about foods with laxative properties have included kiwifruit as a potential candidate for this therapeutic purpose [19–21]. According to the European Food Safety Authority (EFSA) Panel on Nutrition, Novel Foods, and Food Allergens, 'green kiwifruit (var. Hayward) can contribute to the maintenance of normal defecation' is a health claim sufficiently substantiated by mechanistic and clinical evidence [22]. Therefore, in recent years, considering both population ageing and advances in nutritional sciences, increasing attention has been paid by clinicians and the scientific community to non-pharmacological treatments of chronic constipation, especially to any

integrative approach capable of improving intestinal functions and motility without common side effects of laxative drugs, which are reported to be quite overused among elderly subjects and patients with functional digestive disorders [23].

1.4. Research Objectives

The aim of this review is to understand if kiwifruit consumption can improve constipation and intestinal function on the basis of existing clinical evidence.

2. Methods

2.1. Eligibility Criteria

This research was designed as a systematic literature review and its results were reported in accordance with the PRISMA statement [24]. The review protocol was registered in the Open Science Framework (OSF) under the following DOI: 10.17605/OSF.IO/4QBXH (link: https://osf.io/4qbxh, accessed on 1 November 2021). The PRISMA checklist is available for consultation in the Supplementary Materials.

Relevant clinical studies assessing the efficacy of kiwifruit consumption for constipation were considered for inclusion in this review. No publication date or language restrictions were enacted. Studies had to be published in peer-reviewed journals as original research articles to be eligible for inclusion, while conference proceedings and congress abstracts were excluded from the main search and only considered for discussing the topic more comprehensively. The following PICOS criteria were applied for article inclusion in the qualitative synthesis:

- **P (population)**: patients suffering from chronic constipation (any cause of benign origin). Studies involving healthy participants were included all the same, provided that they reported relevant outcomes;
- **I (intervention)**: kiwifruit consumption, preferably peeled (as customary in common dietary habits). Studies with kiwifruit-derived dietary supplements were excluded from the main search but still mentioned in the 'Introduction' Section for better comprehensiveness;
- **C (comparison)**: any type, including no control;
- **O (outcomes)**: bowel movements per day or week and stool consistency (preferably assessed with the Bristol score);
- **S (study design)**: clinical studies, either controlled trials or pre–post studies. In vitro and in vivo laboratory experiments were excluded.

2.2. Information Sources

PubMed, EMBASE, and Cochrane Library were systematically screened for relevant studies from inception up to September 2021.

2.3. Search Strategy

PubMed: (Actinidia[Title/Abstract] OR kiwifruit[Title/Abstract] OR kiwi[Title/Abstract] OR 'Chinese gooseberry'[Title/Abstract]) AND (constipation[Title/Abstract] OR bowel[Title/Abstract] OR intestin*[Title/Abstract] OR enteric[Title/Abstract] OR stool[Title/Abstract] OR abdominal[Title/Abstract] OR abdomen[Title/Abstract]).

EMBASE: (actinidia:ti,ab,kw OR kiwifruit:ti,ab,kw OR kiwi:ti,ab,kw OR 'chinese gooseberry':ti,ab,kw) AND (constipation:ti,ab,kw OR intestinal:ti,ab,kw OR enteric:ti,ab,kw OR bowel:ti,ab,kw).

Cochrane Library: '*kiwifruit*' in Title Abstract Keyword AND '*constipation*' in Title Abstract Keyword-(any word variations were searched).

No database filters were applied to keep the search strategy as wide as possible.

2.4. Selection Process

One investigator (M.A.) screened all the items retrieved after database search by their title and abstract. The other investigator (D.D.) performed a double check on articles eligible for a full-text assessment.

2.5. Data Collection Process

One investigator (M.A.) manually extracted data from studies eligible for inclusion with an Excel spreadsheet. The other investigator (D.D.) randomly performed a double check to ensure data integrity.

2.6. Data Items and Effect Measures

The most important data items extracted from studies included in the review were the patients' characteristics, the specific study design, any relevant details of intervention and control, as well as gastrointestinal outcome measures regarding defecation frequency and stool consistency (mean differences).

2.7. Study Risk of Bias Assessment

Controlled trials eligible for inclusion were evaluated with the help of the Jadad score [25]. Each study was assigned an overall number ranging from −1 to 5 on the basis of its methodological quality: trials scoring 3 or more were considered of high quality, whereas studies characterised by a lesser score were judged as of low quality [26]. Even though the Jadad score criteria strictly require high-quality trials to be double-blinded, a single-blind design was considered as sufficiently sound from a methodological point of view, because of the actual impossibility to fully conceal a dietary intervention such as kiwifruit consumption. The risk-of-bias assessment was used to inform the review discussion.

2.8. Synthesis Methods

First, data were qualitatively synthesised and critically discussed. Then, it was decided to perform a meta-analysis of available study results. The following PICOS criteria were applied for article inclusion in the quantitative synthesis:

- **P (population)**: patients suffering from chronic constipation or healthy participants (only per-protocol and no-intention-to-treat study populations were considered);
- **I (intervention)**: kiwifruit dietary consumption;
- **C (comparison)**: kiwifruit-free diet/placebo pills/control drinks or sources of fibre intake other than kiwifruits (these two study categories were kept separated in a dedicated subgroup analysis);
- **O (outcomes)**: defecation frequency or bowel movements per time period (day or week). It was decided not to meta-analyse data about stool consistency because of heterogeneous outcome measures;
- **S (study design)**: randomised controlled trials.

Means and standard deviations were extracted from trials included in the quantitative synthesis. When missing, standard deviations were imputed from standard errors, as per recommendations issued by the Cochrane Collaboration [27]. Standardised Mean Difference (SMD) was used as a summary statistic in the meta-analysis, and a random-effects model was adopted to better account for heterogeneity among studies. The Hartung–Knapp–Sidik–Jonkman method was chosen since it outperforms the standard DerSimonian–Laird method [28]. Hedges' g was selected as a measure of effect size and statistical heterogeneity was quantified with I^2. The threshold for statistical significance was set at $p < 0.05$. A subgroup analysis was performed to explore any significant changes in the effect size of intervention when compared with different control types. The entire analysis was performed with R, a software for statistical computing, and its results were graphically displayed with a forest plot.

2.9. Reporting Bias Assessment

In case of missing information, it was planned to contact study authors by email. However, there was no need to resort to this method for collecting essential data.

2.10. Certainty Assessment

The certainty in the body of evidence regarding the efficacy of intervention for constipation was evaluated with the internationally recognised four-tier (A, B, C, D) grade system [29].

3. Results

3.1. Qualitative Results

In total, 229 articles (PubMed: 85; EMBASE: 106; Cochrane Library: 38) were retrieved, and eight of them, describing nine clinical studies, were considered eligible for inclusion in this review [30–37]. The PRISMA flow diagram summarising the article selection process is displayed in Figure 1. Three studies that initially appeared to fulfil the PICOS criteria were then excluded because they described laboratory experiments rather than clinical trials [19–21]. The essential characteristics and results of included studies are summarised in Table 2.

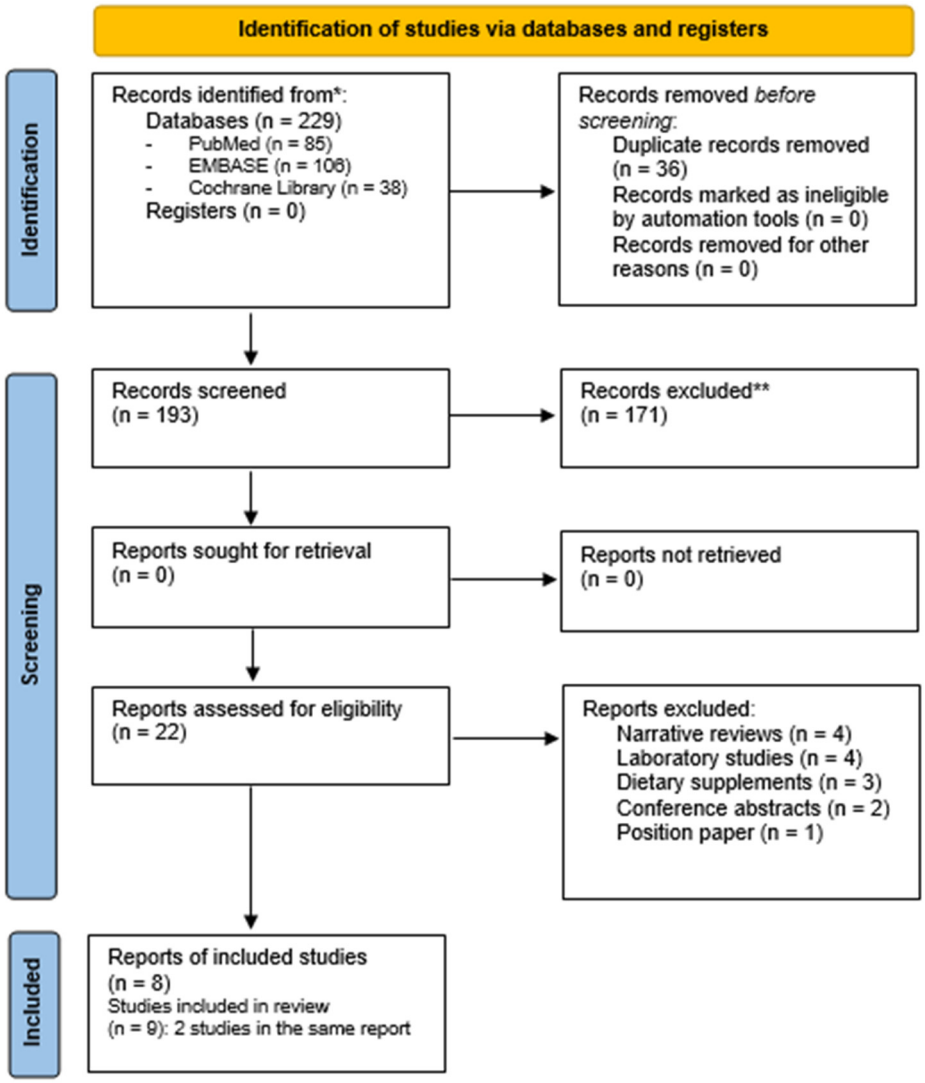

Figure 1. Summary flow diagram representing the article selection process and prepared in accordance with the PRISMA 2020 guidelines [24].

Table 2. Summary and quality of evidence from included studies about kiwifruit consumption for constipation.

Study ID	Population	Study Participants' Diseases §	Lifestyle Habits Prescribed during the Study Period	Drugs Allowed	Drugs Excluded	Differences between Groups at Baseline	Intervention	Comparison	Outcomes (Mean ± SD Unless Otherwise Indicated)	Study Design	Jadad Score	Reference
A	11 healthy subjects (8F/3M), age range: 18–23	None (absence of gastrointestinal symptoms)	Low-flatulogenic diet excluding legumes, vegetables, garlic, onion, cucumber, nuts, cereals, whole-meal bread, and fizzy drinks	–	–	No (cross-over design)	2 peeled GKs every day for 2 weeks	No intervention	BMs/day (int. vs. con.) (mean ± SE): 1.8 ± 0.1 vs. 1.5 ± 0.1 (*) SC (int. vs. con.) (mean ± SE): 3.3 ± 0.2 vs. 2.8 ± 0.1 (*)	Cross-over RCT (2-week washout period)	4	[30]
B	19 healthy subjects + 19 patients with IBS-C (27F/11M), age range: 22–65	None or IBS-C diagnosed according to the Rome III criteria (patients with severe or unstable health conditions were excluded)	Fibre supplements-free diet and no laxatives for at least 2 weeks before starting the study and during the entire trial period	Antidepressants, opioids, anti-inflammatory drugs, anti-diabetic agents	Others, including laxatives	No (cross-over design)	3 peeled YKs every day for 4 weeks	3 unpeeled YKs every day for 4 weeks	-Healthy subjects (peeled YKs): CBMs/week (int.): from 9.7 ± 5.6 to 9.7 ± 5.6 SC (int.): from 3.3 ± 0.7 to 4.0 ± 1.0 (*) -Patients with IBS-C (peeled YKs): CBMs/week (int.): from 6.7 ± 4.8 to 8.7 ± 6.9 SC (int.): from 3.5 ± 1.0 to 3.9 ± 1.0	Cross-over RCT (4-week washout period)	2	[31]
C	32 patients with constipation (32F/0M), age range: 21–65	Mild constipation (patients with severe or unstable health conditions were excluded)				No (cross-over design)	3 peeled YKs every day for 4 weeks	Dietary fibre (Metamucil®): 5 g/day for 4 weeks	CBMs/week (int.): from 4.2 ± 3.1 to 6.9 ± 4.3 (*) CBMs/week (int. vs. con.): 6.9 ± 4.3 vs. 5.5 ± 4.2 SC (int.): from 3.24 ± 1.13 to 4.15 ± 1.26 (*) SC (int. vs. con.): 4.15 ± 1.26 vs. 3.52 ± 1.27 (*)	Cross-over RCT (4-week washout period)	4	[32]
D	14 healthy subjects (6F/8M), age range: 21–33	None (patients with gastrointestinal disorders, recent surgery, or contraindications to MRI scans were excluded)	Abstinence from caffeine, alcohol, and strenuous exercise for at least 48 h prior to outcome assessment	–	Medications affecting intestinal motility	No (cross-over design)	4 peeled GKs every day for 3 days	A control drink once a day for 3 days	DF/day (int. vs. con.): 1.46 ± 0.66 vs. 1.14 ± 0.46 (*) SC (int. vs. con.): significantly softer stools in the GK arm (*)-results only graphically displayed.	Cross-over RCT (15-day washout period)	3	[33]

Table 2. *Cont.*

Study ID	Population	Study Participants' Diseases [§]	Lifestyle Habits Prescribed during the Study Period	Drugs Allowed	Drugs Excluded	Differences between Groups at Baseline	Intervention	Comparison	Outcomes (Mean ± SD Unless Otherwise Indicated)	Study Design	Jadad Score	Reference
E	20 healthy subjects + 33 patients with constipation (42F/11M), age: 49.9 ± 12.0	None or chronic constipation lasting for at least 6 (patients with unstable or severe health conditions were excluded, along with pregnant or breastfeeding women, and subjects unable to understand Chinese)	Average dietary pattern (China) and no changes in physical activity levels during the study period	Laxatives (their use among patients was recorded)	–	Yes (case–control study)	2 peeled GKs every day for 4 weeks administered to patients with constipation	The same intervention in healthy subjects	-Healthy subjects: CBMs/week (int.): from 6.5 ± 1.6 to 7.1 ± 2.2 (*) SC (int.): from 4.0 ± 0.9 to 4.2 ± 0.8 -Patients with constipation: CBMs/week (int.): from 2.2 ± 2.6 to 4.4 ± 4.6 (*) SC (int.): from 3.1 ± 1.9 to 3.3 ± 1.2	Case control study	–	[34]
F	79 patients with chronic constipation (69F/10M), age range: 18–76	IBS-C diagnosed according to the Rome IV criteria with chronic constipation lasting for at least 3 months (patients with unstable or severe health conditions were excluded, along with pregnant women and subjects taking probiotics or antibiotics for any reason)	Avoid any changes in dietary habits and other sources of kiwifruit, prunes, or psyllium	–	Probiotics, antibiotics, opioids, laxative drugs, and supplements	No, except for the abdominal pain score (higher in the kiwifruit group)	2 peeled GKs every day for 4 weeks (n = 30)	Con. 1: 100 g prunes every day (n = 26) Con. 2: 12 g psyllium every day (n = 23) for 4 weeks	-CBMs/week: no significant difference between groups (mean). Int.: from 1.2 to 2.2 (*) Con. 1: from 1.0 to 3.7 (*) Con. 2: from 1.1 to 2.8 (*) -SC: no significant difference between groups (mean). Int.: from 3.2 to 3.6 (*) Con. 1: from 3.1 to 3.6 (*) Con. 2: from 2.9 to 3.1	RCT	3	[35]
G	16 healthy subjects + 54 patients with IBS-C (65F/5M), mean age: 20–30	None or IBS-C diagnosed according to the Rome III criteria (patients using laxatives or who underwent recent surgery were excluded)	Average dietary pattern (Taiwan) and no changes in physical activity levels during the study period	–	Laxatives, dietary supplements, and fortified foods	Yes (defecation frequency was lower among patients with IBS if compared with healthy controls)	2 peeled GKs every day for 4 weeks	2 placebo capsules every day for 4 weeks	DF was significantly higher in the IBS-C int. group compared to the IBS-C con. group after 1 week of treatment (*). However, DF was still significantly lower in the IBS-C int. group compared to healthy controls after 2 weeks of treatment. No significant difference between groups was observed in faecal volume changes.	Placebo-controlled trial	1	[36]

Table 2. *Cont.*

Study ID	Population	Study Participants' Diseases [§]	Lifestyle Habits Prescribed during the Study Period	Drugs Allowed	Drugs Excluded	Differences between Groups at Baseline	Intervention	Comparison	Outcomes (Mean ± SD Unless Otherwise Indicated)	Study Design	Jadad Score	Reference
H	48 healthy subjects (30F/18M), age: 33 ± 1	None	Average dietary pattern (New Zealand) and no changes in physical activity levels during the study period	–	–	No (cross-over design)	1 GK for every 30 kg of body weight on a daily basis for 3 weeks	A kiwifruit-free diet for 3 weeks	Intervention significantly decreased SC (*) without significant variations in CBMs (mean ± SE). Pre-cross-over period (int. vs. con.): DF: 1.40 ± 0.04 vs. 1.18 ± 0.04 SC: 2.34 ± 0.03 vs. 2.90 ± 0.03 Post-cross-over period (int. vs. con.): DF: 1.26 ± 0.04 vs. 1.29 ± 0.03 SC: 2.84 ± 0.03 vs. 2.59 ± 0.03	Cross-over RCT (no washout period)	2	[37]
I	38 healthy subjects (25F/13M), age > 60 years old	None (patients with severe health conditions or unable to provide reliable feedback due to marked cognitive decline were excluded)		Laxatives (their use among patients was recorded)	–	No (cross-over design)			Intervention significantly increased DF and decreased SC (*) (mean ± SE). Pre-cross-over period (int. vs. con.): DF: 1.24 ± 0.11 vs. 1.17 ± 0.07 SC: 2.59 ± 0.10 vs. 2.69 ± 0.09 Post-cross-over period (int. vs. con.): DF: 1.24 ± 0.11 vs. 1.43 ± 0.11 SC: 2.83 ± 0.08 vs. 2.28 ± 0.11	Cross-over RCT (no washout period)		

* Significant difference ($p < 0.05$). [§] Intolerance or allergy to kiwifruits was an obvious exclusion in all studies. Legends: BMs = bowel movements. CBM = complete bowel movements. Con. = control. DF = defecation frequency. F = female participants. GK = green kiwifruit. IBS-C = irritable bowel syndrome–constipation. Int. = intervention. M = male participants. MRI = magnetic resonance imaging. RCT = randomised controlled trial. SC = stool consistency (Bristol score). YK = yellow kiwifruit.

The number of study participants was quite limited within included studies and ranged from a minimum of 11 to a maximum of 79 (median: 20). The number of female subjects ($n = 304$) exceeded that of male individuals ($n = 79$) nearly fourfold. Nutritional and lifestyle habits of study participants, along with potential confounding factors (medicinal drugs and dietary supplements, criteria for enrolment and exclusion of patients, significant differences between groups at baseline), are also reported in Table 2. In particular, laxatives were not allowed in trials B, C, D, F, and G, whereas in the remaining studies these drugs were permitted, but their use was recorded in a diary. In two studies, a reduced laxative use over time was observed in the kiwifruit groups [34,37]. Study participants assigned to intervention groups were asked to consume two to four peeled kiwifruits every day for a period of time ranging from three days to four weeks, depending on specific experimental protocols. In two studies yellow kiwifruits were used [31,32], while in the other trials, only green kiwifruits were administered. Control groups were quite heterogeneous and included placebo pills, other sources of natural fibre, or no intervention, as described in Table 2. Study participants were healthy adults or subjects dealing with chronic constipation, mostly due to IBS. One study was specifically designed to study the effects of kiwifruit consumption in elderly subjects [37]. Most included trials were controlled interventional studies with a cross-over design. In seven out of nine studies, the intervention was associated with a significant increase in complete bowel movements or defecation frequency [30,32–37]; in seven out of nine studies, the intervention was associated with a significant decrease in stool consistency (see Tables 3 and 4 for further details) [30–33,35,37]. Studies A, C, D, and F were characterised by a good methodological quality (Jadad score ≥ 3), thus providing the highest level of available scientific evidence (Table 2). In general, potential sources of bias mostly arose from poor information about randomisation procedures and the impossibility to blind participants to study interventions. No major bias from missing or omitted results was identified.

Table 3. Summary of statistically significant ($p < 0.05$) study results in favour of kiwifruit-based interventions administered to healthy subjects.

Study ID	Population (*n*)	N of Fruits	Duration	Significant Change from Baseline within Intervention Groups		Significant Post-Test Difference between Groups (Int. vs. Con.)		Reference
				DF/CBMs	SC	DF/CBMs	SC	
A	11	2/day	2 weeks			Yes (*)	Yes (*)	[30]
B	19	3/day	4 weeks	No	Yes (*)			[31]
D	14	4/day	3 days			Yes (*)	Yes (*)	[33]
E	20	2/day	4 weeks	Yes (*)	No			[34]
H	48	2–3/day	3 weeks	No	Yes (*)			[37]
I	38			Yes (*)	Yes (*)			

* Significant difference ($p < 0.05$). Legends: CBM = complete bowel movements. Con. = control. DF = defecation frequency. Int. = intervention. SC = stool consistency (Bristol score).

3.2. Quantitative Results

Only five trials were included in the meta-analysis [30,32,33,36,37]. One study was excluded because of its design (case–control study) [34], another one because its control group did not match inclusion criteria (unpeeled kiwifruit consumption) [31], and the last one was ruled out from the meta-analysis since, apart from mean values, neither standard deviations nor standard errors were available [35]. Studies labelled as H and I were reported as different entries (H1, H2, I1, I2) because pre- (H1, I1) and post- (H2, I2) cross-over results were displayed separately in the original article, and therefore, they could only be considered different trials in our quantitative synthesis. The forest plot with study data, sub-group, and overall results are reported in Figure 2. The main result indicated that intervention can significantly increase defecation frequency (g = 0.576; 95% CI: (0.174;

0.978); $p = 0.012$). However, when compared with other sources of fibre, no significant difference was found. The level of statistical heterogeneity among the trials was quite significant ($I^2 = 51\%$). A meta-regression to quantitatively identify any potential moderators of the effect was not feasible because the number of trials was too low (a minimum of 10 studies is required according to widely accepted methodological standards).

Table 4. Summary of statistically significant ($p < 0.05$) study results in favour of kiwifruit-based interventions administered to patients with chronic constipation, mostly related to IBS.

Study ID	Population (*n*)	N of Fruits	Duration	Significant Change from Baseline within Intervention Groups		Significant Post-Test Difference between Groups (Int. vs. Con.)		Reference
				DF/CBMs	SC	DF/CBMs	SC	
B	19	3/day	4 weeks	No	No			[31]
C	32	3/day	4 weeks	Yes (*)	Yes (*)	No	Yes (*)	[32]
E	33	2/day	4 weeks	Yes (*)	No			[34]
F	79	2/day	4 weeks	Yes (*)	Yes (*)	No	No	[35]
G	54	2/day	4 weeks			Yes (*)	No	[36]

* Significant difference ($p < 0.05$). Legends: CBM = complete bowel movements. Con. = control. DF = defecation frequency. Int. = intervention. SC = stool consistency (Bristol score).

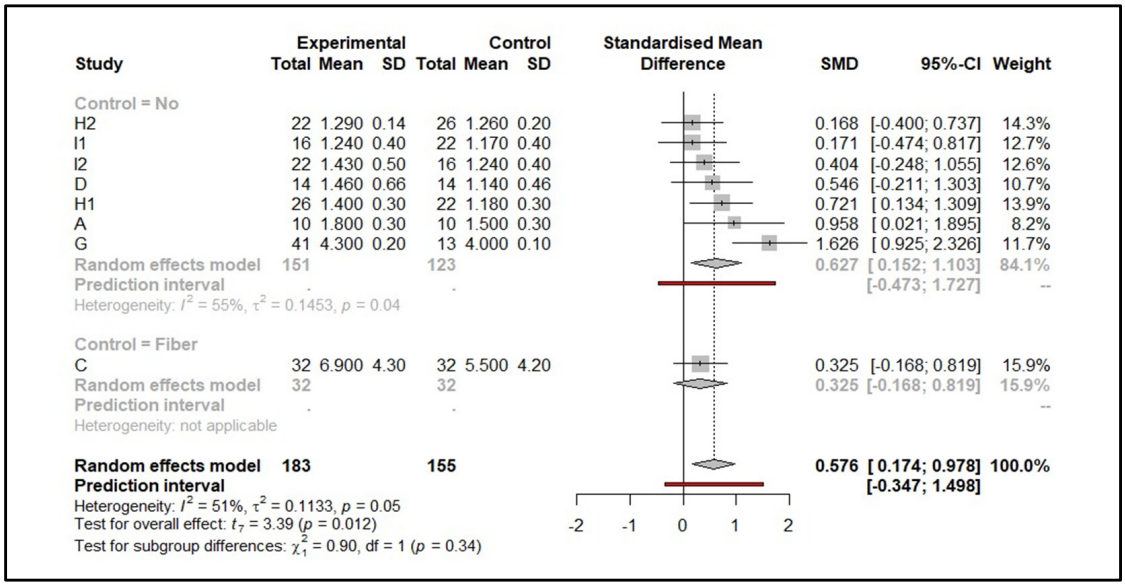

Figure 2. Meta-analysis of controlled trials about the effects of kiwifruit consumption on defecation frequency. Legends. Study A [30]; Study C [32]; Study D [33]; Studies H1, H2, I1, I2 [37]; SMD was adopted as a measure of effect size. Hedges' g was selected as a measure of effect size.

4. Discussion

4.1. A critical Overview of Qualitative–Quantitative Evidence

The cross-over design characterising the majority of included trials may weaken the strength of available evidence and lead to potential under- or over-estimation of the effects of intervention when the 'order' and 'carry-over' biases are not properly taken into account with adequately long wash-out periods [38]. In all but two cross-over trials (H and I) [37], the washout period lasted 2 or more weeks in order to avoid the carry-over effect, and study participants were asked not to introduce any significant lifestyle changes in that period. Trial protocols did not always account for any potential confounding factors, but, at least, laxative use was either prohibited or recorded, thus controlling the impact of these medications on study results (Table 2).

In most included studies, regardless of their experimental design, a significant pre–post improvement was detected in terms of either defecation frequency or stool consistency. When patients affected by constipation were considered, kiwifruit consumption was likely associated with a short-term significant increase in defecation frequency but not always with significant changes in stool consistency (Table 4). Positive results were found both in adult participants and in elderly ones [37]. Available data mostly referred to female subjects, as male individuals were quite underrepresented across included trials, but it should be considered that chronic constipation has a much higher prevalence among women [39], thus justifying these gender differences in enrolment criteria. Significant differences between groups in favour of intervention were reported when kiwifruit consumption was compared with placebo or a kiwifruit-free diet [30,36,37]. No significant differences were found between kiwifruit-based interventions and regular intake of other fibre sources such as psyllium or prunes, especially in patients with chronic constipation [35]. These results were also supported by studies characterised by the highest methodological quality [30,32,33,35] and confirmed by the meta-analysis, in which kiwifruit consumption determined a significant increase in defecation frequency, as observed with the intake of any other sources of fibre. In one study, stool consistency significantly decreased in the kiwifruit group when compared with the fibre group [32]: this may be due to other biochemical components of kiwifruits (water, vitamins, and minerals), which can positively influence gut health, hydration, and increase faecal volume. Results of two clinical trials briefly described in conference proceedings appeared in line with that stated above, thus underscoring once more that kiwifruit consumption can improve stool frequency in healthy volunteers and promote digestive functions in patients with constipation [40,41]. Available study results describe the effects of regular kiwifruit consumption, when, for example, a minimum of two fruits are eaten on a daily basis for several weeks, while no data were retrieved for intestinal effects due to occasional intake. Provided that a meta-regression was not feasible, it is only possible to formulate a few hypotheses about the impact of any potential moderators of the effect on study outcomes: if we only consider healthy or sub-healthy adults, interventions appear to work regardless of individual gender and age, and there seems to be no linear dose–response relationship between kiwifruit quantity (2, 3 or 4/day) and defecation frequency (this is in line with existing evidence about fibre effects on intestinal motility [42]). The effect of treatment duration may play a role as well, but it is unclear how it can impact intestinal functions in the long run because available studies are characterised by relatively short follow-up periods. Interestingly, in one study, kiwifruit consumption was associated with reduced levels of TNF-alpha, a pro-inflammatory cytokine, both in patients with IBS and in healthy subjects, thus suggesting the existence of physiological effects beyond intestinal motility promotion [31].

If strengths, quality, consistency, plausibility, and limitations of existing studies are globally evaluated, it is possible to affirm that there is moderate evidence (GRADE B) in support of the efficacy of kiwifruit to promote intestinal motility and to alleviate constipation. As a practical recommendation, adding two kiwifruits to the daily diet of a patient with chronic constipation of functional aetiology can be a useful starting point to help improve defecation frequency. It is possible to increase the number of kiwifruits eaten every day (never exceeding the threshold of four kiwifruits a day) and to follow this recommendation for 2–4 weeks, possibly repeating it over time if chronic constipation persists.

4.2. Mechanism of Action

Pharmacological mechanisms of action and regulation of intestinal functions induced by kiwifruit are not fully known to date [10]. In general, several components of kiwifruits have been hypothesised to have a role in improving digestive health: natural fibre can increase stool volume, decrease transit time, and influence intestinal microflora composition in such a way as to augment enteric functionality; actinidin has a well-known proteolytic activity; raphides (oxalate crystals) may increase mucin production; water and minerals

can reduce stool consistency and promote intestinal motility; phenolic compounds and vitamin C can have direct antioxidant, immune-modulating, and anti-inflammatory effects on the gut barrier [10,43–46]. Combined together, these effects can help ease constipation, especially in patients with IBS.

4.3. Safety and Tolerability of Intervention

Kiwifruit consumption is quite well tolerated, provided that the consumer is not allergic to its components (cross-reactivity and association with hypersensitivity to pollen, latex, or other exotic foods have been reported in the scientific literature and should always be kept in mind) [47]. In experimental settings, at a maximum dose of four kiwifruits a day, diarrhoea was not reported by study participants [22]. Nevertheless, excessive fruit consumption well above the nutritional intake studied in available trials (i.e., more than four kiwifruits a day) may cause intestinal discomfort, diarrhoea, as well as reduced absorption of other nutrients, since very high fibre intake has been reported to sometimes cause these side effects [48,49]. The average content of Vitamin K in kiwifruits (40.3 µg per 100 g of raw green fruit [4]) should be taken into account when planning a diet for patients who regularly take warfarin and other vitamin K antagonists.

4.4. Study Limitations

In general, the number of relevant studies was quite low, possibly because this topic has mostly been investigated in recent years. Available trials involved a limited number of participants, and some of them were lacking a full description of their methodological details. Overall, publication bias cannot be fully excluded.

5. Conclusions

In conclusion, moderate-quality evidence suggests that kiwifruit dietary consumption can significantly improve complete bowel movements per week and decrease stool consistency. Even though this effect is likely due to the high fibre content of kiwifruits, their consumption can have beneficial effects beyond a mere physiological action on intestinal motility, including a mild anti-inflammatory and antioxidant effect on the gut barrier. Nevertheless, additional studies are recommended to strengthen the consistency of current evidence with larger trials and to further investigate any disease- and patient-related predictors of efficacy of this dietary recommendation, since kiwifruits and their derivatives may be a precious resource in clinical nutrition, especially for elderly care. In particular, it would be useful to achieve adequate study power with sufficiently large sample size, as recommended in two trials indicating that at least from 15 to 22 subjects per study arm are required to demonstrate a statistically significant change, if any [33,37]. More clinical trials should be designed to better investigate the long-term effects of kiwifruit regular consumption and should include a greater diversity of participants in terms of age, gender, and lifestyle characteristics. Future research is also advised to thoroughly evaluate the interaction between kiwifruit consumption and gut microbiota modulation, which is of great interest for preventive and clinical purposes.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/futurepharmacol1010003/s1, Table S1: PRISMA checklist.

Author Contributions: Conceptualisation, M.A. and D.D.; methodology, M.A. and D.D.; validation, M.A. and D.D.; investigation, M.A. and D.D.; resources, M.A. and D.D.; data curation, M.A. and D.D.; writing—original draft preparation, M.A. and D.D.; writing—review and editing, M.A. and D.D.; visualisation, M.A. and D.D.; supervision, M.A. and D.D.; project administration, M.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Crowhurst, R.N.; Gleave, A.P.; MacRae, E.A.; Ampomah-Dwamena, C.; Atkinson, R.G.; Beuning, L.L.; Bulley, S.M.; Chagne, D.; Marsh, K.B.; Matich, A.J.; et al. Analysis of Expressed Sequence Tags from Actinidia: Applications of a Cross Species EST Database for Gene Discovery in the Areas of Flavor, Health, Color and Ripening. *BMC Genom.* **2008**, *9*, 351. [CrossRef]
2. Dias, M.; Caleja, C.; Pereira, C.; Calhelha, R.C.; Kostic, M.; Sokovic, M.; Tavares, D.; Baraldi, I.J.; Barros, L.; Ferreira, I.C.F.R. Chemical Composition and Bioactive Properties of Byproducts from Two Different Kiwi Varieties. *Food Res. Int.* **2020**, *127*, 108753. [CrossRef]
3. Nishiyama, I.; Yamashita, Y.; Yamanaka, M.; Shimohashi, A.; Fukuda, T.; Oota, T. Varietal Difference in Vitamin C Content in the Fruit of Kiwifruit and Other Actinidia Species. *J. Agric. Food Chem.* **2004**, *52*, 5472–5475. [CrossRef]
4. Food Data Central. Available online: https://fdc.nal.usda.gov/ (accessed on 25 August 2021).
5. He, X.; Fang, J.; Chen, X.; Zhao, Z.; Li, Y.; Meng, Y.; Huang, L. Actinidia Chinensis Planch: A Review of Chemistry and Pharmacology. *Front. Pharmacol.* **2019**, *10*, 1236. [CrossRef] [PubMed]
6. Celik, A.; Ercisli, S.; Turgut, N. Some Physical, Pomological and Nutritional Properties of Kiwifruit Cv. Hayward. *Int. J. Food Sci. Nutr.* **2007**, *58*, 411–418. [CrossRef] [PubMed]
7. Lembo, A.; Camilleri, M. Chronic Constipation. *N. Engl. J. Med.* **2003**, *349*, 1360–1368. [CrossRef]
8. Higgins, P.D.R.; Johanson, J.F. Epidemiology of Constipation in North America: A Systematic Review. *Am. J. Gastroenterol.* **2004**, *99*, 750–759. [CrossRef] [PubMed]
9. Annells, M.; Koch, T. Constipation and the Preached Trio: Diet, Fluid Intake, Exercise. *Int. J. Nurs. Stud.* **2003**, *40*, 843–852. [CrossRef]
10. Bayer, S.B.; Gearry, R.B.; Drummond, L.N. Putative Mechanisms of Kiwifruit on Maintenance of Normal Gastrointestinal Function. *Crit. Rev. Food Sci. Nutr.* **2018**, *58*, 2432–2452. [CrossRef]
11. Alame, A.M.; Bahna, H. Evaluation of Constipation. *Clin. Colon Rectal Surg.* **2012**, *25*, 5–11. [CrossRef]
12. Rigby, D.; Powell, M. Causes of Constipation and Treatment Options. *Prim. Health Care Res. Dev.* **2005**, *15*, 41–50. [CrossRef]
13. Bae, S.H. Diets for Constipation. *Pediatr. Gastroenterol. Hepatol. Nutr.* **2014**, *17*, 203–208. [CrossRef]
14. Drummond, L.; Gearry, R.B. Kiwifruit Modulation of Gastrointestinal Motility. *Adv. Food Nutr. Res.* **2013**, *68*, 219–232. [CrossRef]
15. Weir, I.; Shu, Q.; Wei, N.; Wei, C.; Zhu, Y. Efficacy of Actinidin-Containing Kiwifruit Extract Zyactinase on Constipation: A Randomised Double-Blinded Placebo-Controlled Clinical Trial. *Asia Pac. J. Clin. Nutr.* **2018**, *27*, 564–571. [CrossRef] [PubMed]
16. Ansell, J.; Butts, C.A.; Paturi, G.; Eady, S.L.; Wallace, A.J.; Hedderley, D.; Gearry, R.B. Kiwifruit-Derived Supplements Increase Stool Frequency in Healthy Adults: A Randomized, Double-Blind, Placebo-Controlled Study. *Nutr. Res.* **2015**, *35*, 401–408. [CrossRef]
17. Udani, J.K.; Bloom, D.W. Effects of Kivia Powder on Gut Health in Patients with Occasional Constipation: A Randomized, Double-Blind, Placebo-Controlled Study. *Nutr. J.* **2013**, *12*, 78. [CrossRef] [PubMed]
18. Kindleysides, S.; Kuhn-Sherlock, B.; Yip, W.; Poppitt, S.D. Encapsulated Green Kiwifruit Extract: A Randomised Controlled Trial Investigating Alleviation of Constipation in Otherwise Healthy Adults. *Asia Pac. J. Clin. Nutr.* **2015**, *24*, 421–429. [CrossRef]
19. Zhuang, Z.; Chen, M.; Niu, J.; Qu, N.; Ji, B.; Duan, X.; Liu, Z.; Liu, X.; Wang, Y.; Zhao, B. The Manufacturing Process of Kiwifruit Fruit Powder with High Dietary Fiber and Its Laxative Effect. *Molecules* **2019**, *24*, 3813. [CrossRef]
20. Abbasalizadeh, S.; Ebrahimi, B.; Azizi, A.; Dargahi, R.; Tayebali, M.; Ghadim, S.T.; Foroumandi, E.; Aliasghari, F.; Javadi, M.; Izadi, A.; et al. Review of Constipation Treatment Methods with Emphasis on Laxative Foods. *Curr. Nutr. Food Sci.* **2020**, *16*, 675–688. [CrossRef]
21. Montoya, C.A.; Henare, S.J.; O'Donoghue, E.M.; Rosendale, D.; Edwards, P.; Moughan, P.J. Kiwifruit (Actinidia Deliciosa), Compared with Cellulose and Psyllium, Influences the Histology and Mucus Layer of the Gastrointestinal Tract in the Growing Pig. *Food Funct.* **2021**, *12*, 8007–8016. [CrossRef]
22. EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA); Turck, D.; Castenmiller, J.; De Henauw, S.; Hirsch-Ernst, K.I.; Kearney, J.; Knutsen, H.K.; Maciuk, A.; Mangelsdorf, I.; McArdle, H.J.; et al. Green Kiwifruit (lat. Var. Hayward) and Maintenance of Normal Defecation: Evaluation of a Health Claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006. *EFSA J.* **2021**, *19*, e06641. [CrossRef] [PubMed]
23. Xing, J.H.; Soffer, E.E. Adverse Effects of Laxatives. *Dis. Colon Rectum* **2001**, *44*, 1201–1209. [CrossRef]
24. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *Int. J. Surg.* **2021**, *88*, 105906. [CrossRef]
25. Jadad, A.R.; Moore, R.A.; Carroll, D.; Jenkinson, C.; Reynolds, D.J.; Gavaghan, D.J.; McQuay, H.J. Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? *Control. Clin. Trials* **1996**, *17*, 1–12. [CrossRef]
26. Kjaergard, L.L.; Villumsen, J.; Gluud, C. Reported Methodologic Quality and Discrepancies between Large and Small Randomized Trials in Meta-Analyses. *Ann. Intern. Med.* **2001**, *135*, 982–989. [CrossRef]
27. Higgins, J.; Thomas, J. (Eds.) *Cochrane Handbook for Systematic Reviews of Interventions*, 2nd ed.; Wiley Cochrane Series; Wiley-Blackwell: Hoboken, NJ, USA, 2019; ISBN 9781119536628.

28. IntHout, J.; Ioannidis, J.P.A.; Borm, G.F. The Hartung-Knapp-Sidik-Jonkman Method for Random Effects Meta-Analysis Is Straightforward and Considerably Outperforms the Standard DerSimonian-Laird Method. *BMC Med. Res. Methodol.* **2014**, *14*, 25. [CrossRef] [PubMed]
29. Goldet, G.; Howick, J. Understanding GRADE: An Introduction. *J. Evid. Based Med.* **2013**, *6*, 50–54. [CrossRef]
30. Caballero, N.; Benslaiman, B.; Ansell, J.; Serra, J. The Effect of Green Kiwifruit on Gas Transit and Tolerance in Healthy Humans. *Neurogastroenterol. Motil.* **2020**, *32*, e13874. [CrossRef] [PubMed]
31. Eady, S.L.; Wallace, A.J.; Hedderley, D.I.; Bentley-Hewitt, K.L.; Butts, C.A. The Effects on Immune Function and Digestive Health of Consuming the Skin and Flesh of Zespri SunGold Kiwifruit (Var. "Zesy002") in Healthy and IBS-Constipated Individuals. *Nutrients* **2020**, *12*, 1453. [CrossRef]
32. Eady, S.L.; Wallace, A.J.; Butts, C.A.; Hedderley, D.; Drummond, L.; Ansell, J.; Gearry, R.B. The Effect of "Zesy002" Kiwifruit (Var.) on Gut Health Function: A Randomised Cross-over Clinical Trial. *J. Nutr. Sci.* **2019**, *8*, e18. [CrossRef] [PubMed]
33. Wilkinson-Smith, V.; Dellschaft, N.; Ansell, J.; Hoad, C.; Marciani, L.; Gowland, P.; Spiller, R. Mechanisms Underlying Effects of Kiwifruit on Intestinal Function Shown by MRI in Healthy Volunteers. *Aliment. Pharmacol. Ther.* **2019**, *49*, 759–768. [CrossRef] [PubMed]
34. Chan, A.-O.-O.; Leung, G.; Tong, T.; Wong, N.-Y. Increasing Dietary Fiber Intake in Terms of Kiwifruit Improves Constipation in Chinese Patients. *World J. Gastroenterol.* **2007**, *13*, 4771–4775. [CrossRef]
35. Chey, S.W.; Chey, W.D.; Jackson, K.; Eswaran, S. Exploratory Comparative Effectiveness Trial of Green Kiwifruit, Psyllium, or Prunes in US Patients With Chronic Constipation. *Am. J. Gastroenterol.* **2021**, *116*, 1304–1312. [CrossRef]
36. Chang, C.-C.; Lin, Y.-T.; Lu, Y.-T.; Liu, Y.-S.; Liu, J.-F. Kiwifruit Improves Bowel Function in Patients with Irritable Bowel Syndrome with Constipation. *Asia Pac. J. Clin. Nutr.* **2010**, *19*, 451–457.
37. Rush, E.C.; Patel, M.; Plank, L.D.; Ferguson, L.R. Kiwifruit Promotes Laxation in the Elderly. *Asia Pac. J. Clin. Nutr.* **2002**, *11*, 164–168. [CrossRef] [PubMed]
38. Senn, S.S. *Cross-Over Trials in Clinical Research*; John Wiley & Sons: Hoboken, NJ, USA, 2002; ISBN 9780471496533.
39. McCrea, G.L.; Miaskowski, C.; Stotts, N.A.; Macera, L.; Varma, M.G. A Review of the Literature on Gender and Age Differences in the Prevalence and Characteristics of Constipation in North America. *J. Pain Symptom Manag.* **2009**, *37*, 737–745. [CrossRef]
40. Cremon, C.; Ansell, J.; Pagano, I.; Kuhn-Sherlock, B.; Drummond, L.; Barbaro, M.R.; Capelli, E.; Bellacosa, L.; Stanghellini, V.; Barbara, G. Su1659–A Randomized, Controlled, Single-Blind, Cross-over Study Assessing the Effect of Green Kiwifruit on Digestive Functions and Microbiota in Constipated Patients. *Gastroenterology* **2018**, *154*, S565–S566. [CrossRef]
41. Wilkinson-Smith, V.; Dellschaft, N.; Hoad, C.; Marciani, L.; Gowland, P.; Spiller, R. Increase in small bowel water content and fluidity of ascending colon contents induced by kiwifruit is associated with more frequent looser stools in healthy volunteers: A mechanistic MRI study (Oral Presentations). *Neurogastroenterol. Motil.* **2018**, *30*, e13422. [CrossRef]
42. McRorie, J.W.; McKeown, N.M. Understanding the Physics of Functional Fibers in the Gastrointestinal Tract: An Evidence-Based Approach to Resolving Enduring Misconceptions about Insoluble and Soluble Fiber. *J. Acad. Nutr. Diet.* **2017**, *117*, 251–264. [CrossRef]
43. Lee, Y.K.; Low, K.Y.; Siah, K.; Drummond, L.M.; Gwee, K.-A. Kiwifruit (Actinidia Deliciosa) Changes Intestinal Microbial Profile. *Microb. Ecol. Health Dis.* **2012**, *23*. [CrossRef]
44. Chalabi, M.; Khademi, F.; Yarani, R.; Mostafaie, A. Proteolytic Activities of Kiwifruit Actinidin (Actinidia Deliciosa Cv. Hayward) on Different Fibrous and Globular Proteins: A Comparative Study of Actinidin with Papain. *Appl. Biochem. Biotechnol.* **2014**, *172*, 4025–4037. [CrossRef]
45. Henare, S.J.; Rutherfurd, S.M. Digestion of Kiwifruit Fiber. *Adv. Food Nutr. Res.* **2013**, *68*, 187–203. [CrossRef]
46. Allison, M.J.; Cook, H.M.; Milne, D.B.; Gallagher, S.; Clayman, R.V. Oxalate Degradation by Gastrointestinal Bacteria from Humans. *J. Nutr.* **1986**, *116*, 455–460. [CrossRef] [PubMed]
47. Lucas, J.S.A.; Lewis, S.A.; Hourihane, J.O. Kiwi Fruit Allergy: A Review. *Pediatr. Allergy Immunol.* **2003**, *14*, 420–428. [CrossRef] [PubMed]
48. Henley, S.; Misner, S. Dietary Fiber. Available online: http://mail.konjacfoods.com/fiber/fiberar.pdf (accessed on 26 October 2021).
49. Kishimoto, Y.; Kanahori, S.; Sakano, K.; Ebihara, S. The Maximum Single Dose of Resistant Maltodextrin That Does Not Cause Diarrhea in Humans. *J. Nutr. Sci. Vitaminol.* **2013**, *59*, 352–357. [CrossRef] [PubMed]